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Formation and Reactions of Methylol Cellulose

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FORMATION AND REACTIONS OF METHYLOL CELLULOSE

A thesis submitted by

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SUMMARY

The mechanism of cellulose dissolution via the formation of methylol cellulose together with the derivatization of the dissolved methylol cellulose were investigated.

Elucidation of how dimethyl sulfoxide participates in the formation and dissolution of methylol cellulose in the dimethyl sulfoxide/paraformaldehyde (DMSO/PF) solvent system resulted in the discovery that methylol cellulose could also be prepared and dissolved in solvents other than DMSO. The solvents which were found to be successful have the common characteristics of being dipolar, aprotic, and good hydrogen bond acceptors. Solvents found to be successful include pyridine, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methyl-2-pyrrolidinone (NMP) and tetramethylene sulfoxide (TMSO).

Preparation of the peracetate of methylol cellulose was accomplished using acetic anhydride and pyridine. Acetylation of the methylol substituents provided a stable acetal derivative which could then be isolated and characterized by NMR spectroscopy. NMR analysis of the acetate derivative provided direct evidence for the methylol derivative and demonstrated the existence of polyoxymethylene substituents. NMR analysis of the peracetate is a convenient experimental technique for determining the molar degree of substitution (MS) of methylol cellulose.

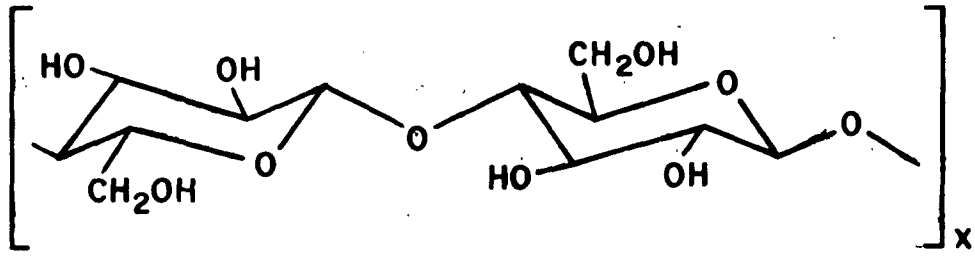
Analysis of the MS of methylol cellulose prepared in the various solvents demonstrated that a high MS is required initially to accomplish dissolution. However, once the cellulose has dissolved, the MS can decrease substantially and still retain the cellulose in solution. The MS required to obtain dissolution and the minimum MS required to keep the cellulose in solution are dependent on the organic solvent which is employed.

Hydroxyethylation of methylol cellulose in the DMSO/PF system was attempted. Chemical analysis of the reaction product indicated small amounts of substitution had been obtained. Gas-liquid chromatographic (GLC) analysis showed no detectable amounts of substitution on the anhydroglucose units of the cellulose. Substitution by the hydroxyethyl groups most likely occurred at the hydroxyl groups of the methylol substituents and were subsequently lost during the acid hydrolysis prior to GLC analysis.

The homogeneous preparation of triphenylmethyl (trityl) cellulose is easily and rapidly accomplished in the methylol cellulose solvent systems. At a reaction temperature of 80° in the presence of pyridine with excess reagent, the methylol substituents are displaced, thus giving trityl cellulose with a degree of substitution (DS) of 1 as the final product. An intermediate product, trityl methylol cellulose, was isolated which indicates that displacement of the trityl methylol acetal substituents occurs. A by-product of this reaction was a new compound, triphenylmethoxymethyl pyridinium chloride.

INTRODUCTION

Cellulose is a naturally occurring linear polymer composed of β-1,4 linked anhydroglucose units. Each of these units has three free hydroxyl groups, one primary and two secondary, which are capable of chemically reacting as typical alcohols.



In nature, cellulose molecules are bound together in submicroscopic and microscopic threadlike bodies called microfibrils and fibrils, respectively. These fibrils, in turn, are combined to form macroscopic bodies or fibers. The degree of order in the solid cellulose structure ranges from amorphous to highly ordered crystalline regions. Due to strong association, primarily in the form of hydrogen bonding, it is difficult to separate the chains.

Cellulose solvents are capable of bringing cellulose chains out of their solid polymeric structure into solution as individual molecules. To accomplish dissolution, the solvent must first penetrate the macro- and micropore system of the cellulose, even into the highly ordered crystalline regions. In this step, hydrogen bonds are disrupted as the cellulose structure is swollen. Next, the solvent must be capable of interacting with the cellulose hydroxyl groups to keep them from reforming hydrogen bonds. If the hydrogen bonds are not hindered to a sufficient degree, the solid cellulose structure may be swollen, yet will remain intact. Often, the cellulose is dissolved when one component of the system interacts with the hydroxyls by forming a

complex or by reacting and forming a cellulose derivative. The resulting derivative is then dissolved.

Cellulose solvents have found a wide range of uses both commercially and in the laboratory. The most important commercial application is the preparation of regenerated cellulose films (cellophane) and cellulose filaments and fibers (rayon). Membranes for dialysis can also be prepared by regenerating dissolved cellulose. An important experimental application of cellulose solvents is the determination of cellulose molecular weight by viscosity measurements. Other experiments in which some cellulose solvents are useful include light-scattering measurements to determine cellulose polymer properties and gel permeation chromatography to obtain molecular weight distributions. Thus, the development and understanding of cellulose solvents is important to many different fields.

Several review articles on swelling and dissolving cellulose have been written (1-6) and may be consulted for more extensive information. The following discussion is intended as a quick overview of the variety of systems capable of dissolving cellulose.

CELLULOSE SOLVENTS

AQUEOUS SOLVENTS

Some of the most widely used systems for dissolving cellulose are aqueous. The types of reagents employed range from strong acids to strong bases. Many strong acids such as sulfuric, phosphoric, and trifluoroacetic acid are capable of dissolving cellulose. However, degradation by hydrolysis or dehydration tends to be a severe problem with these systems. Although strong bases such as inorganic hydroxides and amines are good at swelling cellulose to a high

degree, they are generally limited in their ability to accomplish complete dissolution. Tetraalkylammonium bases or "Triton" solvents, such as trimethylbenzylammonium hydroxide (Triton B), can completely dissolve cellulose. In a base, the cellulose hydroxyls can loose their protons to form an anion. The bulky tetraalkylammonium counterion provides a good separation of the cellulose chains to keep them from recombining.

Metal complexes in aqueous solution have commonly been employed to dissolve cellulose. The cuprammonium hydroxide (cuam) and cupriethylenediamine (cuene) solvents are two of the most common aqueous solvents for cellulose, and both are used for viscometric determination of the degree of polymerization of cellulose. Jayme (7,8) and Jayme and Neuschaffer (9-11) developed analogous solvents possessing different central metal atoms. These systems, along with others, including sodium ferric tartrate (FeTNa), are thought to function by complex formation with the cellulose hydroxyl groups. A coordination compound is thought to form between the cellulose hydroxyls and the chelated metal ion which imparts water solubility to the cellulose.

Most regenerated cellulose is produced by the viscose process. In this process cellulose is swollen in aqueous alkali and then reacted with carbon disulfide to produce the xanthate derivative. Cellulose xanthate, which is soluble in the alkali, may then be regenerated in the desired form in an acid bath.

NONAQUEOUS CELLULOSE SOLVENTS

In an attempt to find alternatives to the classical dissolution of cellulose via the viscose and cuam processes, recent research has turned more to

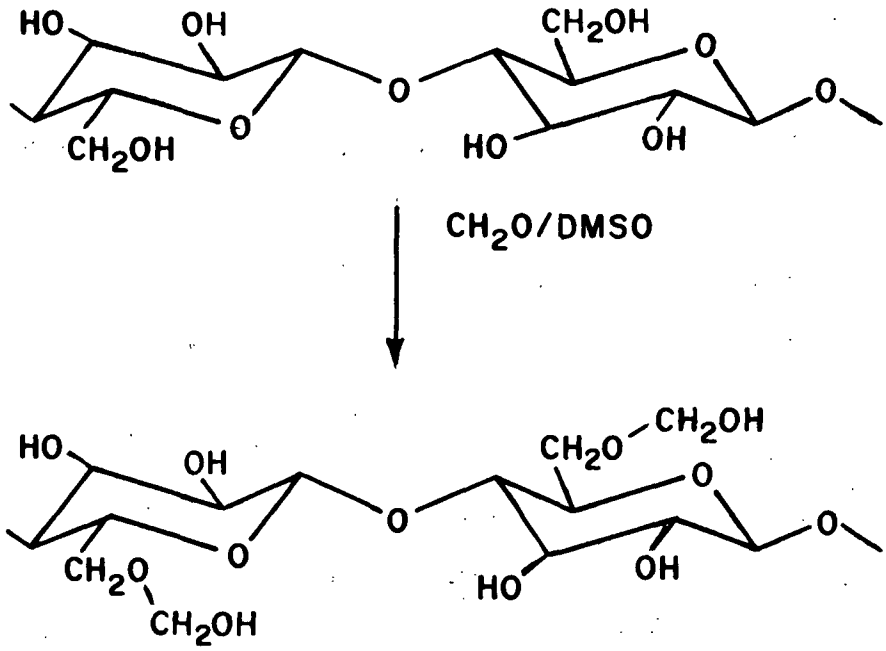
nonaqueous systems. Nonaqueous cellulose solvents offer the potential of ease of preparation and recovery, and some have the advantage of being nondegrading.

Many nonaqueous cellulose solvent systems have nitrogen-containing compounds. Cellulose can be dissolved by the action of nitrosylic compounds, such as N_2O_4, NOCl, and $NO(HSO_4)$, in polar aprotic solvents (12-17). The use of N_2O_4 in N,N-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) has been of particular interest. Methylamine in DMSO has been reported to be capable of dissolving cellulose (18), and the use of hydrazine as a cellulose solvent has been investigated (19). Cellulose has been reported to dissolve in organic solvents containing sulfur dioxide and diethylamine (20-23). Cellulose can be dissolved in various amine oxides (24) and cyclic amine oxides (25-27). Of the amine oxides investigated, N-methylmorpholine-N-oxide had the greatest capacity to dissolve cellulose. N-Alkylpyridinium chlorides are capable of dissolving cellulose (28), with N-ethylpyridinium chloride being the most frequently used. Melts of the amine oxides and N-alkylpyridinium chlorides will dissolve the cellulose, but often an organic solvent is employed as well to facilitate the dissolution and handling processes.

Other solvents for cellulose which have been reported include dihydroxypropyldisulfide (29) and chloral in pyridine or other aprotic solvents (30). In the chloral system, a cellulose derivative with 5-10 moles of chloral per anhydroglucose unit is produced. The cellulose derivative from this system is most likely the hemiacetal of chloral (31).

THE DMSO/PF SOLVENT SYSTEM

A new cellulose solvent system composed of dimethyl sulfoxide (DMSO) and paraformaldehyde (PF) was recently discovered (32,33). As in the chloral solvent system, it is believed that a hemiacetal derivative of cellulose is produced (32,33). This new system was discovered during an attempt to cross-link cellulose dissolved in the N-methylmorpholine-N-oxide solvent. DMSO was present in the system as a diluent, and formaldehyde in the form of PF was used as the cross-linking agent. It was observed that cellulose dissolved faster when PF was present. Further investigation showed that cellulose could easily and quickly be dissolved in DMSO alone without significant degradation when PF was added and the mixture heated to ca. 120°. Subsequent research provided evidence to support the hypothesis that the dissolution was dependent, in part, upon the formation of the hemiacetal derivative, methylol cellulose.



Dissolution mechanism for cellulose in the DMSO/PF solvent system (32,33)

When a solution of the dissolved cellulose in DMSO is freeze-dried, the material obtained is soluble in cold DMSO without further treatment. Formaldehyde is released, and the cellulose is regenerated upon treating the derivative with water. Analysis of the formaldehyde released from the freeze-dried methylol cellulose indicated approximately one methylol group per anhydroglucose unit (32,33). Analysis of the substituent distribution of the cellulose derivatives resulting from the homogeneous methylation and carboxymethylation of the dissolved cellulose indicated that methylol units were located preferentially on the C-6 hydroxyls of the anhydroglucose units (32,34). This observation was later confirmed by a study of the C^{13} NMR spectra of cellulose dissolved in the DMSO/PF solvent system (35).

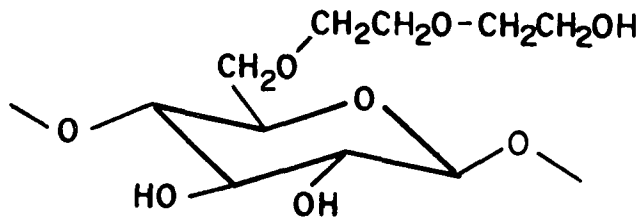
Though the DMSO/PF solvent has been available for only a short time, it has received much interest. The properties and production of rayon fibers from solutions of cellulose in the DMSO/PF solvent have been studied (36-38). The solution properties of methylol cellulose in DMSO have been investigated (39,40), and it has been proposed that this solvent system may be suitable for the determination of the degree of polymerization (DP) of cellulose by viscosity measurements (39). Johnson (41) and Seymour and Johnson (42) looked at some of the variables for the dissolution of cellulose in the DMSO/PF solvent. They obtained solutions which were limited to a maximum concentration of ca. 1% cellulose probably as a result of low dissolution temperatures.

The possibility of dissolving methylol cellulose in solvents other than DMSO has been investigated (5,41-43). It was concluded by these authors that the dissolution of cellulose was restricted to the combination of DMSO and formaldehyde. One report indicated that methylol cellulose could be prepared in other solvents, but would dissolve only in DMSO (43).

The DMSO/PF system has produced much interest and has much potential as a solvent system for cellulose. However, there is much information yet to be gained before a clear understanding of this sytem is obtained.

CELLULOSE DERIVATIZATION

Each anhydroglucose unit of cellulose has three free hydroxyl groups available for substitution. The two secondary hydroxyls at C-2 and C-3 and the primary hydroxyl at C-6 can undergo reactions typical of other alcohols. After a reaction, the number of hydroxyl groups per anhydroglucose unit which are substituted is termed the degree of substitution (DS). The maximum DS of 3 results when all hydroxyl groups of the cellulose are substituted. In certain reactions, such as hydroxyethylation, a new site for subsequent reaction is generated when a cellulose hydroxyl is substituted. Consequently, the term molar degree of substitution (MS) is employed to describe these derivatives. An anhydroglucose unit with two moles of ethylene oxide substituted at OH-6, for example, would have a DS of 1 and an MS of 2. The properties of a cellulose derivative are affected by the DS, MS, degree of polymerization (DP) of the cellulose, and the distribution of the substituents on the cellulose hydroxyls. Consequently, these are important variables to control.



The uniformity of distribution is an important variable of cellulose derivatives and is often difficult to control. A nonuniform substitution generally occurs during heterogeneous derivatization reactions. The highly

ordered crystalline regions of cellulose are less accessible to reagents than the amorphous and surface regions. Uniform access of the reagent to the cellulose might be achieved if the cellulose were dissolved in a suitable medium. This would give a more easily controlled and reproducible reaction and could permit a clearer understanding of other factors which influence the derivatization.

One of the major factors influencing the final substituent distribution is the reactivity of the various cellulose hydroxyl groups. Due to an inductive effect of the ring oxygen of the anhydroglucose unit, the hydroxyl group at C-2 is more acidic than OH-3. Preferential reactivity of OH-2 is evident in many reactions which involve the alkoxide ion, such as methylation with methyl iodide (44) and ethylation with ethyl chloride (45). However, the preference for reaction at OH-2 does not hold true for all etherification reactions.

As the size of the substituent increases, reaction at the more accessible OH-6 becomes predominant. Hydroxyethylation (46,47) and carboxymethylation (48) show some preference for reaction at the primary C-6 hydroxyl, though reaction will also occur at the other hydroxyls. With the bulky p-tolylsulfonyl (tosyl) and triphenylmethyl (trityl) groups, however, reaction can be made to occur almost exclusively at primary alcohols.

REACTIONS IN THE DMSO/PF SYSTEM

Nicholson attempted two etherification reactions of cellulose dissolved in the DMSO/PF solvent system (32,34). Both reactions, methylation and carboxymethylation, showed the same trend; the substituent distribution was affected by the presence of the methylol substituents.

Only materials with a low DS could be obtained from the carboxymethylation reaction. Termination of the reaction apparently resulted due to a lack of solubility of the final product. Depending upon the reaction conditions, the substituent distribution was observed to change. With the mild reagents, chloroacetic acid and triethylamine, the hydroxyl group of the methylol substituents preferentially reacted to form an acetal. The resultant polymer had an IR spectrum characteristic of a carboxymethyl derivative, but acid hydrolysis yielded only glucose. Carboxymethylation of the cellulose hydroxyls was achieved with more active reagents, sodium hydride and methyl bromoacetate. Analysis of the substituent distribution of the resultant carboxymethyl cellulose indicated that the methylol substituents were located preferentially on OH-6. The previous substitution of the cellulose hydroxyls by methylol substituents resulted in a reduced degree of substitution at OH-6.

The blocking effect of the methylol substituents could be reduced by increasing the reaction temperature. Alternately, an increase in the blocking ability could be obtained by first reacting the dissolved cellulose under mild conditions to form an acetal of the methylol groups. The resultant acetal could withstand the more vigorous reaction conditions better than the original hemiacetal.

Methylation of the dissolved cellulose was accomplished using sodium hydride and methyl iodide. Contrary to the prior etherification where DMSO insolubility limited the extent of reaction, methylation proceeded homogeneously throughout the reaction. By increasing the reaction time and the number of sodium hydride/methyl iodide treatments, the DS of the methyl cellulose could be increased to nearly three. Analysis of the substituent distribution gave

results similar to those obtained for the carboxymethylation reaction. Prior substitution by the methylol substituents decreased the amount of substitution at OH-6 in the early stages of reaction.

Attempts to prepare other derivatives in the DMSO/PF solvent system have recently been reported. The preparation of hydroxyethyl cellulose (HEC) in this solvent system has been reported (49). Attempts to react cellulose in the DMSO/PF system with vinyl compounds such as acrylonitrile, methyl methacrylate, and ethyl acrylate have been reported to be unsuccessful (5). Esterification of cellulose dissolved in the DMSO/PF solvent has been reported (41,50,51). The esterification reagents used were acid anhydrides. It should be noted that when acid anhydrides are used in conjunction with DMSO, oxidation of carbohydrates and formation of methylthiomethyl ethers compete with the esterification reactions (52,53).

RESULTS AND DISCUSSION

GENERAL

This research program may be divided into two main areas of investigation: (1) the dissolution of cellulose via the formation of methylol cellulose, and (2) the homogeneous reactions of methylol cellulose.

