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Reactions of Cellulose in the Dimethyl Sulfoxide/ Paraformaldehyde (DMSO/PF) Solvent

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REACTIONS OF CELLULOSE IN THE DIMETHYL SULFOXIDE/ PARAFORMALDEHYDE (DMSO/PF) SOLVENT

A thesis submitted by

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SUMMARY

The mechanism of cellulose dissolution in dimethyl sulfoxide/paraformaldehyde (DMSO/PF) was investigated along with the homogeneous etherification of cellulose in the solvent.

Work was undertaken initially to determine the possibility of a DMSO-formaldehyde complex functioning in the dissolution process. However, spectroscopic analysis of the solvent system did not show any evidence for such a complex. Quantitative estimation of the formaldehyde in solution revealed it to be on the order of less than 0.5%. In a 0.5% cellulose solution, this corresponds to a mole ratio of formaldehyde:anhydroglucose of 5.6:1. Such a low concentration of the critical solvent component suggested the possibility of cellulose derivatization by formaldehyde.

In an attempt to isolate the proposed derivative, a sample of the cellulose-DMSO/PF solution was freeze-dried. The solid material was readily soluble in DMSO at room temperature. Raman spectral analysis of this material revealed the presence of bands characteristic of cellulose derivatives. This material was very unstable in water and decomposed (liberating formaldehyde), resulting in the recovery of unsubstituted cellulose. Quantitative analysis of the liberated formaldehyde indicated a mole ratio of formaldehyde to anhydroglucose of 1:1. Repeated experiments showed that the cellulose derivative formed during dissolution of cellulose in DMSO/PF possessed a molar substitution range of 1.05 to 1.16. All evidence supported the assumption that the derivative responsible for cellulose dissolution was methylol (hemiacetal) cellulose.

Carboxymethylation and methylation of the cellulose in solution was achieved in the DMSO/PF system. Carboxymethylation was attempted with two systems: (1) an organic base (triethylamine) and chloroacetic acid or

methyl chloroacetate, and (2) sodium hydride in conjunction with methyl bromoacetate. Reaction of chloroacetic acid with methylol cellulose in the presence of triethylamine produced only acetalation of the methylol hydroxyl groups. Carboxymethylation of the cellulose was possible when sodium hydride and methyl bromoacetate were employed (19-50°C). The carboxymethyl cellulose (CMC) possessed (in all cases) a low degree of substitution (DS) of ca. 0.20. This limiting DS was attributed to the insolubility of the CMC which hindered further etherification in the DMSO system.

Analysis by gas-liquid chromatography (GLC) of the CMC obtained from such a reaction indicated a preference for etherification at the secondary hydroxyl groups (C-2 and C-3). Further reaction data obtained by either partially removing the methylol groups (sodium hydride interaction at elevated temperature, 50°C) or by blocking them (acetal formation using triethylamine and chloroacetic acid) prior to carboxymethylation supported the assumption that the methylol groups were preferentially located on the C-6 primary hydroxyl groups.

Methylation of cellulose (low to high DS) was achieved in the DMSO/PF solvent with sodium hydride and methyliodide. Analysis (GLC) of low DS methyl cellulose showed the same preference for substitution at C-2 and C-3, thus indicating the presence of the methylol group at C-6.

While the reaction data indicated that the methylol groups (present on the cellulose in DMSO/PF) markedly affect cellulose etherification in the DMSO/PF solvent, they also showed the feasibility of controlling the substituent distribution of cellulose etherifications in homogeneous reactions in DMSO/PF.

INTRODUCTION

CELLULOSE SOLVENTS

Solvents for cellulose may be defined as those media which will dissolve cellulose in any form and permit facile regeneration of the cellulose by change in pH and/or dilution with water. Such cellulose solvents have found considerable use in commercial and research applications.

Commercial uses involve primarily the viscose process. In this process the cellulose is dissolved (in aqueous alkali) by xanthation and subsequently regenerated in the desired form of film, fiber or filament (rayon). Specialty cellulose membranes such as those used for medical purposes are similarly regenerated from other solvents like cadmium oxide/ethylenediamine (cadoxene). Since the end uses of the various regenerated cellulose materials are numerous, this commercial application of cellulose solvent technology is very important.