THE DISSOLUTION OF METHYLOL CELLULOSE

The typical reaction of formaldehyde with cellulose is the formation of acetal cross-links. Thus, the observation that cellulose could be dissolved by reaction with formaldehyde in dimethyl sulfoxide (DMSO) was surprising. It has been demonstrated that the dissolution of cellulose in this system is dependent, in part, on the formation of the hemiacetal derivative, methylol cellulose (32,33). In subsequent research several authors concluded that DMSO is unique in its ability to dissolve methylol cellulose (5,41-43). This specificity for DMSO was puzzling, and it was hoped that some insight into the dissolution mechanism could be gained by understanding the properties of DMSO. This medium must be having some effect, as the normal cross-linking reaction does not occur; and the methylol substituents in this system, unlike most hemiacetals, exhibit substantial stability.

THE DMSO/PF CELLULOSE SOLVENT SYSTEM

DMSO is classified as a dipolar aprotic solvent. Both of these properties are important in the DMSO/PF cellulose solvent system. The dipolar nature of DMSO is important to its proton accepting ability and may be important in the interaction with formaldehyde as well. The dipolar nature of monomeric formaldehyde presents the possibility for a dipole-dipole interaction between

the organic solvent and formaldehyde. It has been reported that nitriles and ketones may form dipole-dipole complexes with DMSO (54). Such an interaction would be expected to enhance retention of formaldehyde in solution and would maintain it in a highly reactive state. Similar interactions have been postulated for other cellulose solvent systems (2).

In the dissolution process, the solvent must penetrate and swell the cellulose structure. Intermolecular cellulosic hydrogen bonds must be disrupted, and the hydroxyl groups must be tied up to keep them from reforming hydrogen bonds with adjacent chains. It is known that DMSO is a powerful hydrogen bond acceptor (55-57), and therefore it is able to interact with the cellulose hydroxyls. It is also known that DMSO is a good swelling agent for cellulose (2,58), which confirms its ability to interact with the cellulose hydroxyls.

The strong interaction of DMSO with hydroxyls has been observed in other systems. It has been observed in NMR spectroscopy that DMSO reduces proton exchange between oxygens so that spin-spin coupling patterns are revealed (59). Schulman, et al. (60) in a study of carbonyl hydrates noted that otherwise unstable gem-diols could be isolated as stable crystalline adducts of strong hydrogen bond acceptors such as DMSO. Similar types of interactions may be important in the stabilization of the methylol substituents.

The interaction of DMSO to stabilize the methylol derivative is primarily by hydrogen bonding through the oxygen of the sulfoxide bond. When a solution of methylol cellulose in DMSO is freeze-dried, the resulting material contains some DMSO which is not readily removed by prolonged freeze-drying (32,33,61). It has been determined that approximately one mole of DMSO is retained per mole of formaldehyde (61). A comparison of the Raman spectrum of freeze-

dried methylol cellulose with the Raman spectrum of pure DMSO (Table I) reveals that there are several changes in the bands due to DMSO. The most important shift is in the sulfoxide stretching frequency, which is observed to decrease by 22 cm^{-1}. This shift is indicative of hydrogen bonding via the oxygen atom of the sulfoxide bond. Donation of a lone pair electron from the oxygen should lower the S-O bond order due to a decrease in the $p\pi \rightarrow d\pi$ bonding (62), resulting in a decrease of the S-O stretching frequency. It might be anticipated that the less hindered oxygen atom would be the primary site of interaction.

TABLE I

COMPARISON OF RAMAN FREQUENCIES OBSERVED FOR PURE DMSO AND DMSO IN FREEZE-DRIED METHYLOL CELLULOSE

Raman Frequency (cm^{-1})			
DMSO (Liquid)	DMSO (Methylol Cellulose)	Shift	Assignment (63)
311	310	-1	C-S-C deformation
338	342	+4	C-S-O deformation
387	390	+3	C-S-O deformation
672	679	+7	C-S stretch
702	712	+10	C-S stretch
957	957	0	Methyl rock
1048	1026	-22	S=O stretch
1423	1422	-1	C-H deformation
2916	2924	+8	C-H stretch
3001	3011	+11	C-H stretch

Besides the dipolar nature and hydrogen bond accepting abilities, another characteristic of DMSO which is important is its aprotic nature. Formaldehyde will react with any activated protons, such as those attached to oxygen or nitrogen atoms. Formaldehyde will also react with protons which are alpha to a double or triple bond, such as those of α-picoline or acetonitrile. In the cellulose-DMSO system, however, formaldehyde will react with the cellulose hydroxyls but not with DMSO.

From a consideration of the properties and characteristics of DMSO, the dissolution mechanism for cellulose in the DMSO/PF system, as shown in Fig. 1, is proposed. After the cellulose is swollen, the formaldehyde or its solvent complex can penetrate the structure more rapidly and uniformly. The DMSO can also act as a proton transfer agent in the transition state as the methylol derivative is formed. Once the methylol derivative has formed, the DMSO may stabilize the hemiacetal. One possible mode of interaction is a four-centered complex as shown. Such an interaction has been postulated as an intermediate state for the interaction of DMSO with thiols (64).

NEW METHYLOL CELLULOSE SOLVENTS

According to the previous discussion of the ways in which DMSO may interact with the formaldehyde, cellulose, and methylol cellulose, it appeared likely that other organic solvents should also work in the place of DMSO, even though previous indications were that DMSO was unique in its ability to dissolve methylol cellulose (5,41-43). Pyridine is aprotic and is a good hydrogen bond acceptor. It has been reported that pyridine can form a 1:1 complex with formaldehyde (65). In the chloral system, which also results in the formation of a hemiacetal derivative of cellulose, it has been noted that cellulose will dissolve much faster in N,N-dimethylformamide (DMF) by the action of chloral

when pyridine is added to the system (31). From this information, it was decided that pyridine would also be a likely solvent for the dissolution of methylol cellulose. Cellulose powder in pyridine was heated to 85°, and formaldehyde gas was bubbled into the system. Dissolution occurred rapidly, and a clear solution was obtained in about 15 minutes.

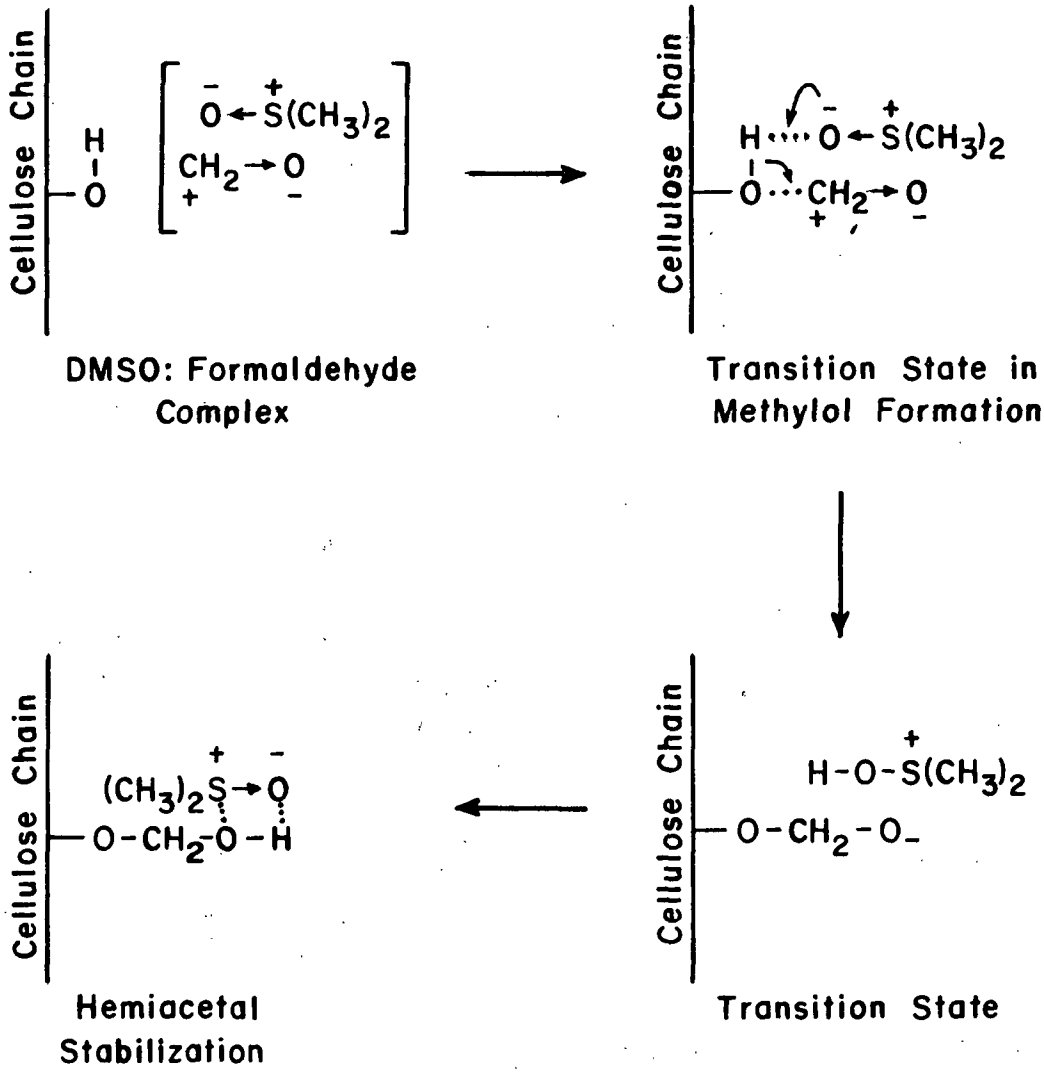
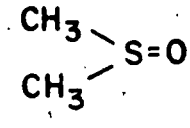
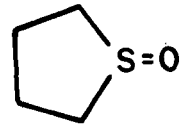


Figure 1. Potential Role of DMSO in Formation and Dissolution of Methylol Cellulose

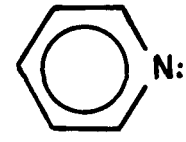
Once it was shown that one solvent other than DMSO could be used to prepare and dissolve methylol cellulose, it was decided that other solvents with similar properties may be capable of similar results. Subsequent investigation has shown that methylol cellulose can be prepared and dissolved in pyridine, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methyl-2-pyrrolidinone (NMP), and tetramethylene sulfoxide (TMS). It seems likely that other solvents may be added to this list.



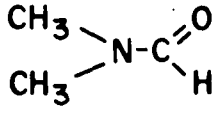
Dimethyl sulfoxide (DMSO)



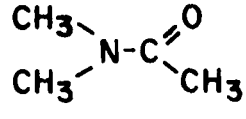
Tetramethylene sulfoxide (TMSO)



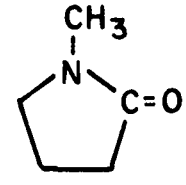
Pyridine



N,N-Dimethylformamide (DMF)



N,N-Dimethylacetamide (DMA)



N-Methyl-2-pyrrolidinone (NMP)

Each of the solvents which has been found to be successful has the common characteristics of being dipolar, aprotic, and is a good hydrogen bond acceptor. Each is also relatively small in size and therefore is capable of penetrating the cellulose structure more readily than similar but bulky molecules.

Properties of several organic solvents are presented in Table II. Six of the solvents, as previously mentioned, have been found suitable for preparing solutions of methylol cellulose. The dissolution process was tried without

TABLE II

PROPERTIES OF ORGANIC SOLVENTS

	Dimethyl sulfoxide	Tetramethylene sulfoxide	N,N-Dimethylformamide	N, N-Dimethylacetamide	N-Methyl-2-pyrrolidinone	Pyridine	Acetone	Tetramethylene sulfone	Acetonitrile
Molecular Weight	78.1	104.2	73.1	87.1	99.1	79.1	58.1	120.2	41.0
Boiling Point	189	-	153	165	202	115	56.2	285	81.6
Dipole Moment	4.3	-	3.86	3.81	4.09	2.3	2.88	4.81	3.92
$\Delta\nu$PFP*(67)	367	380	305	356	339	485	232	186	184
Solubility Parameter	12.0	-	12.1	10.8	11.3	10.7	9.9	13.4	9.9

* Relative basicity of solvent as measured by shift of OH stretching frequency of p-fluorophenol.

success in acetone, tetramethylene sulfone (sulfolane), and acetonitrile. Other dipolar aprotic solvents which were tried without success include benzonitrile, 2,6- and 3,5-lutidine, ethylene carbonate, and propylene carbonate.

As was noted previously in the discussion of the DMSO/PF system, several properties of the solvent may be important in the dissolution process. The properties which are considered to be important include: (1) hydrogen bond-accepting capabilities to allow interaction with cellulose hydroxyls, (2) a relatively small size to facilitate penetration into the cellulose structure, (3) an aprotic nature to eliminate possible reactions with formaldehyde, and (4) a dipolar nature to allow interaction with monomeric formaldehyde and stabilization of the resultant methylol derivative. A comparison of the molecular weights listed in Table II indicates that these aprotic solvents are similar in size and relatively small. Each solvent listed has a dipole moment, but there is no correlation between a high dipole moment and success as a solvent for methylol cellulose. These properties are important, but only when in combination with a good proton accepting ability of the solvent.

The relative basicity of a solvent can be determined from the decrease which it causes in the stretching frequency of a proton source (66) such as p-fluorophenol (PFP) (67). The shift of the infrared OH stretching frequency of PFP ($\Delta\nu$ PFP), which is the result of interaction with the solvent molecules, is listed in Table II. These data show that solvents which are effective for producing solutions of methylol cellulose are good proton acceptors, as indicated by a large $\Delta\nu$ PFP value. The other solvents are poorer in this ability. For a solvent to be effective in the dissolution of cellulose via the formation of methylol cellulose, it must be dipolar, aprotic, relatively small in size, and have good proton affinity.

Another property of the solvent, which has been applied in the discussion of methylol cellulose dissolution (68), is the solubility parameter. The solubility parameter applies to the miscibility of liquids or amorphous polymers. For cellulose, however, the crystalline regions and hydrogen bonding capabilities of the polymer introduce factors which are not compatible with the theory behind solubility parameters (69). As can be noted from the data in Table II, pyridine and DMF have much smaller solubility parameters than tetramethylene sulfone, yet the latter solvent was not effective for accomplishing dissolution.

Dissolution of Cellulose

Solutions of methylol cellulose in the new solvent systems have been prepared by two slightly different experimental techniques. Solutions of methylol cellulose were prepared in all of the solvents by bubbling formaldehyde gas into a stirring slurry of cellulose in the organic solvent. The slurry was kept at the desired temperature, generally 85°, in a thermostatically controlled oil bath. Formaldehyde gas, generated by the thermal decomposition of paraformaldehyde in an external flask, was bubbled through the slurry until a clear solution was obtained. In the temperature range of ca. 75-90°, solutions were generally limited to a maximum concentration of 1-2% cellulose.

In DMA, NMP, and TMSO, methylol cellulose solutions were prepared as previously described for DMSO (31,32). Paraformaldehyde with a suitably low decomposition temperature (<130°) was added directly to the stirring slurry of cellulose which was heated to a temperature of 120-125°. With this procedure, solutions of 5% cotton linters and 10% solutions of WCF-1 cellulose ($\overline{DP}_w$ 500) have been prepared. This procedure was not effective for dissolving

cellulose in pyridine and DMF. Cellulose solutions can be prepared over a range of temperatures. However, when the source of formaldehyde is paraformaldehyde which is added directly into the slurry, temperatures greater than ca. 110° are generally required to ensure effective thermal decomposition of the paraformaldehyde.

It has been shown that when methylol cellulose in the DMSO/PF solvent system is isolated by freeze-drying, approximately one mole of formaldehyde is bound per anhydroglucose unit (32,33,61). Characterization of the methylol celluloses generated in the new solvents indicates that the molar degree of substitution (MS) of the derivative can vary quite substantially. The method of analysis will be discussed later. It has been found that the MS of the methylol cellulose can be as high as 20-25. The high values were obtained at the lower dissolution temperatures where formaldehyde gas was bubbled into the slurry, and the solution was cooled immediately after dissolution had been accomplished. At lower temperatures where extended polyoxymethylene side chains are formed, gel formation occurs more readily, thus limiting the maximum cellulose concentration obtainable. A large MS due to low dissolution temperatures probably accounts for the limited concentrations of cellulose (ca. 1%) observed by Seymour and Johnson in the DMSO/PF system (41,42).

The Nondegrading Nature of the New Solvents

As might be expected from previous observations with the DMSO/PF system (39), the new methylol cellulose solvent systems were also found to be nondegrading. Cellulose was dissolved in pyridine, DMF, and DMA using formaldehyde gas. After dissolution had been achieved and the solution was cool, the cellulose was regenerated in hot (75°) water. The DP of the starting material and the regenerated celluloses was determined from the molecular weight distributions obtained by gel permeation chromatography (GPC) of the

carbanilate derivatives (70). As can be seen from the data in Table III, little degradation of the cellulose occurred during the dissolution process. The deviation from the starting material values apparently is a result of the regeneration procedure employed, as is demonstrated by the DPs obtained from a sample which had been treated by the regeneration process without prior dissolution.

TABLE III

DP OF CELLULOSE AND REGENERATED CELLULOSE

	$\overline{DP}_n$	$\overline{DP}_w$
Starting material (WCF-1)	276	505
Starting material treated by regeneration process	234	426
Regenerated cellulose from methylol cellulose prepared in:		
Pyridine	251	463
DMF	236	455
DMA	216	446

ANALYSIS OF THE METHYLOL SUBSTITUENTS

The presence of the methylol substituents can be confirmed and the MS determined for these systems by NMR analysis of the peracetylated material. Acetylation of the methylol substituents prevents their loss during isolation of the polymer by precipitation in water. Complete acetylation of the methylol hydroxyl groups and unsubstituted glucose hydroxyl groups is easily accomplished using acetic anhydride and pyridine and is confirmed by lack of OH

stretch in the IR spectra. Except for the sulfoxide solvents, the acetylation reagents were added directly to the solution of methylol cellulose in the organic solvent.

In the sulfoxide systems, reaction of the sulfoxide with acetic anhydride results in undesirable side reactions such as oxidation of the cellulose and formation of methylthiomethyl ethers (52,53). As these side reactions would interfere with the analysis to be performed, it was decided to remove the methylol cellulose from the sulfoxides prior to acetylation. It was discovered early in the present work that methylol cellulose could be precipitated from solution by the addition of nonsolvents such as carbon tetrachloride, hexane, benzene, and ethyl ether. Because of safety problems due to the penetrating and carrying ability of DMSO, it was decided to use ethyl ether for the precipitation work. After precipitation and washing with ethyl ether, the methylol cellulose from the sulfoxide systems was easily acetylated using acetic anhydride and pyridine.