Another significant use of such solvents is for the investigation of cellulose solution properties. For example, molecular weight determinations of cellulose by viscosity measurement are routinely performed in various nondegrading solvents. Light scattering and other optical determinations require a solvent which, in addition to being nondegrading, is clear and colorless. Also, fractionation of cellulose in solution has become a useful method of obtaining molecular weight distributions. This has been accomplished by fractional precipitation from sodium ferric tartrate (FeTNa) with mannitol and by exclusion column chromatography (gel permeation) employing cellulose nitrates, acetates and cellulose/cadoxene solutions (1-4). From these applications, the importance of cellulose solvents, for both commercial and research purposes, can be readily appreciated.

For purposes of discussion, cellulose solvents may be classified as either aqueous or nonaqueous. The aqueous solvents for cellulose are numerous and include the mineral acids as well as the metal ion complex solvents. Nonaqueous systems are attracting increased attention, since they are for the most part nondegrading and relatively easy to prepare. Briefly, we will examine some of the common aqueous solvents for cellulose which involve metal complex ions.

AQUEOUS SOLVENTS

Cuprammonium hydroxide (cuoxam) and cupriethylenediamine (cuene) were perhaps the most common solvents for cellulose prior to 1960 (5). The value of these aqueous solvents for viscosity measurement was somewhat limited by the fact that substantial cellulose degradation occurred in the alkaline solution. With cuene, this degradation could be retarded by exclusion of oxygen from the system throughout the procedures. In addition, the deep blue color of these solvents prohibited most optical investigations. As a result, its applicability for various pulp analyses was limited.

Analogous solvents possessing different central metal atoms were later discovered by Jayme, et al. (6-10). These included cobalt, zinc, nickel, and cadmium complexes with ethylenediamine (cooxene, zincoxene, nioxene, and cadoxene). Preparation of the cobalt and zinc complex solutions is extremely difficult; also, the stability of these complexes is limited. For this reason, they must be used soon after preparation. Cadoxene has proved to be very useful because of its relative ease of preparation and the resulting clear, colorless solutions of cellulose obtained. While degradation of the cellulose dissolved in cooxene, zincoxene and nioxene is not reported, the degradation in cadoxene is reported to be slight and is similar to that

observed in oxygen-free cuene solutions (11). An excellent review of these aqueous cellulose solvents is given in the text by Bikales and Segal (12).

So far the aqueous solvent systems containing the heavy metal atoms have involved complexing between metal ions and either ethylenediamine or ammonia. The basic composition of these complexes, as reported by Jayme, can be illustrated as follows:

$$M(en)_3(OH)_2 \text{ or } M(NH_3)_6(OH)_2$$

where M can be cobalt, zinc, nickel or cadmium and (en) denotes ethylenediamine.

Another cellulose solvent which is thought to function due to a metal complex is the sodium ferric tartrate (FeTNa) system. Work by Bayer indicated that a 3:1 (tartrate:iron) complex interacts with the C-2 and C-3 cellulose hydroxyl groups, gradually allowing dissolution of the cellulose-tartrate complex in the aqueous medium (13). Later the characteristics of the alkaline ferric-tartrate bonds were investigated by Hanby and found to relate to the cellulose dissolving ability of the system (14). Perhaps the foremost asset of this ferric-tartrate solvent is that it does not significantly degrade the cellulose upon dissolution, even in the presence of atmospheric oxygen. This solvent has a color associated with the complex ranging from brown to a yellow green thus hampering light scattering investigations; it has found substantial success as a solvent for viscosity determinations.

These aqueous solvents are all thought to involve metal complex ions containing organic ligands or ammonia. This complex then interacts (complex displacement by cellulose) with the cellulosic hydroxyl groups to produce a

cellulose-solvent complex which results in water solubility. In addition to the problems incurred with the alkaline degradation of the cellulose and the intensely colored solutions, complete regeneration of cellulose, without metal complex contamination, can be difficult.

NONAQUEOUS ANHYDROUS SOLVENTS

Although relatively few in number, anhydrous cellulose solvents have recently attracted increased interest. They are generally easier to prepare and are nondegrading in nature. The discovery that dinitrogen tetroxide and nitrosyl chloride were capable of inducing cellulose dissolution in diethylamine and dimethyl sulfoxide revived interest in such systems (15,16). These nonaqueous systems are generally believed to function by formation of uncharged cellulose derivatives. In particular, both dinitrogen tetroxide and nitrosyl chloride are thought to form cellulose nitrite. This derivative is soluble and stable in certain organic solvents, and can be easily hydrolyzed by interaction with water, regenerating cellulose.