The MS of the methylol cellulose was determined from the PMR spectra of the isolated peracetates. The PMR spectra of the peracetates dissolved in deuterochloroform were recorded and integrated. A typical PMR spectrum of methylol cellulose triacetate (MS ca. 9.5) is presented in Fig. 2. Protons of the acetyl methyl groups resonate at δ 2.08 ppm. The cellulosic ring protons are observed as a broad band occurring between ca. 3.2-5.3 ppm. Protons of methylene groups attached to O-acetyl substituents resonate at 5.33 ppm, while the other methylene protons of the polyoxymethylene chains resonate at 4.88 ppm. From the integral of the spectrum, the MS of the methylol cellulose was determined. That portion of the integral due to the O-acetyl substituents was set equal to 9 protons (trisubstituted). The seven ring protons of the anhydroglucose unit were then subtracted from the remaining

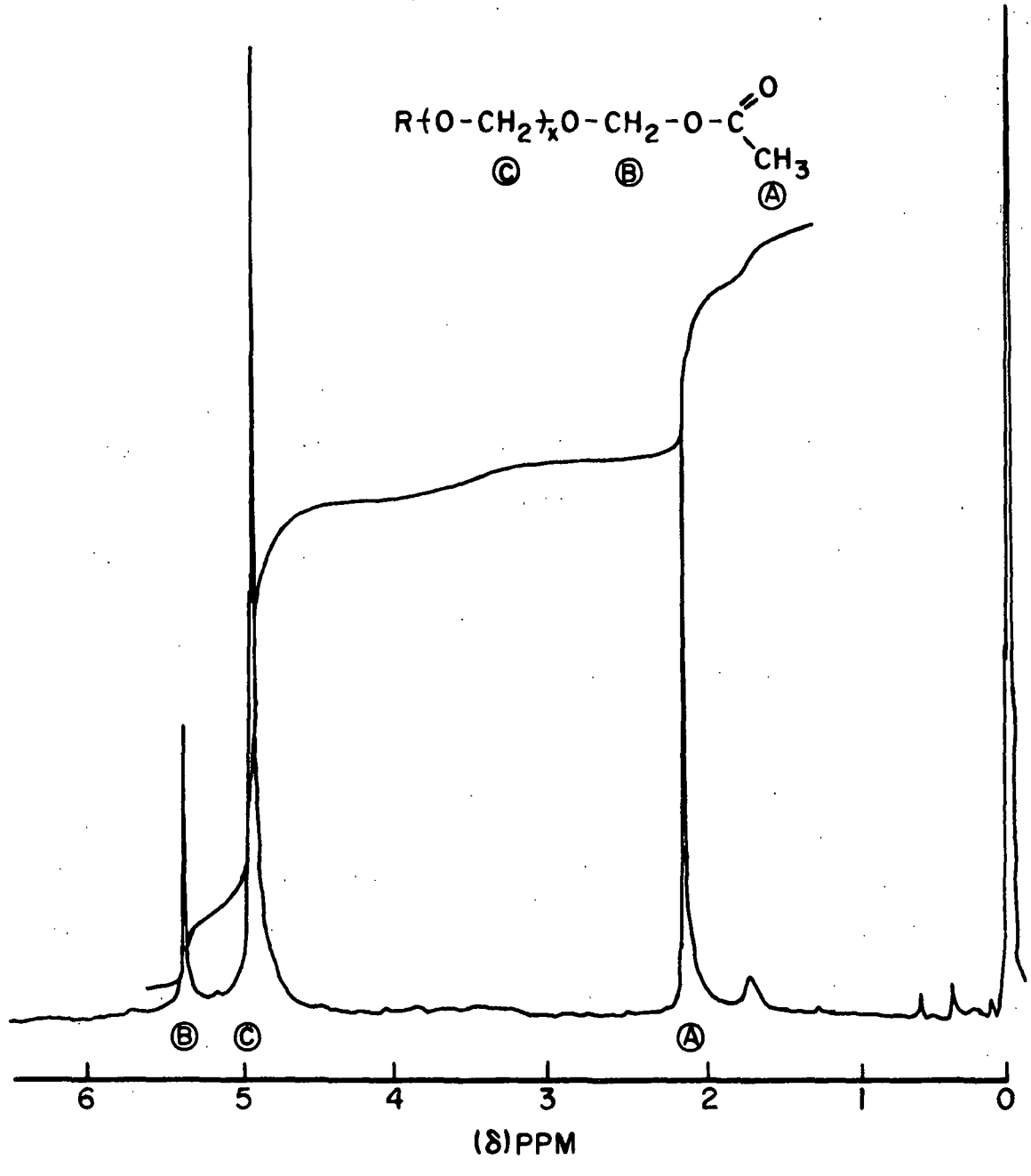


Figure 2. PMR Spectrum ($CDCl_3$) of Methylol Cellulose Acetate

integral, thus leaving the number of protons per anhydroglucose unit which were contributed by the methylol substituents. The MS is equal to one-half the value of the methylol protons per anhydroglucose unit. Further discussion of methylol cellulose acetate and the results from the MS determinations will be presented later.

Previous analyses of formaldehyde in methylol cellulose was accomplished by titration using the sodium bisulfite method (32). This procedure was compared to the newly developed method employing NMR analysis of the peracetates. A sample of freeze-dried methylol cellulose, which had been extracted with water and titrated, was found to have an MS of 1.1. A value of 1.1 was also obtained by PMR analysis of the methylol cellulose peracetate. This confirms the observation that approximately one mole of formaldehyde is present per anhydroglucose unit after freeze-drying, and also demonstrates that little or no formaldehyde is lost during the acetylation reaction.

To further verify the lack of degradation of the methylol substituents during acetylation, several samples were acetylated employing varying amounts of acetic anhydride and pyridine. For a given methylol cellulose, the MS was found to be independent of the amount of acetylating reagents employed as long as there was an excess of reagent.

The possibility existed that free polyoxymethylene chains, if present in solution, might interfere with the MS determination by NMR analysis. It was shown, however, that free polyoxymethylene chains were not present in the isolated methylol cellulose acetate samples, and therefore do not interfere with the analysis. The MS of the isolated samples was determined by NMR analysis as previously described. The acetylated polymer was next subjected to exclusion chromatography on a column of Porasil B. Due to the large molecular weight difference between the cellulose and any polyoxymethylene chains

which might be present, separation should easily be accomplished. NMR analysis of the eluted methylol cellulose acetate indicated that the MS was identical to that of the original sample, as shown in Table IV.

TABLE IV

EFFECT OF POLYOXYMETHYLENE CHAINS ON NMR DETERMINATION OF METHYLOL CELLULOSE MS

Solvent System	MS Before Fractionation	MS After Fractionation
Pyridine	13.1	13.2
DMF	18.4	18.4
DMA	15.8	15.6

Examination of the behavior of free polyoxymethylene chains in these systems indicates that the above observation is reasonable. Paraformaldehyde was thermally decomposed in pyridine until a clear solution was obtained. After acetylation, no precipitate was obtained upon pouring the solution into ice water. The aqueous solution was extracted with chloroform to isolate the acetylated material. NMR analysis of this isolated material indicated that only very short chains (mono-, di-, and trimers) were present. This is consistent with the previous observations for the DMSO/PF system (32,33). Since only low molecular weight polyoxymethylene chains are present, and polyoxymethylene acetates up to at least DP 5 are soluble in water (71), it is apparent that any low molecular weight polymers will be washed away in the work-up procedure and will not interfere with the analysis for the MS.

PROPERTIES OF METHYLOL CELLULOSE SOLVENTS

As might be anticipated, there are differences in the various methylol cellulose solvents. In order to compare the properties of the new solvents,

cellulose was dissolved in each of the solvents and, after dissolution, the MS of the methylol cellulose was determined as a function of time at constant temperature. A 1% solution of cellulose in the organic solvent (w/v) and a temperature of 85° were taken as the standard conditions. [When the cellulose solution became clear, the formaldehyde gas stream was stopped, and this time was defined as $\underline{T} = 0$.] Aliquots taken at various time intervals were cooled immediately in an ice-water bath and then acetylated using acetic anhydride and pyridine. As was mentioned previously, methylol cellulose in the sulfoxides was precipitated and washed with ethyl ether prior to acetylation. The acetylated polymer was isolated by precipitation in ice water followed by drying *in vacuo*.

Results from the MS analysis are presented in Table V and in Fig. 3. One of the major differences observed between the various solvents was the degree of substitution required to obtain a clear solution (MS at $\underline{T} = 0$). The MS of methylol cellulose at the initial dissolution point was reproducible for a given solvent with the dissolution conditions employed. It might be expected that when using different conditions, in particular a different cellulose source or a different method of introducing formaldehyde, the values obtained might deviate from those presented in Table V. However, the observed trends should be the same. It was shown that the MS required to obtain a clear solution in the various solvents followed the order DMF > NMP > DMA > DMSO > TMSO > pyridine. The MS required to keep the methylol cellulose in solution, however, did not follow this same trend. Methylol cellulose in pyridine, for example, would precipitate from solution when the MS dropped below *ca.* 3, but would stay dissolved in DMSO until the MS would drop below *ca.* 0.5. The approximate order for the minimum MS reqired to maintain solution was pyridine > DMF > DMA, NMP > DMSO, TMSO. It has been observed that methylol cellulose

which is isolated from solution and has an MS greater than ca. 3 is soluble in each of the solvents. When the MS is greater than ca. 1.5 but less than ca. 2, methylol cellulose is no longer soluble in pyridine and DMF. Methylol cellulose which has been isolated by freeze-drying and has a DS close to one is soluble only in DMSO or TMSO. Therefore, the data obtained for the MS when methylol cellulose precipitates from each of the solvents are consistent with data for the MS required for redissolution.

TABLE V

INITIAL AND FINAL MS VALUES FOR DISSOLVED METHYLOL CELLULOSE

Solvent	MS at T=0	Estimate of MS at Precipitation Point
DMF	23.6± 1.2	2.0
NMP	21.9± 1.1	1.5
DMA	20.9± 0.3	1.5
DMSO	18.8± 1.2	0.5
TMSO	16.2*	0.5
Pyridine	15.1± 1.1	3.0

*One experiment for TMSO, other values are average of three experiments.

It is of interest to note that there appears to be a correlation between the MS of methylol cellulose at the initial dissolution point and the proton accepting ability of the solvent. The relative basicity of a solvent can be determined from the decrease which it causes in the stretching frequency of a proton source (66). The interaction of the solvent as a proton acceptor was measured by observing the shift in frequency of the C-D stretching band

of deuterochloroform in the Raman spectrum. A 5% solution of $CDCl_3$ in each of the solvents was prepared, and the position of the C-D stretching frequency was observed. The shift in frequency was calculated by comparison with the observed frequency in carbon tetrachloride. These data together with data which have been reported for a similar experiment employing p-fluorophenol as the proton source (67) are presented in Table VI.

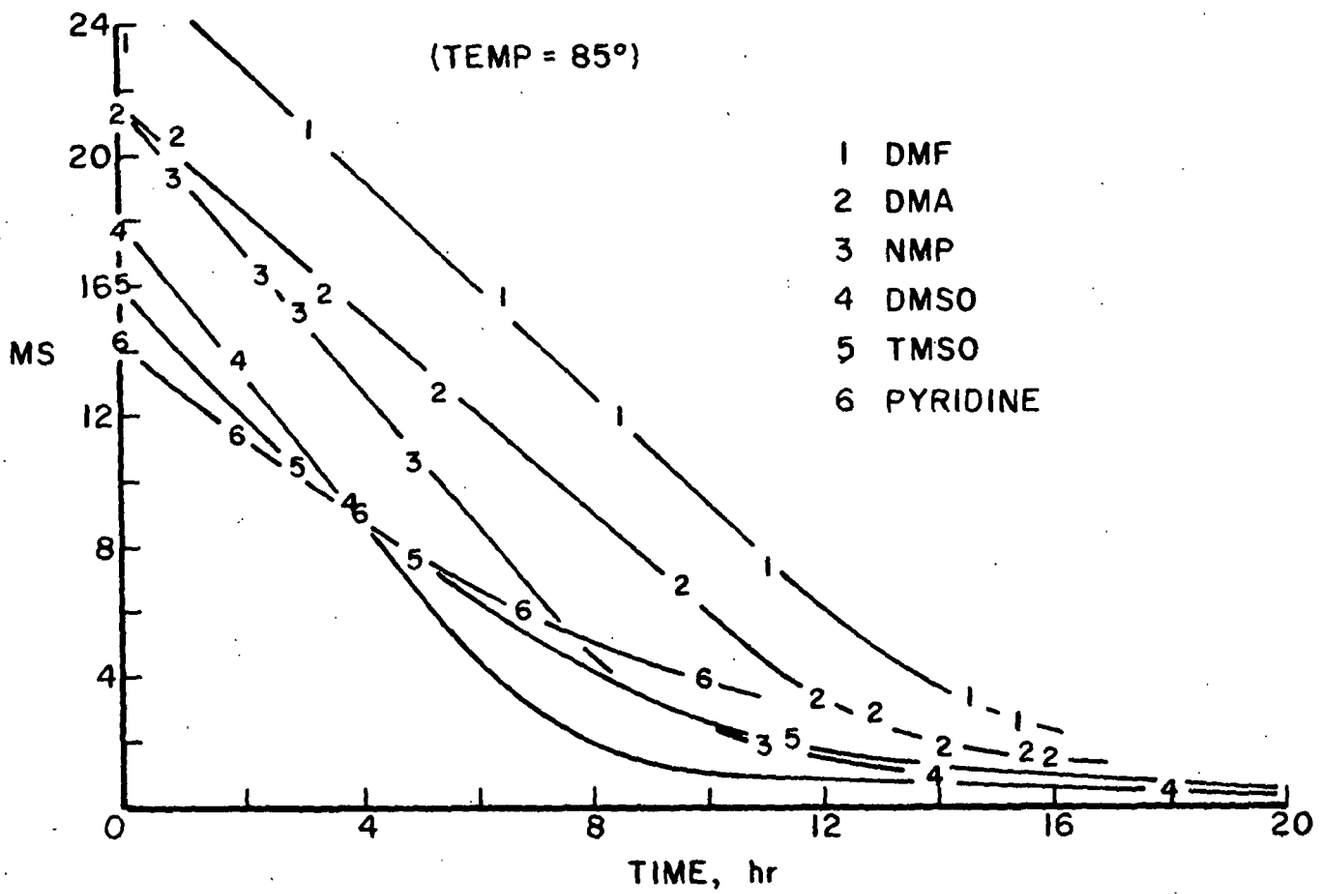


Figure 3. MS of Methylol Cellulose vs. Time

The changes in the MS of methylol cellulose as a function of time at constant temperature (85°) are shown in Fig. 3. It can be seen that the initial loss of formaldehyde is essentially linear with time in all cases, but as the MS becomes small, a deviation from the initial rate occurs. It was hoped that some conclusions could be reached from the initial loss rate

in each of the solvents. It was determined, however, that although the change in MS was linear with time for the initial loss, and the intercept at time zero (MS required for dissolution) was relatively constant, the rate or slope of the line was not easily reproduced. Although the reason for these variations is not clear, it is possible that a number of variables may be affecting the outcome, such as trace impurities in the solvents, as well as changes in the moisture content of the system due to changes in humidity. Either acidic or basic impurities could increase the rate of depolymerization of the polyoxymethylene chains (71). The effect of these and other variables would have to be studied further before definite conclusions can be reached about the effect the solvent is having on the rate of loss of formaldehyde from the methylol cellulose.

TABLE VI

CORRELATION BETWEEN INITIAL MS OF METHYLOL CELLULOSE AND PROTON ACCEPTING ABILITY OF THE SOLVENT

Solvent	MS at T=0	Shift in Frequency (cm^{-1})	
		$CDCl_3$	PFP (67)
Pyridine	15.1	28	485
TMSO	16.2	27	380
DMSO	18.8	25	367
DMA	20.9	16	356
NMP	21.9	16	339
DMF	23.6	11	305

At low MS values (ca. 7 and lower) the substituent distribution may affect the rate of decrease of the MS. The depolymerization of polyoxymethylene chains occurs at the ends. Therefore, it is apparent that one chain of DP 12, for example, will depolymerize at one-third the rate of three chains of DP 4.

Due to an unequal distribution of substituents on the hydroxyls of the anhydroglucose unit, at low MS values, the methylol substituents would be depleted from the various sites unequally. Consequently, the effective number of chains releasing formaldehyde would be reduced, which would show as a slower decrease in the MS, as was observed.

However, not all of the deviation from the initial rate can be explained as being due to the unequal substituent distribution. In DMSO, in particular, it is apparent that the solvent stabilizes the small amount of formaldehyde bound directly to the cellulose, most likely at the C-6 hydroxyl. This shows as a long period where the MS is very low and decreasing at a very slow rate. This observed difference in the stabilizing ability of the various solvents may be important to the commercial application of the methylol cellulose solvent systems. In essentially every case where cellulose is to be regenerated as a fiber or film, it will be important to remove residual solvent and formaldehyde. If the solvent interacts strongly to stabilize the methylol substituents, as in the case of DMSO, the regeneration process may be more difficult. Difficulties have been encountered in the process of regenerating cellulose from the DMSO/PF system. Several regeneration baths have been required to render the regenerated cellulose fibers insoluble in DMSO (5).

PHYSICAL ASPECTS OF THE DISSOLUTION PROCESS

It has been observed that when cellulose is dissolved in the DMSO/PF system, several changes occur in the physical nature of the solution. Initially, it is observed that the stirring slurry becomes more fluid and easier to stir as paraformaldehyde (or formaldehyde) is first introduced into the system. This is followed by a stage where a thixotropic mass or a dope is

formed. The final stage is a reduction in viscosity as the residual paraformaldehyde is decomposed and the solution becomes clear.

From an understanding of the changes in the MS of methylol cellulose as a function of time, these observations about the changes in the physical nature of the solution are easily explained. As formaldehyde is introduced into the system, it reacts with the surface regions. This reaction disrupts the fiber to fiber entanglements and allows for better dispersion of the fibers; thus the slurry is stirred more easily. This process is demonstrated quite clearly when cotton linters are dissolved in one of the solvents using formaldehyde gas. The fibers remain entangled in a ball until the gas is introduced, after which, within a very short time, the fibers readily disperse to form a slurry. During the next stage, the long polyoxymethylene chains are formed, which force the cellulose molecules apart. This process accounts for the dramatic increase in the viscosity of the solution and also accounts for the large excess of paraformaldehyde required to obtain dissolution. In the final stage, the polyoxymethylene substituents break down, thus releasing formaldehyde gas and decreasing the viscosity of the solution.

The amount of paraformaldehyde required to accomplish dissolution of the cellulose is dependent upon the conditions employed. Less formaldehyde is required when paraformaldehyde is added directly to the system, as opposed to decomposing the paraformaldehyde in an external flask and bubbling the resulting gas through the system. Individual molecules and very tiny bubbles are produced by the decomposition of paraformaldehyde in solution; therefore, this process is more efficient than the absorption of formaldehyde from the large gas bubbles produced when formaldehyde is bubbled into the solution. It has also been observed that proportionately less paraformaldehyde is required when a more concentrated cellulose solution is being prepared. For

example, a 3% solution of cellulose WCF-1 in DMSO requires ca. 1.5 g PF/1 g cellulose to accomplish dissolution, while a 10% solution of the same cellulose requires only about 0.75 g PF/g cellulose. Apparently the increased density of reaction sites and increased viscosity of the solution allows for greater efficiency of the reaction and greater retention of the formaldehyde gas.

REACTIONS OF METHYLOL CELLULOSE

ACETYLATION

The acetylation of cellulose in the DMSO/PF solvent system by the action of acetic anhydride and pyridine has recently been reported (41,50,51). At least a portion of the methylol cellulose undergoes the desired acetylation reaction. However, the disadvantage of employing acetic anhydride in the presence of DMSO is that a number of side reactions can occur.

A mixture of DMSO and acetic anhydride has been employed for the oxidation of primary and secondary alcohols (52,53). Besides oxidation of the alcohol, formation of a methylthiomethyl ether may occur. A possible mechanism for the reactions of an alcohol in DMSO/acetic anhydride has been reported (53) and is shown in Fig. 4.

DMSO and acetic anhydride (Ac_2O) react to form the acyloxysulfonium ion (I), which is a labile intermediate susceptible to attack by an alcohol. The alkoxydimethylsulfonium ion (II) which is formed by reaction with the alcohol may lose a proton to form the ylide (III). Rearrangement of (III) can result in the formation of the methylthiomethyl ether (V) or dimethyl sulfide and the carbonyl compound (VI). The preference of the reaction to proceed to oxidation or ether formation is dependent upon the composition of the acetic anhydride-DMSO mixture. The acetylation reaction (IV) does not usually occur

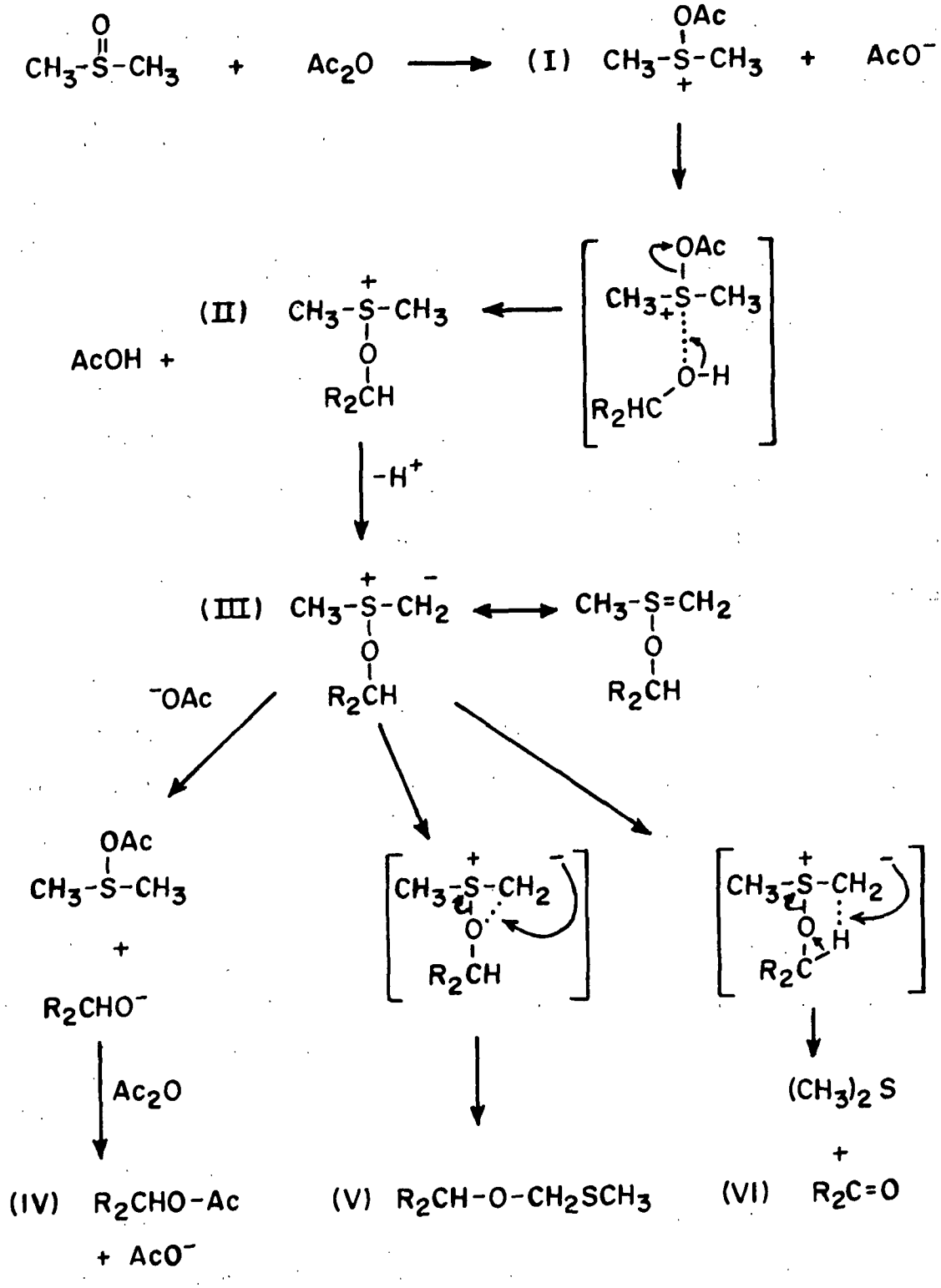


Figure 4. Potential Reactions of an Alcohol in Dimethyl Sulfoxide/ Acetic Anhydride (53)

in DMSO and acetic anhydride, though it is a possible pathway. It was observed that acetate formation from cholesterol occurred when triethylamine was present (53). The presence of pyridine in the acetylation reaction of methylol cellulose in the DMSO/PF system may promote acetate formation as well.

In the present work, it was observed that the oxidation of methylol cellulose occurred when the acetylation reaction was attempted in DMSO as evidenced by the formation of dimethyl sulfide. Other workers have also noted that the oxidation of cellulose competes with the esterification reaction in the DMSO/PF system (41,50). Whenever acetic anhydride is used in conjunction with DMSO, the oxidation of alcohols and formation of methylthiomethyl ethers are potential competing reactions.

One of the most convenient methods of preparing methylol cellulose acetate without the interference of DMSO is to dissolve the cellulose in a solvent other than DMSO as previously described. Pyridine is a common solvent used for acetylation of carbohydrates, and DMF has been used in acetylation reactions of cellulose (72). DMA and NMP are also compatible with acetic anhydride. An alternate approach is to remove the DMSO prior to acetylation by precipitating the dissolved methylol cellulose from the DMSO solution by the addition of nonsolvents such as benzene, carbon tetrachloride, or ether. Due to the potential health problems as a result of the penetrating and carrying ability of DMSO, ether was generally preferred due to its lower toxicity. If the MS of the methylol cellulose is high enough, i.e., greater than ca. 3, the cellulose may be redissolved in pyridine and reacted homogeneously. With a low MS material, the reaction is heterogeneous initially and becomes homogeneous as the reaction proceeds.

The infrared spectra of methylol cellulose triacetate and cellulose triacetate are presented in Fig. 5. The lack of absorbance in the OH stretching region (3000-4000 cm^{-1}) indicates that there are essentially no free hydroxyls. The small peak at 3480 cm^{-1} is believed to result from an overtone of the strong C=O stretching band at 1740 cm^{-1}. Comparison of the spectrum of methylol cellulose triacetate with that of cellulose triacetate indicates the presence of the methylol substituents. The extra absorbances at ca. 950 and 1100 cm^{-1} correspond to the strong bands observed at 940 and 1090 cm^{-1} for paraformaldehyde polymers and their derivatives (73,74). Bands in these two regions have also been regarded as characteristic of aromatic compounds which contain an $-O-CH_2-O-$ group (75).

As described earlier, two types of methylol substituents may be observed in the PMR spectrum of methylol cellulose acetate. The difference in chemical shift is due to the presence of an O-acetyl substituent adjacent to the methylol unit which shifts that resonance downfield (5.33 ppm) relative to the other methylol units (4.88 ppm). In some cases, a third peak due to methylol substituents could be resolved at 4.90 ppm.

Recently, the PMR spectrum of methylol cellulose acetate has been reported (51). These workers assigned the observed resonance at δ 5.31 ppm to the methylol substituent at the C-6 hydroxyl. The resonance at 4.88-4.90 ppm was said to be due to methylol substituents at OH-2 and OH-3 of the anhydroglucose unit. The present work, however, presents evidence which does not agree with these assignments. Analysis of the integral of the spectra showed that if the resonance due to the acetyl methyl groups (2.08 ppm) was equal to 9 protons, then the resonance at 5.31 ppm must be a result of 6 protons, i.e., one methylol substituent per acetate group. With the high MS of some of the methylol celluloses in this work, it is readily apparent that the resonance

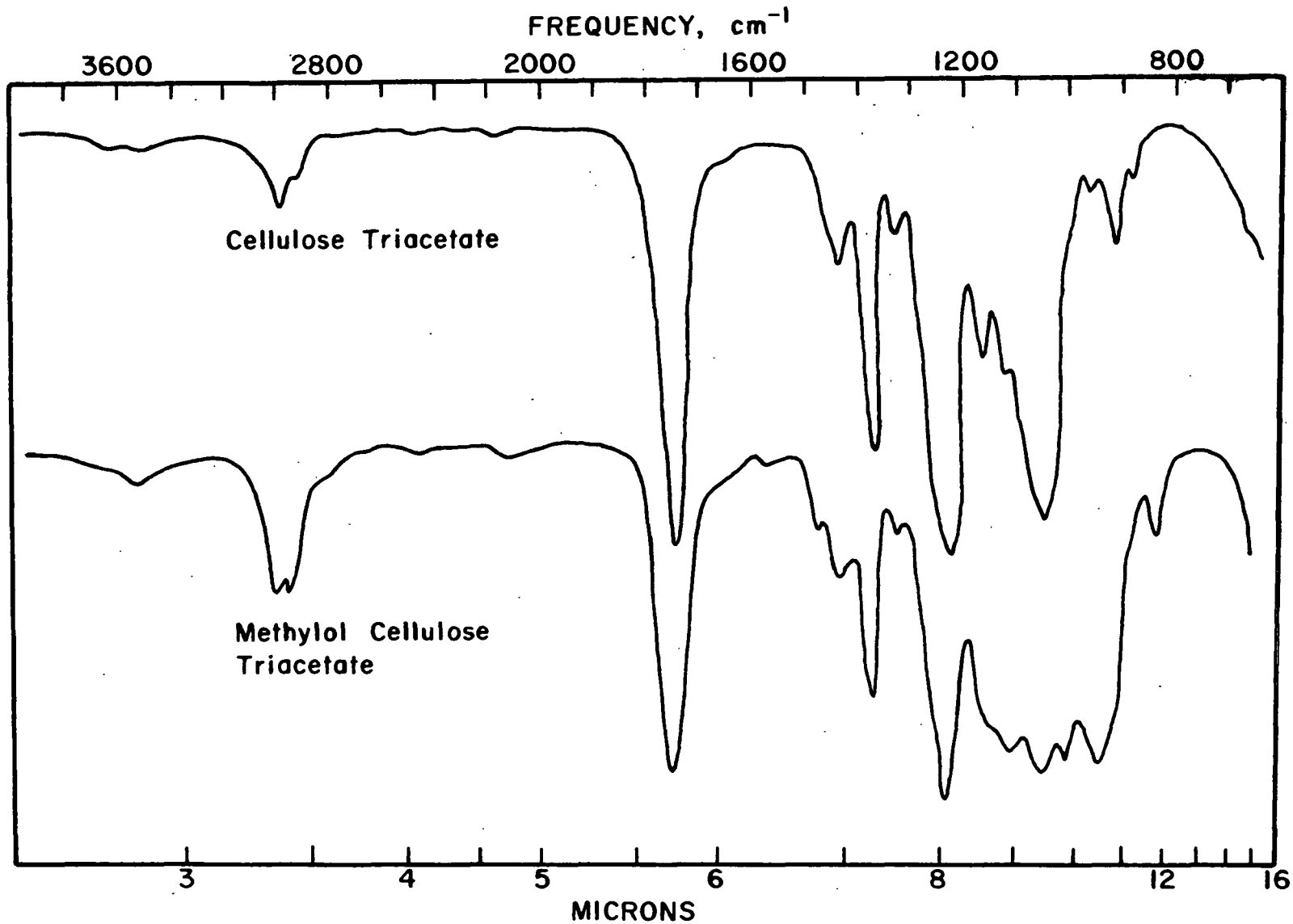


Figure 5. Infrared Spectra of Cellulose Triacetate and Methylol Cellulose Triacetate

at 4.88 ppm is a result of internal methylol units of the polyoxymethylene substituents. The increased intensity of this peak can be noted in Fig. 6 upon increasing the MS from 2.9 to 6.1.

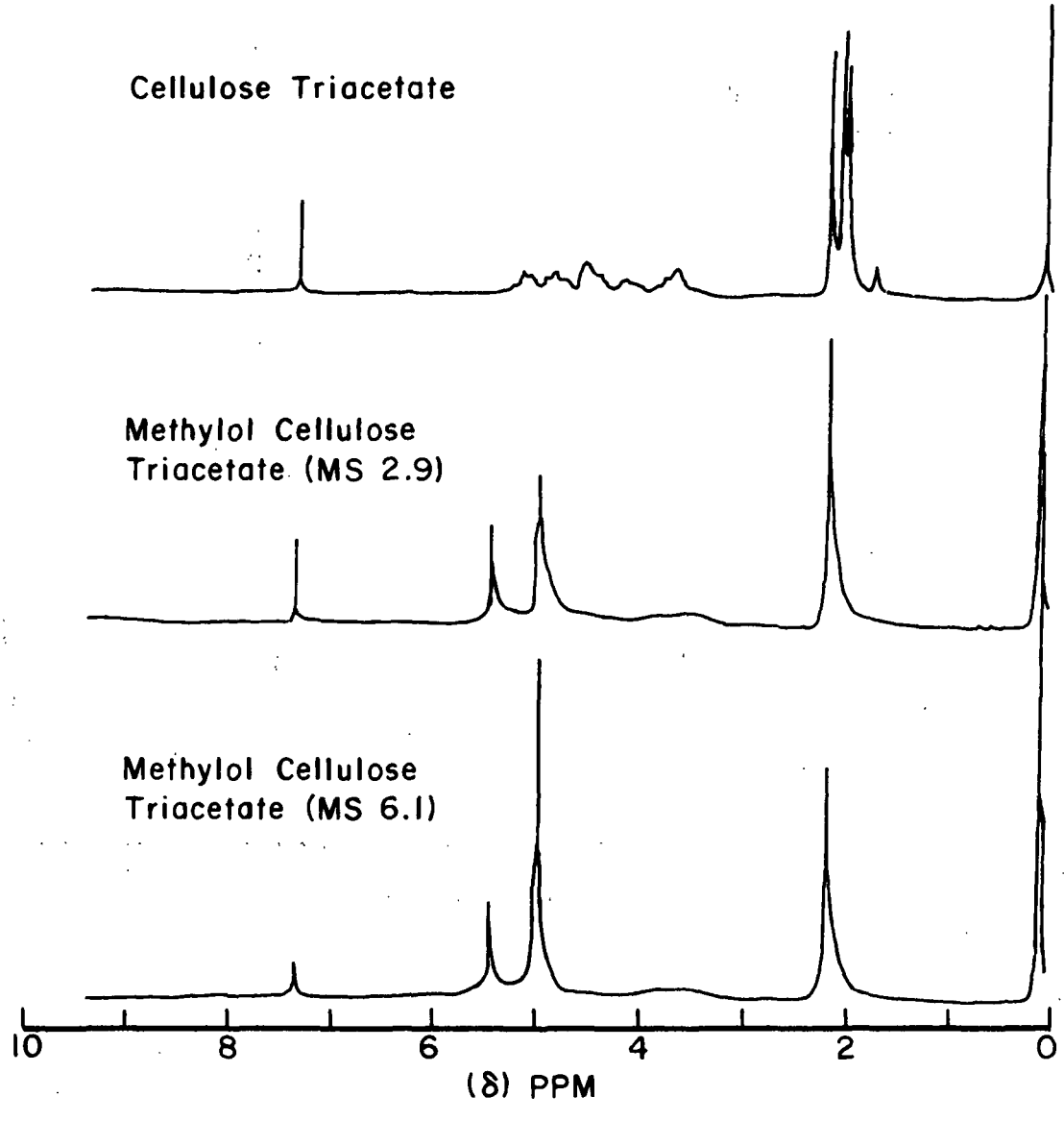


Figure 6. PMR Spectra ($CDCl_3$) of Cellulose Triacetate and Methylol Cellulose Triacetate

Three signals appear for the acetyl methyl substituents in the PMR spectrum of cellulose triacetate (Fig. 6). The peaks are observed at 2.09, 1.99 and 1.94 ppm and have been assigned to O-acetyl substituents at OH-6, OH-2, and OH-3, respectively (76). For methylol cellulose triacetate, only one resonance is observed (2.08 ppm) for samples of relatively high MS. As

the MS becomes small, i.e., 1, additional signals appear in the acetyl methyl region of the spectrum (Fig. 7).