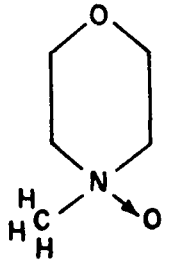
Analogous to the nitrogen systems, other workers have found that sulfur dioxide can effectively interact with cellulose, resulting in solubility in organic media (acetonitrile or dimethyl sulfoxide) (17,18). Further investigation of this system revealed that a three component solvent system of sulfur dioxide, dialkylamine and another organic solvent was capable of dissolving cellulose. A recent review of this work along with a historical development of cellulose solvents in general was published by Philipp and coworkers (19).

Another solvent which developed out of the sulfur dioxide/amine investigation was the methylamine/dimethyl sulfoxide (DMSO) solvent. In contrast to the nitrogen and sulfur systems which are thought of as derivatizations,

this amine/DMSO solvent is believed to function due to a hydrogen-bonded amine-DMSO complex which interacts with the cellulose to form a dimethyl sulfoxide-soluble complex (20).

Japanese workers have recently found that cellulose could be dissolved in DMSO, dimethyl formamide (DMF), dimethyl acetamide, or N-methyl-2-pyrrolidone which contained 5-10 moles anhydrous chloral per mole anhydroglucose (21). Further study on the modification (acetylation) of cellulose in this system has been reported (22).

Johnson (23) recently discovered that certain cyclic amine oxides were capable of dissolving cellulose. Of the family of cyclic amine oxides investigated, N-methylmorpholine-N-oxide (I) had the greatest capacity to dissolve cellulose.



N-Methylmorpholine-N-oxide (I)

A wide variety of cellulose samples were found to be soluble in this system. In contrast to other solvents, Johnson did not believe a cellulose derivative was formed; that is, the cellulosic hydroxyl groups were not reacting with the cyclic amine oxide. He investigated the possibility of forming derivatives of cellulose while in solution (cyclic amine oxide). Reactions investigated were esterifications (acetylation, propionylation and butyrlation) and etherification (cyanoethylation). Although the DS

levels were not given, all reactions were reported to be possible in the cyclic amine oxide solvent system.

CELLULOSE DERIVATIZATION

Since some of the cellulose solvent systems have been shown to be compatible with certain cellulose derivatizations, the nature of homogeneous cellulose reactions can be studied. Investigation of such homogeneous cellulose derivatization could lead to improved understanding of the factors influencing the reactivities of cellulose hydroxyl groups.

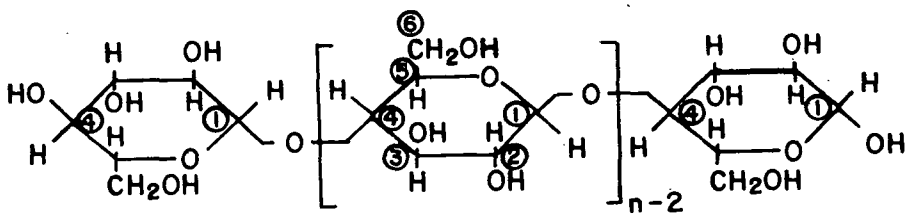
Cellulose derivatives are often characterized by their degree of substitution (DS) and their distribution of substituents. Since both characteristics affect the properties and subsequently the end uses of the cellulose derivative, these are important variables to control.

The results of cellulose derivatizations usually depend upon constraints or factors which originate from the basic cellulosic structure. Such constraints may be traced to: accessibility (crystallinity), hydroxyl group reactivity and reagent reactivity.

It is generally acknowledged that the highly ordered inner crystalline regions of cellulose are less accessible to reagents than either the amorphous (less crystalline) or surface regions. This leads to nonuniform substitution of cellulose during derivatization. One way to eliminate the accessibility constraint would be to decrystallize the cellulose by dissolution in a suitable reaction medium. This would allow uniform access of the reagent to the cellulose and permit a more meaningful study of the other factors influencing derivatization.

Although the reactivity of the derivatizing reagent affects the final derivatization of the cellulose (by side reactions), this can be controlled by choosing a reagent that will minimize these side reactions. By far a more influential restraint would be the cellulosic hydroxyl group reactivities. There has been a substantial amount of investigation into the hydroxyl group reactivities for various reactions but, for the most part, they have been conducted in the heterogeneous state. Conceivably, by studying cellulose reactions in homogeneous solutions, the hydroxyl group reactivities could be investigated independently of accessibility restraints.

The reactivities of the cellulosic hydroxyl groups are usually measured by quantitative analysis of the substituents at each position. Since cellulose (II) is composed of many identical β-1,4 linked anhydroglucose units, the three possible positions for derivatization are the hydroxyl groups at C-2, C-3 and C-6.



(II)

ETHERIFICATION

Patents concerning cellulose ethers date back to the early 1900's (24,25). Primarily two types of reactions are employed. The more common of the reaction types is nucleophilic substitution. An example of such a reaction is the methylation of cellulose with methyl iodide.

$$\text{Cell-OH} + \text{OH}^{\ominus} \rightleftharpoons \text{Cell-O}^{\ominus} + \text{HOH} \qquad (1)$$

$$\text{Cell-O}^{\ominus} + \text{CH}_3\text{-I} \longrightarrow \text{Cell-O-CH}_3 + \text{I}^{\ominus} \qquad (2)$$

The reaction is a substitution; iodide is replaced by the cellulose anion $\text{Cell-O}^{\ominus}$.

Other examples of such cellulose etherifications are: ethylation, carboxymethylation and benzylation. These reactions are irreversible and give rate-controlled distribution of substituents. Similarly, reactions involving ring opening of the reagent prior to forming the cellulose ether are irreversible. A commercial example of such a reaction would be hydroxyethylation of cellulose with ethylene oxide.

A reversible etherification reaction is characterized by the Michael addition. This reaction is reversible and proceeds by way of an alkali-catalyzed addition of an activated vinyl group to the cellulosic hydroxyls (26). Perhaps the foremost example of this reaction type is the cyanoethylation of cellulose with acrylonitrile.

$$\text{Cell-OH} + \text{OH}^{\ominus} \rightleftharpoons \text{Cell-O}^{\ominus} + \text{HOH} \qquad (1)$$

$$\text{Cell-O}^{\ominus} + \text{CH}_2\text{=CH-C}\equiv\text{N} \rightleftharpoons \text{Cell-O-CH}_2\text{-}\underset{\ominus}{\text{CH}}\text{-C}\equiv\text{N} \qquad (3)$$

$$\text{Cell-O-CH}_2\text{-}\underset{\ominus}{\text{CH}}\text{-C}\equiv\text{N} + \text{HOH} \rightleftharpoons \text{Cell-O-CH}_2\text{-CH}_2\text{-C}\equiv\text{N} + \text{OH}^{\ominus} \qquad (4)$$

All reactions of the Michael type are reversible and give equilibrium-controlled substituent distributions.

SUBSTITUENT DISTRIBUTION

For a kinetically controlled system (nucleophilic substitution) the quantitative distribution of components among the three possible sites of reaction (hydroxyl groups at C-2, C-3, and C-6) are often taken as an

indication of the relative hydroxyl group reactivities. The experimentally observed molar distribution of carboxymethyl groups at the three reaction sites (2, 3, and 6) of carboxymethyl cellulose are reported to be 2:1:2.5 (27). These quantitative data are often translated as hydroxyl group reactivity, indicating that the C-6 hydroxyl is slightly more reactive than either the C-2 or C-3.

Considerable experimental evidence indicates the C-2 hydroxyl group is the most acidic in cellulose (28). As a result, many equilibria and rate controlled reactions, which involve the alkoxide ion, appear to react preferentially at this site. Exceptions are reactions in which steric hindrance is important; i.e., tritylation and tosylation which react primarily with the C-6 hydroxyl groups (29). The preferential reactivity of C-2 is particularly evident in the methylation of polysaccharides by the Williamson synthesis. Although this preference has been reported for both homogeneous and heterogeneous cellulose methylation, it does not hold true for all other etherifications (30-32). For instance, the closely related hydroxyethylation has indicated a preference for the C-6 primary hydroxyl group, when ethylene oxide is used as the reagent, while ethylation with ethyl chloride prefers the C-2 position (33,34).

The preference for the less sterically hindered C-6 hydroxyl group is manifest in most other etherifications. An increase of the size of the etherification substituent to hydroxyethyl, cyanoethyl, benzyl, or carboxymethyl seems to magnify this effect, thus indicating steric restraints due to cellulose-reagent interaction (27,35,36).