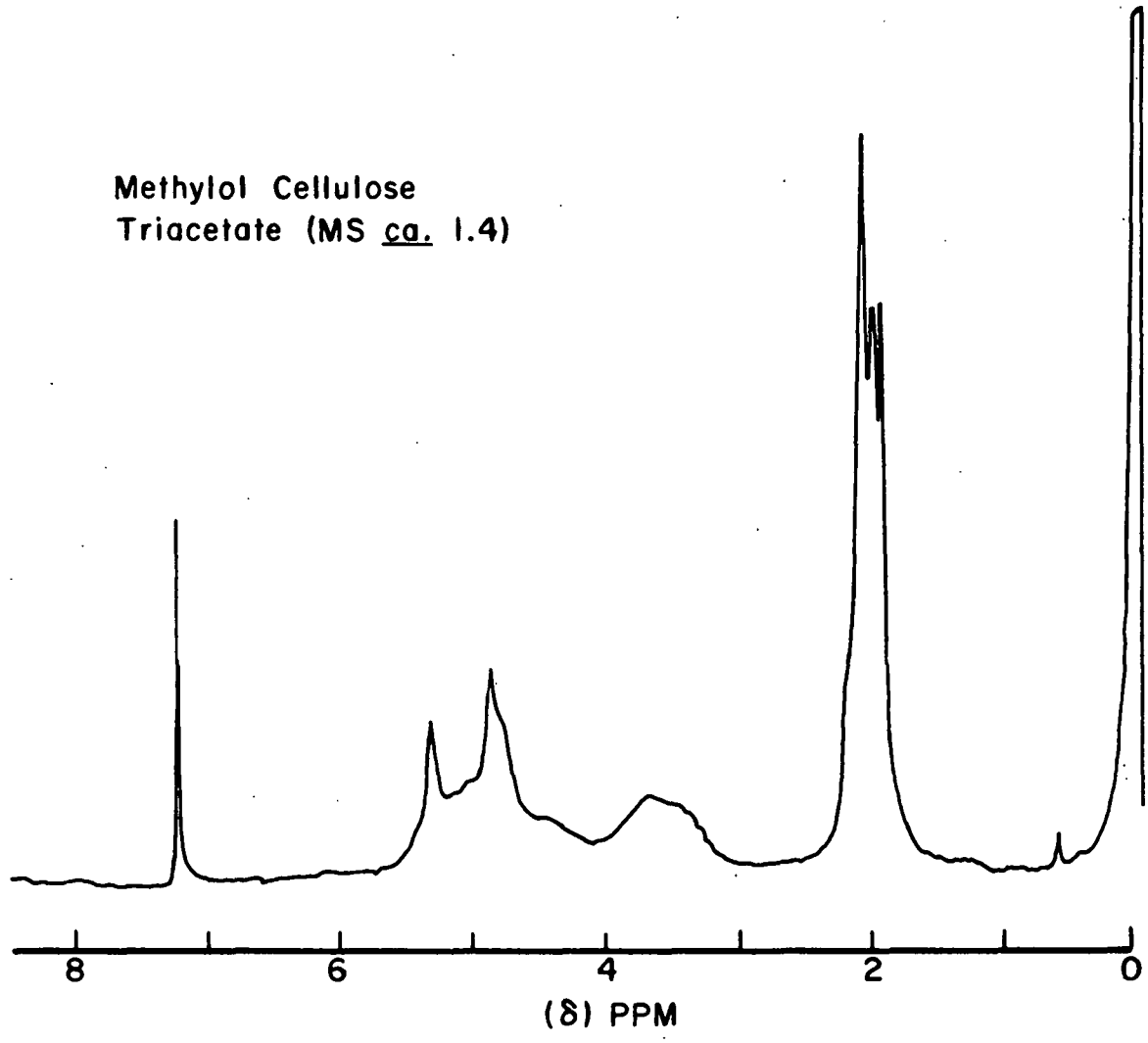


Figure 7. PMR Spectrum ($CDCl_3$) of Methylol Cellulose Triacetate (MS ca. 1.4) Showing Additional Acetyl Methyl Resonances

HYDROXYETHYLATION

One commercially important derivative of cellulose is hydroxyethyl cellulose (HEC). HEC may be prepared by the heterogeneous reaction of alkali cellulose with ethylene oxide in a water and isopropanol mixture. A competing side reaction is the production of ethylene glycol. It was hoped that HEC could be prepared homogeneously in the DMSO/PF solvent system. Comparison

of the substituent distribution of the derivative from this system with conventionally prepared HEC should give some insight into factors influencing the reactivity of the various cellulose hydroxyls. It was found, however, that this reaction was less successful than anticipated.

Analysis of the substituent distribution of HEC tends to be complicated due to the presence of poly(ethylene oxide) substituents. Once ethylene oxide has reacted with a cellulose hydroxyl, a new site for reaction is generated. Subsequent substitution of the newly formed hydroxyethyl group results in poly(ethylene oxide) side chains (Fig. 8). Therefore, after acid hydrolysis, the potential number of differently substituted glucoses to be analyzed by gas-liquid chromatography (GLC) could be quite large. At low degrees of substitution, however, mono-substituted glucoses should be the dominant products.

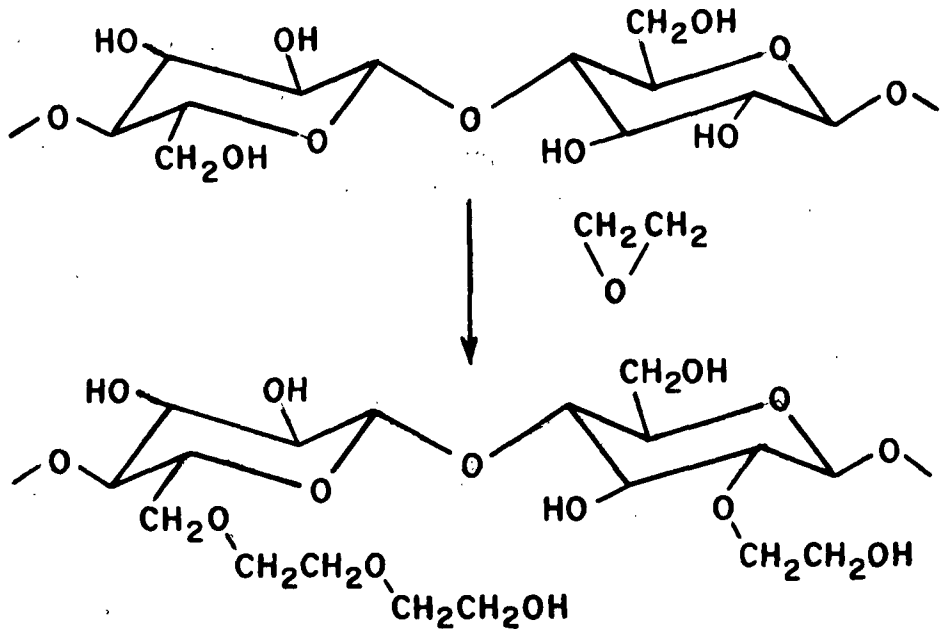


Figure 8. Reaction of Cellulose to Form Hydroxyethyl Cellulose (HEC)

A characteristic of 2-O-(2-hydroxyethyl) glucose which complicates the GLC analysis is its ability to form intramolecular cyclization products or 1,2-O-ethylene glucoses as shown in Fig. 9. These sugars must be taken into account when analyzing the substituent distribution, otherwise the determined amount of substitution at OH-2 will be in error. The cyclization occurs during the acid hydrolysis of the cellulose derivative prior to GLC analysis. Thus, the formation of the 1,2-O-ethylene glucoses would be difficult or impossible to eliminate.

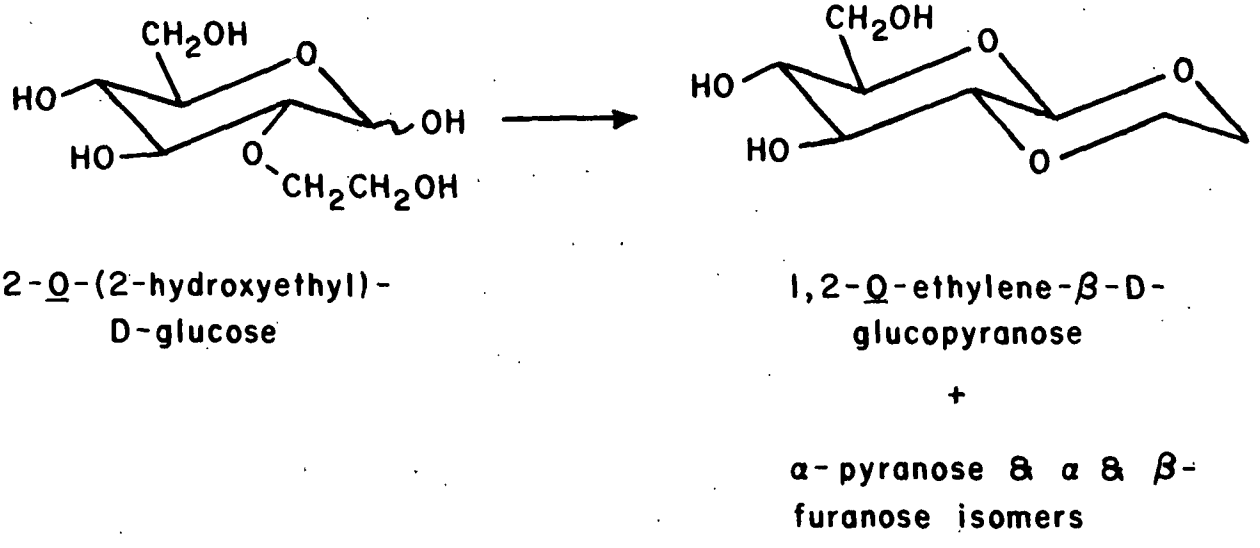


Figure 9. Intramolecular Cyclization of 2-O-(2-Hydroxyethyl)-D-Glucose to give 1,2-O-Ethylene-D-Glucoses

During the synthesis of the model compounds which were required for the GLC analysis, problems were noted with one reported procedure. It has been reported that mono-substituted hydroxyethyl glucoses could be prepared by reaction of 2-bromoethanol with the appropriately blocked glucose alkoxide (77). However, it was found that only starting material could be isolated after the reaction. Closer scrutiny of the original work showed that the reported melting points and carbon-hydrogen analyses for the "hydroxyethylated" sugars matched those of the starting materials. Therefore, for this study, the mono-substituted hydroxyethylated sugars were synthesized by reduction of the corresponding carboxymethyl sugars (78).

Previous analysis of hydroxyethylated glucoses by GLC has been accomplished as the trimethylsilyl ether derivatives (47,79,80). This procedure results in two peaks for each sugar due to separation of the α- and β-anomers. By reducing the sugars to the corresponding alditols, it was hoped that the chromatograms would be simplified due to elimination of the anomeric differences. However, attempts to use the alditol acetate derivatives showed a lack of resolution of even the mono-substituted sugars. It was found that only one peak for each sugar was observed when the acetate derivative of the reducing sugar was employed, as the peaks from the α- and β-anomers were coincident. Figure 10 is a chromatogram of the acetylated hydrolyzate from a commercial sample of HEC (Hercules Natrosol 180L) which has an MS of ca. 1.8. This figure illustrates the separation which could be obtained on a 7 ft OV-225 column for the acetylated hydroxyethyl glucoses. The peaks in Fig. 10 were identified by comparison with known compounds.

Hydroxyethylation of cellulose dissolved in the DMSO/PF system gave a product with a relatively insignificant amount of substitution. The reaction was carried out by first dissolving cellulose in the DMSO/PF solvent system followed by the addition of sodium hydride to the solution to produce the cellulose alkoxide. Ethylene oxide was then introduced into the system. After isolation by precipitation in isopropanol and drying, the polymer was analyzed to determine the degree of substitution. Chemical analysis to determine the MS indicated only low degrees of substitution. Analysis by GLC showed no observable amounts of hydroxyethylated sugars.

Chemical analysis to determine the MS of hydroxyethyl groups was carried out by the Morgan method (81). In this procedure, the hydroxyethyl substituents are cleaved by hydroiodic acid and analyzed as ethylene and ethyl iodide.

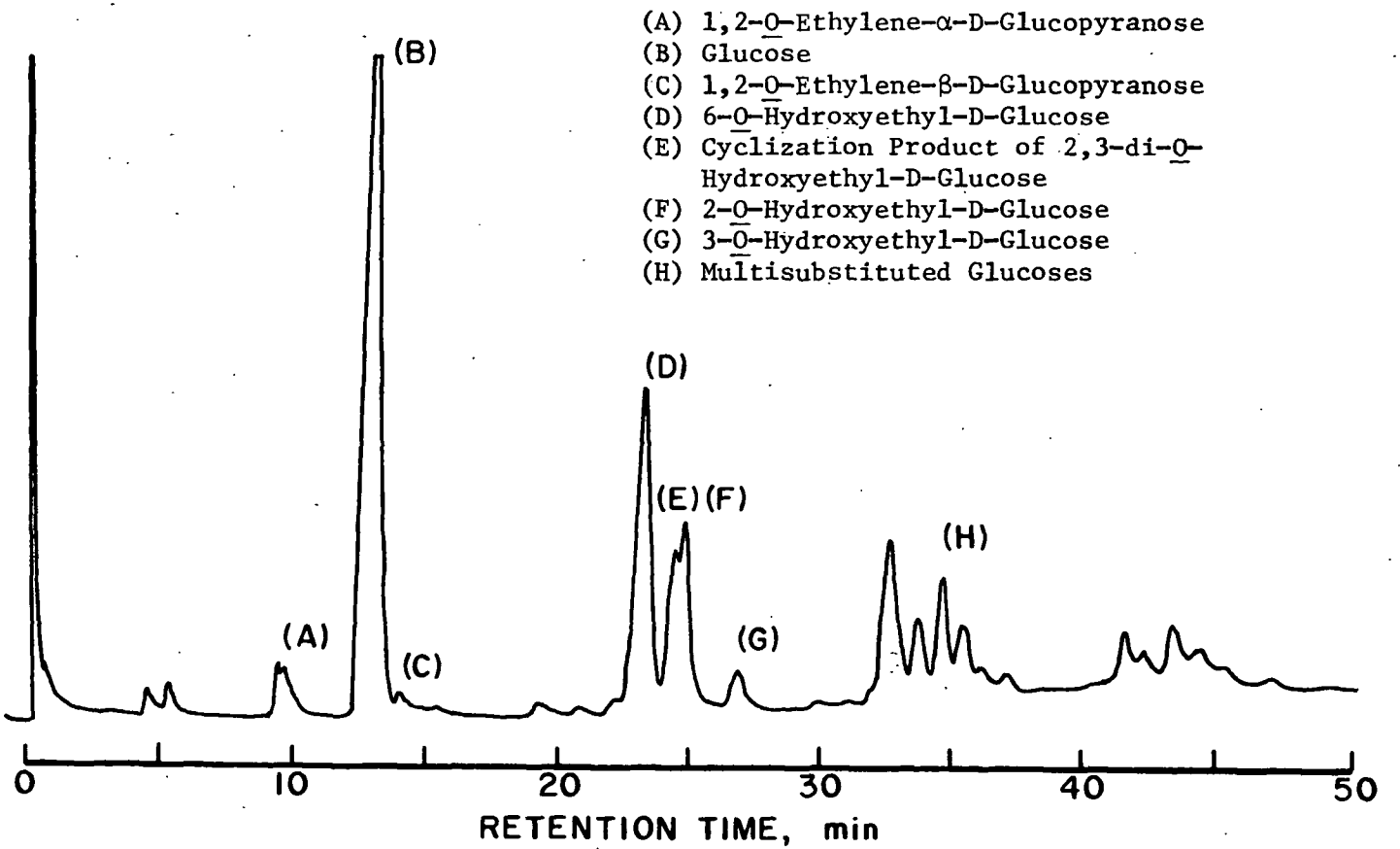


Figure 10. Gas Chromatogram of Hydrolyzate from Commercial HEC (ms ca. 1.8) Illustrating the Separation of Possible Components as the Acetate Derivatives

According to this type of analysis, some hydroxyethylation of cellulose had taken place in the DMSO/PF system, though not to the extent claimed in a recent patent on this reaction (49). Examples of the degrees of substitution obtained are presented in Table VII. Several other reactions were attempted in the DMSO/PF system which employed varying amounts of sodium hydride and ethylene oxide. The results were similar to those presented in Table VII. In no case was significant substitution obtained.

TABLE VII

MS OF HYDROXYETHYL CELLULOSE FROM THE DMSO/PF SYSTEM DETERMINED BY THE MORGAN METHOD OF ANALYSIS

	Reaction Conditions		
	Temperature	Moles of Ethylene Oxide Per Anhydroglucose Unit	MS
1	23	10.5	0.25
2	23	10.1	0.04
3	40	9.9	0.19
4*	22	10.1	5.8

*From Reference 49.

A sample of freeze-dried methylol cellulose from the DMSO/PF system which had not been reacted with ethylene oxide was analyzed by the Morgan method. The methylol substituents from this sample caused some interference with the Morgan method, as an MS of 0.17 for "hydroxyethyl" substituents was obtained. Formaldehyde can react with hydroiodic acid to give iodomethane and diiodomethyl ether (71). These compounds would be detected as ethyl iodide, thus accounting for the interference in this analysis procedure. If the hydroxyethylated polymer produced in the DMSO/PF system contains methylol substituents as a result of acetal formation, the Morgan method may give an MS value which is higher than the actual value.

GLC analysis of the cellulose hydrolyzate showed no detectable mono-, di-, or tri-substituted hydroxyethyl glucose. It is possible that glucoses with large degrees of substitution were present but not detected in the GLC analysis. Glucoses with high degrees of substitution had long retention times and lacked intensity due to band broadening.

Comparison of the two methods of analysis indicates that reaction with the dissolved methylol cellulose probably occurred at the methylol substituents. The resultant acetal substituents would be cleaved in the acid hydrolysis required for the GLC analysis and, therefore, would not be detected in this procedure. This is similar to the results obtained for carboxymethylation of cellulose in the DMSO/PF system using mild conditions (32,34). As mentioned previously, if acetal substituents were present, then the actual MS of hydroxyethyl groups may be even lower than that which was determined by the Morgan method of analysis.

Ethylene oxide in this system may be consumed by polymerization reactions. Polymerization of the ethylene oxide may be initiated by the cellulose alkoxide, excess sodium hydride, or the anion of DMSO (dimsyl ion). It is reported that in dilute solution, the acidity of alcohols is *ca.* 10^3 times that of DMSO (82), so that the dimsyl ion is present only in minor equilibrium quantities. However, the rate of proton exchange between DMSO and alkoxide ions is very fast, being diffusion controlled (83,84). If a trap for the DMSO anion is present, the reaction may proceed entirely via this mechanism (82). The polymerization of ethylene oxide by the dimsyl anion has previously been reported (85,86). Therefore it is possible that the ethylene oxide is consumed by polymerization initiated by the dimsyl anion. However, the polymerization might also be initiated by excess sodium hydride. Due to the limited quantities of the dimsyl ion which may be present, the latter explanation

may be more important. Determination of the actual mechanism or relative importance of the various pathways might be obtained by isolation of the poly-(ethylene oxide) polymers and analysis of the end groups. For this study, however, the important result was that the reaction with cellulose hydroxyls was not favorable.

In the event that reaction with the methylol substituents was a major problem, an approach was taken to block the methylol groups prior to reaction with ethylene oxide. The triphenylmethyl group is so bulky that reaction occurs almost exclusively with primary alcohols, which should include the hydroxyl groups of methylol substituents. The triphenylmethyl derivative of the dissolved cellulose was prepared and then reacted with ethylene oxide. Analysis of the reaction product by GLC showed no detectable amount of hydroxyethylated sugars. If the hydroxyls at C-6 were available, there is the possibility that they might react with ethylene oxide in DMSO. However, both the methylol and triphenylmethyl substituents tend to block this position, making it unavailable for reaction.

The reaction of methylol cellulose to form the triphenylmethyl derivative, while not solving the problems associated with the hydroxyethylation reaction, became an informative study in itself.

TRIPHENYLMETHYLATION

The triphenylmethyl (trityl) substituent is often used as a blocking group in carbohydrate synthesis. Due to its bulky nature, it will react almost exclusively with primary alcohols. For cellulose, one would expect a maximum trityl DS of 1, since there is only one primary alcohol per anhydroglucose unit. In general, this result is observed experimentally, unless very forcing conditions are employed.

Triphenylmethyl cellulose has typically been prepared from cellulose in the heterogeneous state (87). More recently, it has been reported that trityl cellulose may be prepared homogeneously in the cellulose solvent composed of N-ethylpyridinium chloride and DMSO (28,88).

In the present work with the cellulose solvent systems based on the methylol derivative, it was demonstrated that trityl cellulose with a DS of one can also be prepared homogeneously. The hemiacetal substituents of methylol cellulose should behave as primary alcohols. If a methylol unit is located at one of the secondary hydroxyls and it is subsequently substituted, then the DS of the resulting trityl cellulose could easily be greater than one. It was hoped that the reaction of trityl chloride with methylol cellulose would yield the acetal which would allow more information to be gained about the methylol substituent distribution. It was discovered, however, that the trityl methylol acetal which could be isolated early in the reaction was unstable and easily displaced, thus leading to the ultimate formation of the ether derivative, trityl cellulose.

Cellulose was dissolved in the appropriate solvent by the action of formaldehyde, as previously described. Triphenylmethyl chloride was added as the alkylating agent, and pyridine was employed as the base and scavenger for hydrochloric acid generated by the reaction.

When the MS of the methylol cellulose was low (i.e., 1 to 4), tritylation proceeded homogeneously throughout the entire reaction time. However, when the MS of the methylol cellulose was high (i.e., 10–20) as a result of not reducing the methylol content by prolonged heating after the initial dissolution, it was found that a by-product of the tritylation reaction would precipitate out.

The precipitate was identified as a new compound, triphenylmethoxymethyl pyridinium chloride. As shown in Fig. 11, this product could be produced either by the loss of the trityl methylol acetal or by loss of the hemiacetal followed by subsequent reaction of the formaldehyde-pyridine complex with trityl chloride. The structure of this product was determined from the ^{13}C and ^{1}H NMR spectra. Analysis of the carbon, hydrogen, nitrogen, and chlorine content of the material also matched the proposed structure. The compound melted with decomposition to form trityl chloride as a residue.

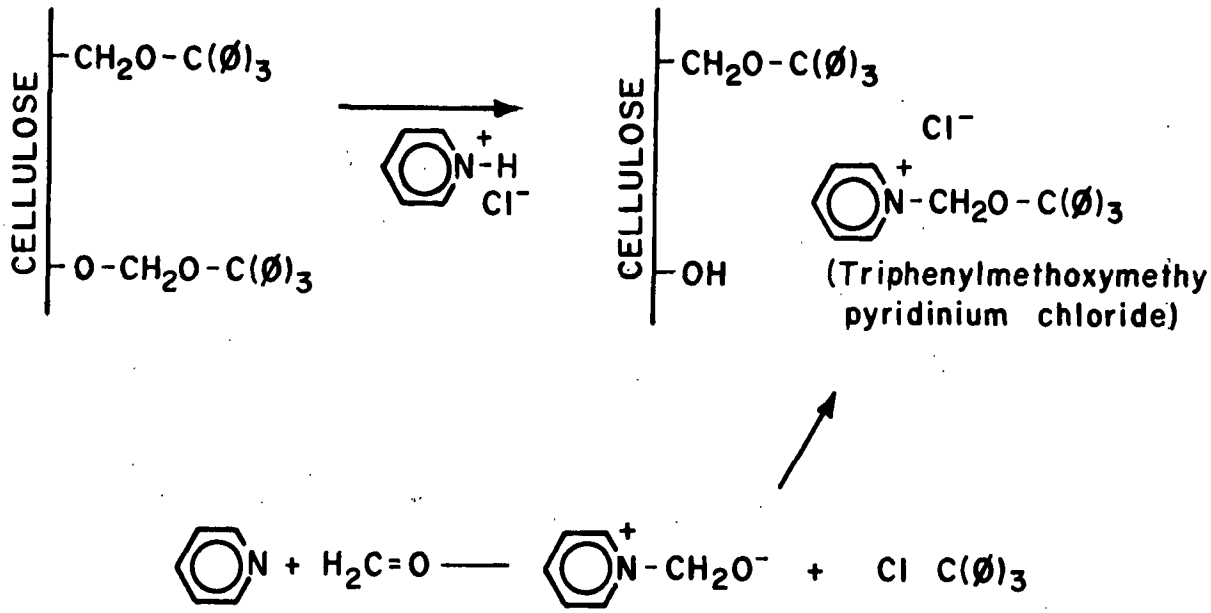


Figure 11. Formation of Triphenylmethoxymethyl Pyridinium Chloride During the Tritylation of Cellulose in the Methylol Cellulose Solvent Systems

It was found that in the first part of the reaction, a derivative with trityl methylol acetal substituents could be isolated, especially if the initial methylol MS was high. As can be seen in Fig. 12, the trityl content of the cellulose rapidly increased and leveled off at a maximum DS of one. NMR analysis of the final product showed that there were no methylol units left with the derivative. A comparison of the NMR spectra of trityl cellulose

and trityl methylol cellulose is shown in Fig. 13. The methylol protons were found to resonate at 4.78 ppm. A comparison of the infrared spectra of the two derivatives, as shown in Fig. 14, indicates an absorbance due to the methylol units at ca. 950 cm^{-1}. This absorbance was also observed in the spectra of methylol cellulose acetate as previously discussed.

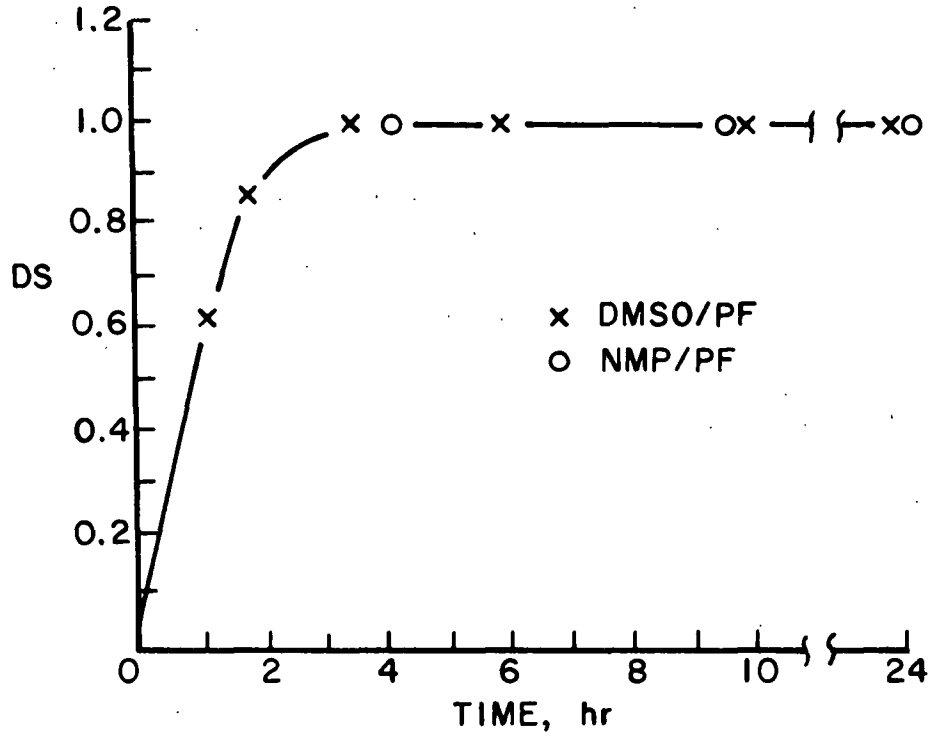


Figure 12. Tritylation of Methylol Cellulose Degree of Substitution (DS) vs. Time

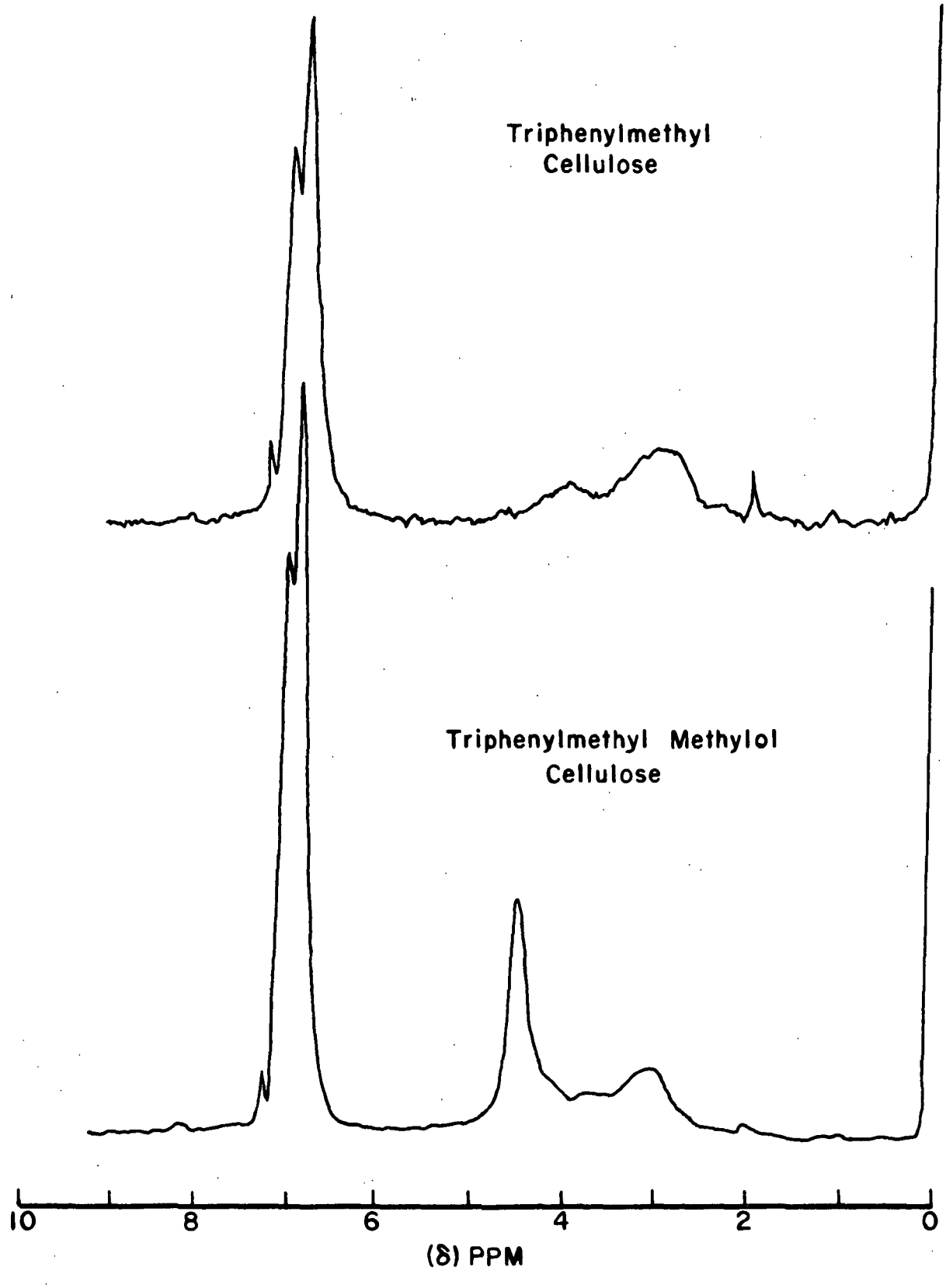


Figure 13. PMR Spectra ($CDCl_3$) of Triphenylmethyl Cellulose and Triphenylmethyl Methylol Cellulose

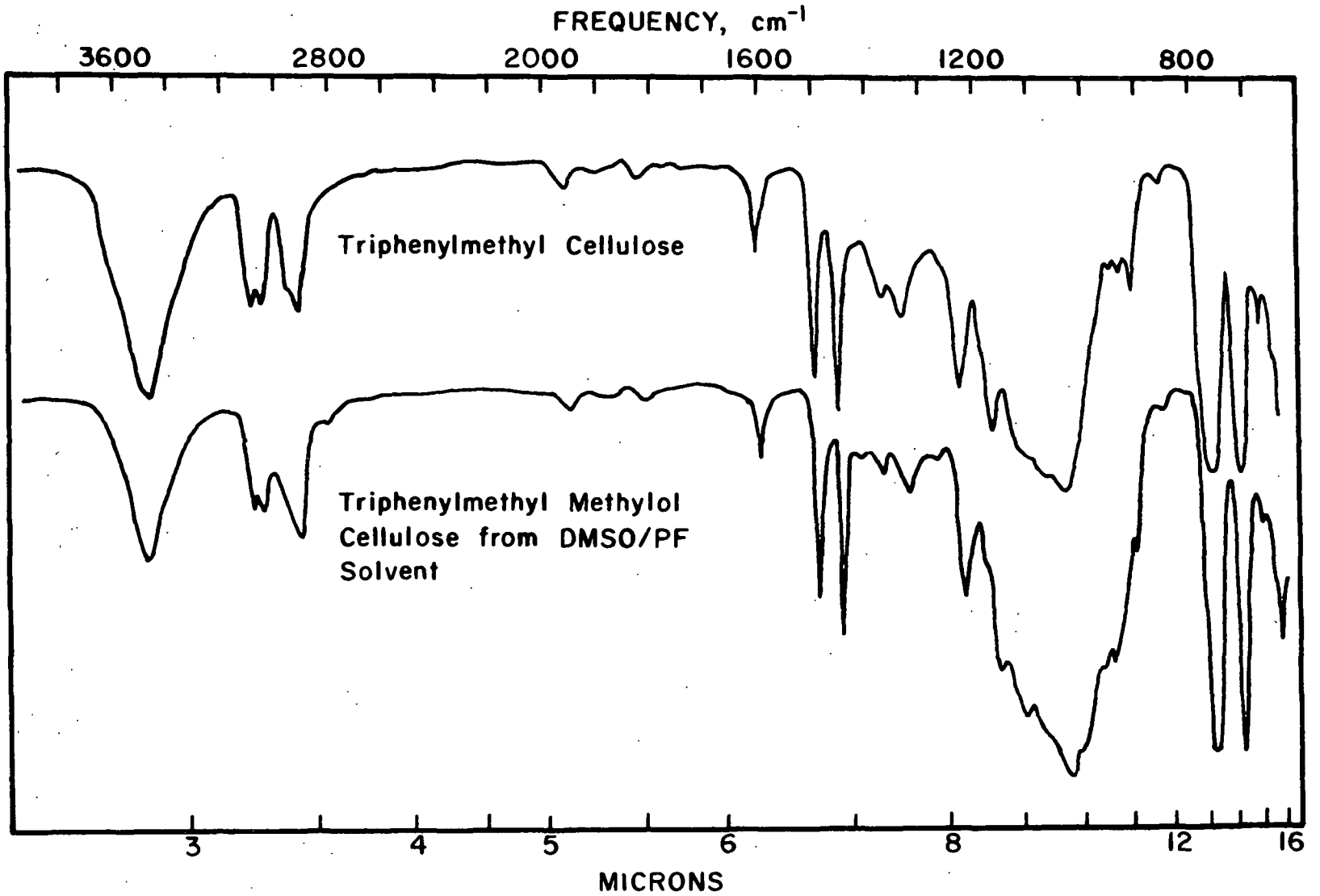


Figure 14. IR Spectra of Triphenylmethyl Cellulose and Triphenylmethyl Methylol Cellulose

CONCLUSIONS

Properties of the organic solvent which were found to be important for the dissolution of cellulose via the formation of methylol cellulose include a dipolar aprotic nature, good hydrogen bond accepting capabilities, and a relatively small size. Support for this conclusion was obtained by demonstrating that methylol cellulose could be prepared and dissolved in solvents other than DMSO which also have these properties. The solvents found to be successful include pyridine, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methyl-2-pyrrolidinone (NMP) and tetramethylene sulfoxide (TMSO).

It was also demonstrated that a high molar degree of substitution (MS) of the methylol cellulose was required to obtain dissolution. Bulky polyoxymethylene substituents are required to assist in the separation of the cellulose molecules in the solid cellulose structure. It was shown that the MS required to obtain dissolution was related to the proton accepting ability of the organic solvent. Once the cellulose has been dissolved, the MS can decrease substantially and still retain the cellulose in solution. The minimum MS required to retain solubility is also dependent upon the organic solvent which was employed.

Homogeneous acetylation of methylol cellulose was easily accomplished. NMR analysis of methylol cellulose acetate provided direct evidence for the methylol derivative and demonstrated the existence of polyoxymethylene substituents. NMR analysis of peracetylated methylol cellulose provided a novel and convenient experimental technique for the determination of the MS of methylol cellulose.

The preparation of triphenylmethyl (trityl) cellulose is possible in the methylol cellulose solvent systems. Trityl methylol acetal substituents are unstable and are lost during the course of the reaction, thus giving as the final product the ether derivative, trityl cellulose, with a DS of one.

Homogeneous hydroxyethylation of methylol cellulose resulted in minor degrees of substitution. GLC analysis of the reaction product showed no detectable amounts of substitution on the anhydroglucose units. Hydroxyethylation apparently occurs preferentially at the hydroxyls of the methylol substituents.

EXPERIMENTAL

GENERAL METHODS

Melting points (m.p.) were determined on a Thomas-Hoover capillary apparatus which had been calibrated against known compounds.

Optical rotations were measured on a Perkin-Elmer 141MC polarimeter.

Gas-liquid chromatography (GLC) analyses were conducted on a Varian Aerograph 1200 gas chromatograph equipped with a hydrogen flame ionization detector and a Honeywell Electronic 16 recorder with a Disc integrator. The stainless steel column (7 ft x 0.125 inch) was packed with 3% OV-225 on 100/120 mesh Gas-Chrom Q.

Nuclear magnetic resonance (NMR) spectra were determined on a JEOL FX 100 Fourier transform spectrometer. The instrument was equipped with a dual probe which allowed the measurement of either ^{1}H NMR or ^{13}C NMR spectra.

Raman spectra were measured with a SPEX 1401 Raman spectrometer (3/4 meter-Czerny-Turner double monochrometer spectrometer) with photoelectric recording. The radiation source was a Coherent Radiation Model 52A argon ion laser. A laser wavelength of 514.5 nm was used. The slit widths were set for a minimum resolution of 5 cm^{-1}.

REAGENTS

CELLULOSE

Whatman CF-1 cellulose powder was used throughout this work as the cellulose source. This chromatographic grade material required no further purification. The number average degree of polymerization (DP_n) was determined to be ca. 275.

PARAFORMALDEHYDE

Paraformaldehyde was obtained from Tridom Chemical Company, Hauppauge, N.Y. This material had a suitably low decomposition temperature (<120°C) and thus could be used in those systems where paraformaldehyde was added directly to the system. For the systems where paraformaldehyde was decomposed in an external flask, other sources of paraformaldehyde could be used, as the decomposition temperature was not as critical. However, the moisture content of the paraformaldehyde should be less than ca. 3%.

SOLVENTS

Dimethyl sulfoxide (Eastman Kodak Co.) was reagent grade (<0.2% water) and did not require further purification.

N,N-Dimethylformamide (J.T. Baker Chemical Co.) was also reagent grade and did not require purification (0.01% water).

N,N-Dimethylacetamide and N-methyl-2-pyrrolidinone were obtained from Aldrich Chemical Co. These reagents were fractionally distilled in vacuo prior to use.

Pyridine (J.T. Baker Chemical Co. and Mallinckrodt) was purified by fractional distillation. For those experiments which required anhydrous pyridine, the solvent was refluxed with barium oxide prior to fractional distillation.

Tetramethylene sulfoxide (Aldrich) was used as obtained. Purification of the solvent, for reuse, was by distillation in vacuo from calcium hydride.

PREPARATION OF COMPOUNDS

1,2:5,6-DI-O-ISOPROPYLIDENE-α-D-GLUCOFURANOSE

This compound was prepared according to the procedure of Glenn, et al. (89). Pulverized zinc chloride (40 g) was added to a stirred suspension of anhydrous D-glucose (50 g) in acetone (350 mL). Phosphoric acid (2.5 g, 85%) was added and the mixture was stirred at room temperature for 30 hours. At the end of the reaction time, the unreacted glucose was removed by filtration. The filtrate was made alkaline with aqueous sodium hydroxide (30 mL, 50%). The insoluble inorganic material was removed by filtration, and the yellowish filtrate was concentrated in vacuo. The residue was diluted with water (100 mL) and then extracted with chloroform (3 x 100 mL). The combined chloroform extracts were washed with water, dried with calcium chloride, and concentrated in vacuo to give a white residue (m.p. 85-95°). Crystallization from chloroform:hexane (1:2, v/v) raised the m.p. to 104-108°. Crystallization from low boiling petroleum ether gave a product with a m.p. 110-111°. Literature (90): m.p. 110-111°.

3-O-CARBOXYMETHYL-1,2:5,6-DI-O-ISOPROPYLIDENE-α-D-GLUCOFURANOSE, METHYL ESTER

This compound was prepared according to the procedure of Shyluk and Timell (91). Sodium hydride (4 g), 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (20 g) and ethyl ether (300 mL) were stirred in an atmosphere of nitrogen for 18 hours. Methyl bromoacetate (20 mL) was added and stirring was continued. At the end of the reaction (52 hr), excess hydride was decomposed by the careful addition of methanol. Ether (300 mL) and water (200 mL) were added to the reaction mixture. The ether layer was extracted, washed with water (4 x 100 mL), and dried over anhydrous sodium sulfate. Evaporation of

the ether solution followed by recrystallization from isopropyl ether yielded white needles; m.p. 103-104.5, $[\alpha]_D$ -3.2° (c 1, $CHCl_3$). Literature (91): m.p. 104-105, $[\alpha]_D$ -3.5 (c 1.5, $CHCl_3$).

3-O-(2-HYDROXYETHYL)-1,2:5,6-DI-O-ISOPROPYLIDENE-α-D-GLUCOFURANOSE

The carboxymethyl methyl ester derivative was reduced to the hydroxyethyl derivative according to the procedure of Shyluk and Timell (78). The 3-O-carboxymethyl-di-O-isopropylidene glucose (5 g) was dissolved in anhydrous ethyl ether (75 mL), and lithium aluminum hydride (1.25 g) was added in a nitrogen atmosphere. The mixture was stirred under nitrogen at room temperature for 6 hours. The excess hydride was decomposed by the cautious addition of ethyl acetate, followed by addition of ethanol and a small amount of water. The mixture was dried with anhydrous sodium sulfate and filtered. The filtrate was evaporated to a sirup which could not be induced to crystallize. $[\alpha]_D$ -34.0° (c 1, H_2O).

3-O-(2-HYDROXYETHYL)-D-GLUCOSE

The isopropylidene blocking groups were removed from the hydroxyethylated sugar by refluxing the compound (2 g) in water (100 mL) with Amberlite IR-120 (H^+) ion exchange resin (10 mL). The reaction was complete within 48 hours. The resin was removed by filtration, and the solution was evaporated to a sirup. After several months, this monosubstituted sugar crystallized. Recrystallization from absolute ethanol yielded white crystals: m.p. 125-127°, $[\alpha]_D$ 52° (c 2, H_2O). Literature (78): m.p. 125-126°, $[\alpha]_D$ 51.8°.

6-O-ACETYL-1,2:3,5-DI-O-METHYLENE-α-D-GLUCOFURANOSE

This compound was prepared according to the procedure of Hough, et al. (92). Glacial acetic acid (200 mL) was added to anhydrous D-glucose (50 g) in water

(20 mL). Paraformaldehyde (55 g) was added followed by the cautious addition of concentrated sulfuric acid (25 mL). The mixture was heated on a steam bath for 1 hour and then cooled. Water (200 mL) was added and the liquor extracted with chloroform (3 x 150 mL). The chloroform layer was washed with water until neutral and then dried over anhydrous sodium sulfate. The solution was evaporated to a sirup which gave crystals upon refrigeration. The crystals were isolated and recrystallized from methanol: m.p. 103-104°, $[\alpha]_D$ 44° (c 0.77, MeOH). Literature (92): m.p. 104°, $[\alpha]_D$ 46.5 (c 0.67, MeOH).

6-O-CARBOXYMETHYL-1,2:3,5-DI-O-METHYLENE-α-D-GLUCOFURANOSE

The procedure followed for the preparation of this compound was that of Shyluk and Timell (91). 6-O-Acetyl-1,2:3,5-di-O-methylene-α-D-glucofuranose (15 g) was deacetylated in chloroform:methanol (1:1, v/v) using methanolic sodium methoxide (1N). The solution was deionized with Amberlite IR-120 (H^+), filtered to remove the resin, and evaporated to a sirup.

The deacetylated dimethylene glucose (10 g) was dissolved in dioxane (250 mL). Sodium hydride (2 g) was added and the mixture stirred for 18 hours in an atmosphere of nitrogen. Methyl bromoacetate (25 mL) was added, and the mixture was allowed to react for 30 hours. At this time, methyl bromoacetate (10 mL) was again added, and the mixture was allowed to react for an additional 48 hours. The excess hydride was decomposed by the addition of methanol. The desired product was isolated by centrifuging the reaction mixture and evaporating the resultant supernatant to a sirup. The carboxymethyl methyl ester derivative was purified by fractionation on a column (1 m x 25 mm) packed with silica gel. The solvent used was chloroform:ethyl acetate (1:1, v/v).

6-O-(2-HYDROXYETHYL)-1,2:3,5-DI-O-METHYLENE-α-D-GLUCOFURANOSE

According to the procedure of Shyluk and Timell (78), the 6-O-carboxymethyl methyl ester (5 g) was dissolved in absolute tetrahydrofuran (125 mL). Lithium aluminum hydride (1.3 g) was added with stirring in a nitrogen atmosphere. The hydride addition produced a very exothermic reaction. The mixture was refluxed under nitrogen for 3 hours. The hydride was decomposed and the compound isolated as previously described for 3-O-(2-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.

6-O-(2-HYDROXYETHYL)-D-GLUCOSE

The methylene blocking groups were removed from the hydroxyethylated sugar by refluxing the sugar in water with Amberlite IR-120 (H^+) ion exchange resin. The reaction was complete within 48 hours. The resin was removed by filtration, and the resulting solution was evaporated to a sirup. Crystallization and recrystallization from absolute ethanol yielded a product with a melting point of 148-149°, $[\alpha]_D$ 48.5°. Literature: m.p. 106-107°, $[\alpha]_D$ 48.7° (78); m.p. 148-150°, $[\alpha]_D$ 49° (93); m.p. 147-150°, $[\alpha]_D$ 49° (46).

1,2-O-ISOPROPYLIDENE-α-D-GLUCOFURANOSE

This compound can be prepared by the controlled removal of one isopropylidene group from 1,2:3,5-di-O-isopropylidene-α-D-glucofuranose (90). Alternately, the mono-O-isopropylidene compound can be prepared without the isolation of the di-O-isopropylidene compound (94). The latter procedure was employed in the present work.

D-Glucose (50 g) and acetone (1000 mL) were stirred vigorously in an ice bath. Sulfuric acid (40 mL, concentrated) was added in 20 mL portions at 15-minute intervals. The stirring was continued for 5 hours, during which time the temperature of the solution was allowed to rise to room temperature. The solution was again cooled in an ice bath and then slowly neutralized with 50% sodium hydroxide. Sodium bicarbonate (7.5 g) was added, and the solution was allowed to stand overnight. After the salts were removed by filtration, the acetone solution was concentrated *in vacuo*. Water (600 mL) was added and the mixture distilled under vacuum at 60-70° to a volume of *ca.* 400 mL. The aqueous mixture was adjusted to pH 2 with concentrated hydrochloric acid and then heated for 4 hours at 40° with stirring. At the end of the allowed reaction time, the pH was adjusted to 8 with sodium hydroxide. Insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* and then placed in a refrigerator to allow crystallization to occur. The material obtained had a melting point of 158-160°. Recrystallization from ethyl acetate gave a product with m.p. 159-160°. Literature (94): m.p. 160°.

1,2-O-ISOPROPYLIDENE-3,5,6-TRI-O-BENZYL-α-D-GLUCOFURANOSE

This compound was prepared according to the procedure of Finan and Warren (95). 1,2-O-Isopropylidene-α-D-glucofuranose (15 g) and powdered sodium hydroxide (35 g) were stirred together in benzyl chloride (150 mL). The mixture was heated to 80° in an oil bath. At the end of the reaction (2 days) the mixture was diluted with water (125 mL) and extracted with ether (200 mL). The ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to a brownish sirup. The sirup was purified by column chromatography using a silica gel column (1 m x 25 mm) and petroleum ether (30-60°):ethyl ether (2:1, v/v).

METHYL 3,5,6-TRI-O-BENZYL-α,β-D-GLUCOFURANOSIDE

A portion of the product from above (6 g) was dissolved in anhydrous methanol (75 mL), and solvent exchanged Amberlite IR-120 (H^+) resin (15 mL) was added. The mixture was brought to reflux temperature and allowed to react for 3 days. The removal of the isopropylidene group and subsequent glycosidation was followed by TLC using ethyl ether:petroleum ether (30-60°) (1:2, v/v). At the end of the reaction, the mixture was cooled, the resin filtered off, and the methanol solution evaporated to a brown sirup. The crude glycoside was purified by column chromatography using a silica gel column (1 m x 25 mm) and ethyl ether:low boiling petroleum ether (1:2, v/v) as the fractionation solvent.

METHYL 2-O-CARBOXYMETHYL-3,5,6-TRI-O-BENZYL-α,β-D-GLUCOFURANOSIDE, METHYL ESTER

According to the procedure of Shyluk and Timell (91), methyl 3,5,6-tri-O-benzyl-α,β-D-glucofuranoside (5 g) was dissolved in anhydrous ethyl ether (50 mL), and sodium hydride (1 g) was added to the solution. The mixture was stirred in an atmosphere of nitrogen for 18 hours, at which time methyl bromoacetate (5 mL) was added. After 24 hours, an additional treatment with sodium hydride (1 g) and methyl bromoacetate (5 mL) was employed. After 3 days, the excess hydride was decomposed with methanol, and the compound was isolated by extraction with ether and water. The sirup could not be induced to crystallize even after purification by column chromatography and so was taken, as such, into the next step.

METHYL 2-O-(2-HYDROXYETHYL)-α,β-D-GLUCOFURANOSIDE

The carboxymethyl methyl ester (2.5 g) was dissolved in tetrahydrofuran (50 mL), and lithium aluminum hydride (1.3 g) was added, again following the procedure of Shyluk and Timell (78). The mixture was refluxed for 5 hours under nitrogen. After the mixture had cooled, excess hydride was decomposed with ethyl acetate, and then ethanol (15 mL) and water (1 mL) were added. The gray gelatinous mixture was dried over anhydrous sodium sulfate, and after filtration, the filtrate was evaporated to a sirup.

METHYL 2-O-(2-HYDROXYETHYL)-α,β-D-GLUCOFURANOSIDE

The sirup from above was debenzylated by catalytic hydrogenation. The sirup (4.6 g) was dissolved in methanol (200 mL), and palladium on charcoal (1 g) was added. The mixture was stirred under a hydrogen atmosphere. The reaction was complete in ca. 3 days. Filtration and evaporation of the solution yielded a sirup. Hydrolysis of the sirup with Amberlite IR-120 (H^+) resin in water gave a mixture of 1,2-O-ethylene glucoses and 2-O-(2-hydroxyethyl)-D-glucose which was used for identification of the 2-O-(2-hydroxyethyl)-D-glucose peak in the GLC analysis of hydroxyethyl cellulose.

1,2-O-ETHYLENE-D-GLUCOSES

The intramolecular cyclization products of 2-O-(2-hydroxyethyl)-D-glucose were isolated by fractional crystallization of the hydrolyzate from above. 1,2-O-Ethylene-α-D-glucopyranose was found to have a m.p. of 134-135°. Literature (96): 134-135°. 1,2-O-Ethylene-β-D-glucopyranose crystallized and had a m.p. of 209-210°. Literature (96): m.p. 210-211°.

METHYL 4,6-O-BENZYLIDENE-α-D-GLUCOPYRANOSIDE

This compound was prepared according to the procedure of Richtmeyer (97). Methyl α-D-glucopyranoside (30 g), zinc chloride (25 g), and benzaldehyde (75 mL) were stirred together for 48 hours. At the end of the reaction time, the solution was poured with rapid stirring into a cold solution of sodium bisulfite (450 mL, 10%) to remove excess benzaldehyde. Crystallization resulted upon refrigeration. The crystals were washed with cold sodium bisulfite solution, water, and low boiling petroleum ether in succession. Recrystallization from water yielded fine white crystals: m.p. 163-164°, $[\alpha]_D$ 113° (c 1, $CHCl_3$). Literature (97): m.p. 163-164°, $[\alpha]_D$ 110° (c 2, $CHCl_3$).

METHYL 2,3-DI-O-CARBOXYMETHYL-4,6-O-BENZYLIDENE-α-D-GLUCOPYRANOSIDE, DIMETHYL ESTER

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (15 g) was dissolved in dioxane (250 mL), and sodium hydride (5 g) was added. The resulting mixture was stirred under nitrogen for 18 hours. Additional sodium hydride (2.5 g) was added, and methyl bromoacetate (35 mL) was added in two portions during the 4-day reaction period. The mixture was centrifuged, and the supernatant was evaporated to a reddish sirup: $[\alpha]_D$ 5.3° (c 1, $CHCl_3$).

METHYL 2,3-DI-O-(2-HYDROXYETHYL)-4,6-O-BENZYLIDENE-α-D-GLUCOPYRANOSIDE

The dicarboxymethyl methyl ester (1.5 g) was dissolved in absolute tetrahydrofuran (25 mL), and lithium aluminum hydride (0.8 g) was cautiously added with cooling applied to the flask. The solution was brought to reflux temperature under nitrogen. After refluxing for 4 hours, the mixture was

cooled and the excess hydride was decomposed with ethyl acetate. The solids were removed by filtration and washed with ethanol. The filtrate was evaporated to a sirup *in vacuo*. Fine white crystals of the dihydroxyethyl derivative were obtained by crystallization from isopropyl ether: m.p. 119-120°. Literature (98): m.p. 119-121°.

2,3-DI-O-(2-HYDROXYETHYL)-D-GLUCOSE

The benzylidene group and the methyl aglycon were removed by dissolving the sugar (1 g) in water (50 mL) and refluxing the solution with Amberlite IR-120 (H^+) resin. The reaction was followed by TLC using chloroform:methanol (3:1, v/v). The resin was removed by filtration, and the filtrate was evaporated to a sirup.

CELLULOSE TRICARBANILATE

Cellulose percarbanilate which was required for the determination of the cellulose DP was prepared according to the basic procedure of Schroeder, *et al.* (70). Cellulose (2 g) was dried in an oven (105°) for 2 hours. The dried cellulose was then slurried in anhydrous pyridine (100 mL), and the slurry was heated to 80° in a thermostatically controlled oil bath. Phenyl isocyanate (30 mL) was slowly added with stirring. After 2 hours, additional phenyl isocyanate (15 mL) was added. The mixture was kept at 80° for 2 days at which time the solution was cooled and methanol (5 mL) was added. Pyridine (100 mL) was added and the solution was then poured in a fine stream into methanol (800 mL) containing acetic acid (5 mL). The precipitated carbanilated polymer was allowed to settle, and the supernatant was siphoned from the mixture. The remaining liquid was removed by centrifugation. The carbanilate was washed with water containing acetic acid (800:5), washed with water (800 mL), then freeze-dried to give a white powder.

CELLULOSE DEGREE OF POLYMERIZATION DETERMINATION

Cellulose degree of polymerization (DP) was determined by gel permeation chromatography (GPC) of the cellulose percarbanilate derivative. Cellulose percarbanilate (15 mg) was dissolved in tetrahydrofuran (10 mL). The dissolved polymer was then chromatographed on four Styragel columns (Waters Associates). A Varian 8500 liquid chromatograph utilizing a Perkin-Elmer LC-55 spectrophotometer equipped with a flow cell detector was employed. The GPC columns had previously been calibrated with essentially monodisperse fractions of polystyrene. The DP of the cellulose was calculated from the resultant chromatogram with the aid of a previously prepared computer program (99).

CELLULOSE DISSOLUTION PROCEDURES

LOW TEMPERATURE DISSOLUTION

Whatman CF-1 cellulose powder (1 g) was suspended in the organic solvent (100 mL). The slurry was stirred and heated to the desired temperature, generally ca. 85°. At this point, paraformaldehyde (ca. 10 g) was added to another flask which was heated to ca. 190°. The flask containing the paraformaldehyde was then stoppered to force the gas which was generated through tubing to the reaction flask. An illustration of the assembly is presented in Fig. 15. Within a few minutes (5-10) after the start of the formaldehyde gas, a noticeable dissolution of the cellulose was observed. The formaldehyde gas was continually bubbled into the solution until a clear solution was obtained (15-30 min). Continued heating of the clear solution resulted in the loss of formaldehyde and subsequent lowering of the MS of the methylol cellulose.

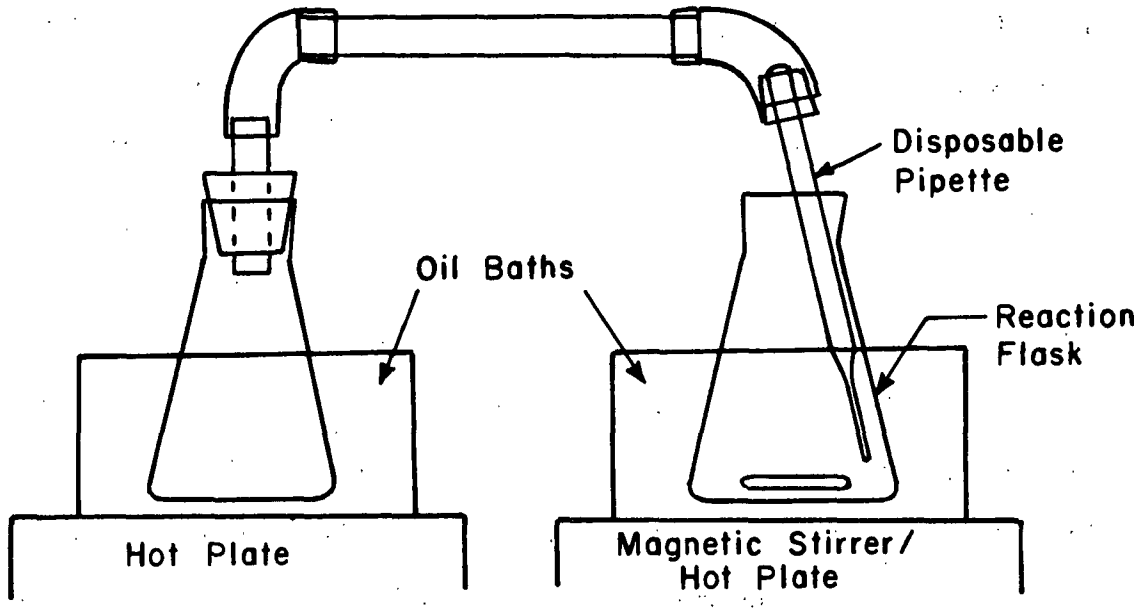


Figure 15. Illustration of the Apparatus Employed in the Dissolution of Cellulose in an Organic Solvent by the Action of Formaldehyde Gas

CELLULOSE DISSOLUTION IN THE DMSO/PF SYSTEM

Stock solutions of cellulose were prepared for subsequent reactions. Whatman CF-1 cellulose powder (9 g) was suspended in DMSO (300 mL) in a 600 mL beaker. The slurry was heated with stirring to 125°. Paraformaldehyde (13.5 g) was added. A drop in temperature was observed for the solution, followed by generation of formaldehyde gas. The solution became clear within a few minutes. Continued heating for a period of ca. 30 minutes was employed to reduce the MS of the methylol cellulose. The solution was cooled, freeze-dried for a period of three days, and then redissolved in DMSO (300 mL).

ACETYLATION OF METHYLOL CELLULOSE

The acetylation reaction was generally carried out as a derivatization reaction for the analysis of the MS of methylol cellulose from the various solvent systems. Consequently small samples were employed. Reactions using greater quantities of methylol cellulose (i.e., 10 g) were also carried out

using an appropriate increase in reagents and were found to proceed easily as well. An aliquot (10 mL) of the cellulose solution containing ca. 0.1 g cellulose was pipeted from the solution and cooled in an ice-water bath. For cellulose dissolved in pyridine, DMF, DMA, and NMP, the methylol cellulose was acetylated directly by adding pyridine (15 mL) and acetic anhydride (10 mL) with stirring. For cellulose in the sulfoxides, the methylol cellulose was isolated from the solvent by precipitation with ethyl ether (100 mL). The precipitate was washed with ethyl ether (50 mL) after which pyridine (25 mL) and acetic anhydride (10 mL) were added. The acetylation reaction was allowed to proceed for 18 hours at room temperature. The acetylated polymer was isolated at the end of the reaction time by precipitation in ice water (300 mL). The peracetate was filtered, washed with water, and dried in vacuo (45°). The dry polymer was dissolved in deuterochloroform for analysis by NMR.

HYDROXYETHYLATION OF METHYLOL CELLULOSE

Initial attempts to prepare hydroxyethyl cellulose (HEC) in the DMSO/PF system were carried out in a 1000 mL 3-necked round-bottomed flask fitted with a dry ice condenser. The system was purged with dry nitrogen and a slow flow of nitrogen was passed through the system during the reaction. Gas from the reactor was passed through a trap filled with water prior to venting to the atmosphere. One-hundred milliliters of DMSO containing ca. 3 g (0.019 mole) of dissolved cellulose was treated with sodium hydride (1.0-2.75 g, 0.042-0.114 mole). Ethylene oxide was introduced into the system by means of a cold water jacketed syringe. Reactions were allowed to proceed from 3 to 24 hours. At the end of the allowed reaction time, the contents of the reaction flask were poured into isopropanol containing acetic acid. In this manner, the excess hydride was decomposed, and the cellulosic material was precipitated. The precipitate was filtered and then washed with isopropanol and acetone to remove

dimethyl sulfoxide and residual poly(ethylene oxide) contaminants. The washed precipitate was then dried *in vacuo* (45°) and analyzed by GLC or by the Morgan method (81). Analysis of the material isolated from this system indicated that no significant amount of substitution of the cellulose had occurred.

It was decided that with the apparatus described above, the dry ice condenser may not be totally effective for preventing ethylene oxide gas from escaping from the system. Evaporation of the solution in the water trap resulted in a residual liquid which had an IR spectrum identical to that of ethylene glycol, thus supporting the conclusion that at least some of the ethylene oxide was escaping. To circumvent the problem with the escape of ethylene oxide, the experiments were repeated employing a closed pressure bottle. With the closed system, however, again no significant amount of substitution of the cellulose had occurred.

MORGAN METHOD OF ANALYSIS FOR HYDROXYETHYL SUBSTITUENTS

The following reagents are required for this analysis:

Hydroiodic acid: Constant boiling (b.p. 126-7°, sp.gr. 1.70)

Silver nitrate solution: Silver nitrate (15 g) in water (50 mL) is added to absolute ethanol (400 mL). Several drops of nitric acid are added. The solution is standardized against 0.05N ammonium thiocyanate.

Bromine solution: Bromine (1 mL) is added to glacial acetic acid (300 mL) which is saturated with dry potassium bromide (5 g). This solution is stored in a dark bottle and standardized against 0.05N sodium thiosulfate.

Potassium iodide: 10% aqueous solution

Sulfuric acid: 10% aqueous solution

Sodium thiosulfate: 0.05N standard solution

Ammonium thiocyanate: 0.05N standard solution

Starch indicator: 1% aqueous solution

Ferric ammonium sulfate: saturated aqueous solution

Cadmium sulfate: 5% aqueous solution

Red phosphorous

The apparatus used is shown in Fig. 16.

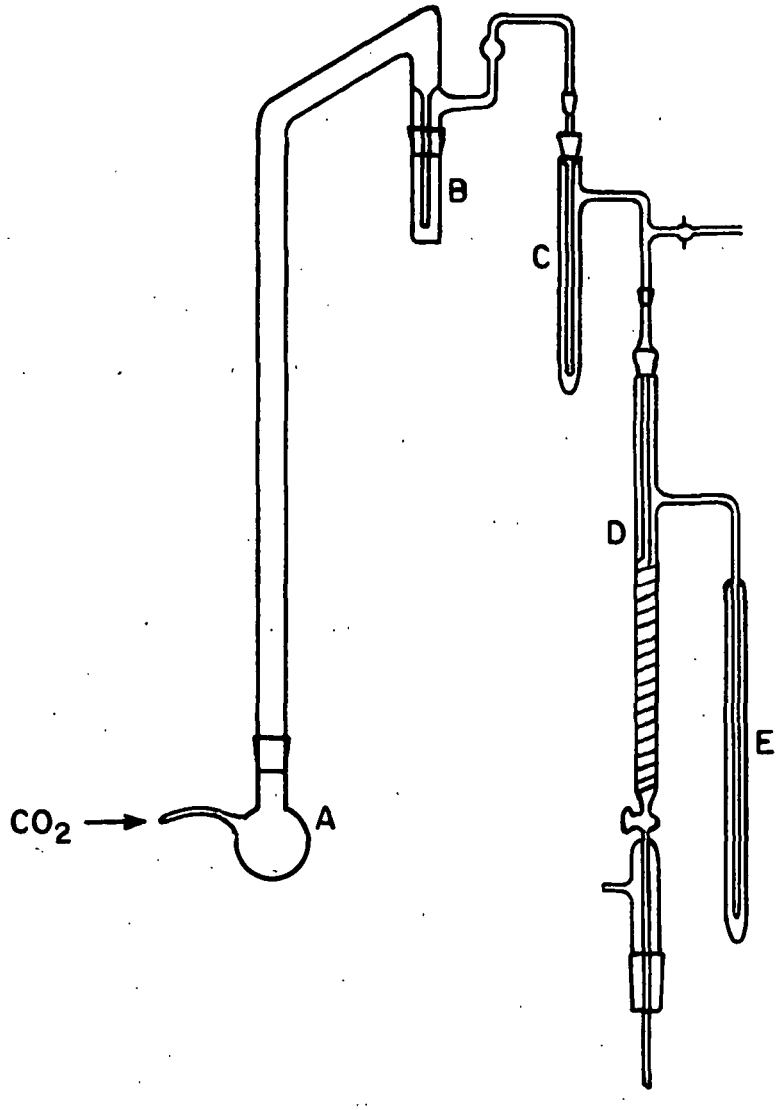


Figure 16. Diagram of Apparatus Used for the Determination of Hydroxyethyl Content of HEC

According to the method described by Morgan (81), a weighed sample of HEC (ca. 100 mg) was added to hydroiodic acid (10 mL) in Flask A as shown in Fig. 16. The acid solution was then heated in an oil bath (140-145°) for 2 hours, while

a stream of CO_2 (1 bubble per sec) was passed through the system. The resulting ethyl iodide was collected in trap C by a silver nitrate solution (10 mL). Ethylene was collected in trap D which contained a bromine-glacial acetic acid solution (15 mL). Trap B contained red phosphorus suspended in a 5% aqueous solution of cadmium sulfate. Trap E contained 10% potassium iodide (10 mL).

At the end of the reaction, traps D and C were disconnected. The carbon dioxide source was disconnected, and the heat was removed from Flask A. The contents of trap C were diluted to 150 mL with water, heated to boiling, cooled, and titrated with 0.05N ammonium thiocyanate using ferric ammonium sulfate solution (3 mL) as an indicator. The contents of trap D were added to an Erlenmeyer flask which contained water (150 mL) and 10% potassium iodide solution (10 mL). The solution in trap E was added to this flask together with 10% sulfuric acid (5 mL). The quantity of ethylene which had been generated by the hydrolysis of HEC was determined by titration with 0.05N sodium thiosulfate using starch indicator (2 mL) for the end point. The percent hydroxyethyl content of the sample was calculated from the difference between blank titrations and the titrations of the corresponding bromine and silver nitrate traps (81).

$$\frac{\text{Difference in mL of } Na_2S_2O_3 \times N \times 2.203}{\text{grams of sample}} = \%\ C_2H_4O \text{ as } C_2H_4$$

$$\frac{\text{Difference in mL of } NH_4SCN \times N \times 4.405}{\text{grams of sample}} = \%\ C_2H_4O \text{ as } C_2H_5I$$

$$\frac{\%\ \text{ethylene oxide}}{(100 - \%\ \text{ethylene oxide})} \times \frac{162}{44.05} = \text{hydroxyethyl groups per anhydroglucose unit (MS)}$$

GAS-LIQUID CHROMATOGRAPHIC ANALYSIS

In order to study the substituent distribution of hydroxyethyl cellulose by gas-liquid chromatography (GLC), it was necessary to break down the polymer to the monomeric glucose units and then derivatize the glucoses to make them suitable for analysis.

Hydrolysis

Samples of the dried HEC were hydrolyzed according to the basic procedure of Klug, et al. (100). The hydrolysis employed an initial treatment with 72% sulfuric acid (1 hr, 25°) followed by a secondary treatment with 5.5% sulfuric acid (5 hr, reflux temperature) under nitrogen. Upon completion of the hydrolysis, the solution was cooled and neutralized to pH 5.5 with barium hydroxide. The mixture was then digested for 1 hour at ca. 80° to assist in the coagulation of the barium sulfate precipitate. The insoluble barium salts were removed by filtration through a bed of Celite. The filtrate was concentrated in vacuo.

Reduction of the Sugars to Alditols

After the acid hydrolysis of the cellulose derivative, the neutralized and filtered hydrolyzate was concentrated to a volume of ca. 600 mL/1 g of carbohydrate. Sodium borohydride (4 g/1 g carbohydrate) was added to the aqueous solution. At the end of the allowed reaction time (2 hr), excess borohydride was decomposed by the addition of acetic acid (2N). The solution was then deionized by passing it through a column of Amberlite IR-120 (H^+) ion exchange resin (50 mL resin/1 g borohydride). The deionized solution was evaporated to a sirup in vacuo. Methanol (50 mL) was twice added and evaporated to dryness.

Acetylation

The dry sirupy sugars either from the acid hydrolysis or from the reduction reaction were acetylated prior to GLC analysis. Pyridine (30 mL/1 g sugar) was added, and the solution was cooled in an ice bath. Acetic anhydride (30 mL) was then added with stirring. The reaction mixture was allowed to warm to room temperature. At the end of the reaction time (18 hr), the acetylation mixture was poured with stirring into ice water (300 mL). The aqueous solution was extracted with chloroform, and the chloroform layer was washed with HCl (1N) and then with water to remove residual pyridine. The chloroform solution was then dried with anhydrous sodium sulfate and concentrated *in vacuo*. The acetylated sugars in chloroform were analyzed by GLC.

GLC Conditions

The acetylated sugars were chromatographed on a 7 ft (0.125 inch) stainless steel column packed with 3% OV-225 on 100/120 mesh Gas-Chrom Q. The conditions employed for the acetate derivatives were:

Column temperature: 180-240° at 2°/min

Injector temperature: 250°

Detector temperature: 270°

Nitrogen flow rate: 40 mL/min

Hydrogen pressure: 10 psig

Identification of the components of the chromatogram was accomplished by comparison of the retention times with those of known compounds. Since no reaction was observed for cellulose in the DMSO/PF system with ethylene oxide, the determination of response factors and more complete identification of the compounds (i.e., mass spectrometry) was deemed unnecessary.

TRIPHENYLMETHYLATION OF METHYLOL CELLULOSE

Cellulose (5 g, 0.031 mole) was dissolved in the appropriate solvent (100 mL) using paraformaldehyde (10 g), and then the solution was kept at 80° to decrease the MS of the methylol cellulose. A solution of triphenylmethyl (trityl) chloride (25 g, 0.090 mole) in pyridine (100 mL) was heated to ca. 80° and then added to the cellulose solution. The solutions were preheated to allow a more accurate analysis of the rate of reaction at short reaction times. The tritylation reaction was also found to be successful if all of the components were mixed at room temperature and then heated to 80°. The reaction mixture was stirred at 80°, and samples were taken at various time intervals. The trityl cellulose was isolated by precipitation into isopropanol. The resultant cellulose derivative was washed with isopropanol and dried in vacuo.

DEGREE OF SUBSTITUTION OF TRIPHENYLMETHYL CELLULOSE

According to the procedure previously described by Helferich (101), the degree of substitution (DS) of the tritylated cellulose was determined by hydrolyzing a weighed sample with concentrated sulfuric acid. After 1 hour at room temperature, the sulfuric acid solution was cautiously poured into a beaker of ice water. The triphenylmethanol (tritanol) which precipitated was filtered, washed with water, dried, and weighed. The DS of the sample was then determined from the weight of tritanol and the weight of the sample.

$$\frac{\text{Weight tritanol} \times 243/260}{(\text{Weight sample} - \text{weight tritanol} \times 243/260)} \times \frac{162}{243} = \text{DS of trityl cellulose}$$

TRIPHENYLMETHOXYMETHYL PYRIDINIUM CHLORIDE

The by-product from the tritylation of methylol cellulose was determined to be triphenylmethoxymethyl pyridinium chloride. This material was submitted

for carbon, hydrogen, nitrogen, and chlorine analyses. Calculated: C, 77.41; H, 5.72; N, 3.61; Cl, 9.14. Found: C, 77.15; H, 6.01; N, 3.69; Cl, 9.32. This material had a decomposition point of 206°. After decomposing, the product which remained had a melting point of ca. 110°, which is close to that of triphenylmethyl chloride (112-113°).

NOMENCLATURE

DMA = Dimethylacetamide

DMF = Dimethylformamide

DMSO = Dimethyl sulfoxide

DP = Degree of polymerization

DS = Degree of substitution

GPC = Gel permeation chromatography

GLC = Gas-liquid chromatography

HEC = Hydroxyethyl cellulose

IR = Infrared

MS = Molar degree of substitution

NMP = N-Methyl-2-pyrrolidinone

NMR = Nuclear magnetic resonance

PF = Paraformaldehyde

PMR = Proton magnetic resonance

TMSO = Tetramethylene sulfoxide

Trityl = Triphenylmethyl

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