One important reason to investigate hydroxyl group reactivity is to gain improved control of cellulose etherification. Such control may then

result in more uniform modification. Since the degree of substitution (DS) of a cellulose ether as well as the substituent distribution determines its solubility and final utilization, commercial control over uniformity of substitution is important. For example, a nonuniform cellulose derivatization will result in a product possessing undesirable characteristics such as mixed solubility; that is, portions of the derivative will be soluble in the chosen solvent, while other portions (unreacted) will not. Cellulose derivatives should be uniformly substituted throughout the cellulose chain and among the hydroxyl groups.

THE DIMETHYL SULFOXIDE/PARAFORMALDEHYDE (DMSO/PF) SOLVENT SYSTEM

A limited research program was initiated to investigate homogeneous reactions of cellulose in N-methylmorpholine-N-oxide diluted with dimethyl sulfoxide (DMSO) (37). This new cyclic amine oxide cellulose solvent seemed ideal for studying cellulose reactions in solution since hydrogen bonding effects should be uniform and effects of crystallinity versus amorphous regions would be eliminated. Under such homogeneous conditions perhaps better control of a particular cellulose reaction could be achieved.

Since Johnson (23) demonstrated the feasibility of cellulose derivatization in the N-methylmorpholine-N-oxide solvent system, our objectives were the control of such reactions (derivatizations). Reactions initially investigated using N-methylmorpholine-N-oxide were cyanoethylation and carbamoethylation. It soon became apparent that etherification could be achieved but only to a very low degree of substitution (DS). Variation of the conditions and catalysts still failed to produce a product with a higher DS. Since no definite control over these reactions in the N-methylmorpholine-N-oxide system was exhibited, another class of cellulose reactions, that of cross-linking, was then investigated.

INITIAL OBSERVATION

Dissolution of cellulose in N-methylmorpholine-N-oxide was accomplished by slow addition of powdered cellulose to the melted cyclic amine oxide (85°C). This procedure required 1-2 hours since only small amounts of cellulose could be added at a time. Stirring and dilution with DMSO was necessary in the later stages. After sufficient dilution, the cellulose solution could be cooled to room temperature without solidification. If DMSO dilution was performed prior to cellulose addition, dissolution required 2-3 hours with stirring at 85-90°C.

Of the cross-linking reagents investigated (aqueous formalin, formaldehyde and toluene diisocyanate), only formaldehyde (from paraformaldehyde) was compatible with the N-methylmorpholine-N-oxide system. Prior to attempting the homogeneous cross-linking, a check of component compatibility was performed. A sample of cellulose, cyclic amine oxide, DMSO and paraformaldehyde (PF) were heated together with stirring at 85°C. Since cellulose dissolution normally required 1-3 hours, it was very surprising to observe the complete dissolution of the cellulose within 10-15 minutes.

In an effort to determine what components were responsible for this tremendously accelerated dissolution, the experiment was repeated except that N-methylmorpholine-N-oxide was omitted. Upon being heated to the point where paraformaldehyde decomposed at an appreciable rate (liberating formaldehyde), the cellulose dissolved within 5-10 minutes. These were the circumstances and reaction conditions which led to the discovery of the new cellulose solvent, dimethyl sulfoxide/paraformaldehyde (DMSO/PF) (37).

PROPERTIES OF THE NEW SOLVENT

It was found that this new system was capable of dissolving a wide variety of cellulose samples ranging in degree of polymerization (DP_n) from 16 to 8,000. Samples of various pulps were also subjected to the dissolution procedure and found to partially dissolve (38).

One of the most encouraging aspects of this solvent system was the ease with which cellulose could be regenerated. By simply diluting the clear colorless cellulose-DMSO/PF solution with water, cellulose could be recovered. Analysis of the regenerated cellulose by IR and Raman spectroscopy indicated that the cellulose was unsubstituted. A comparison of the Raman spectrum of the regenerated cellulose to that of known cellulose II is illustrated in Fig. 1.

Another property of this solvent which made it attractive was its nondegrading nature. This was demonstrated by Swenson using viscometry (39).

The new cellulose solvent possessed many desirable characteristics. It was easy to prepare, clear and colorless, nondegrading, it allowed complete regeneration of the cellulose and it was composed of two very common chemicals, DMSO and formaldehyde (paraformaldehyde).

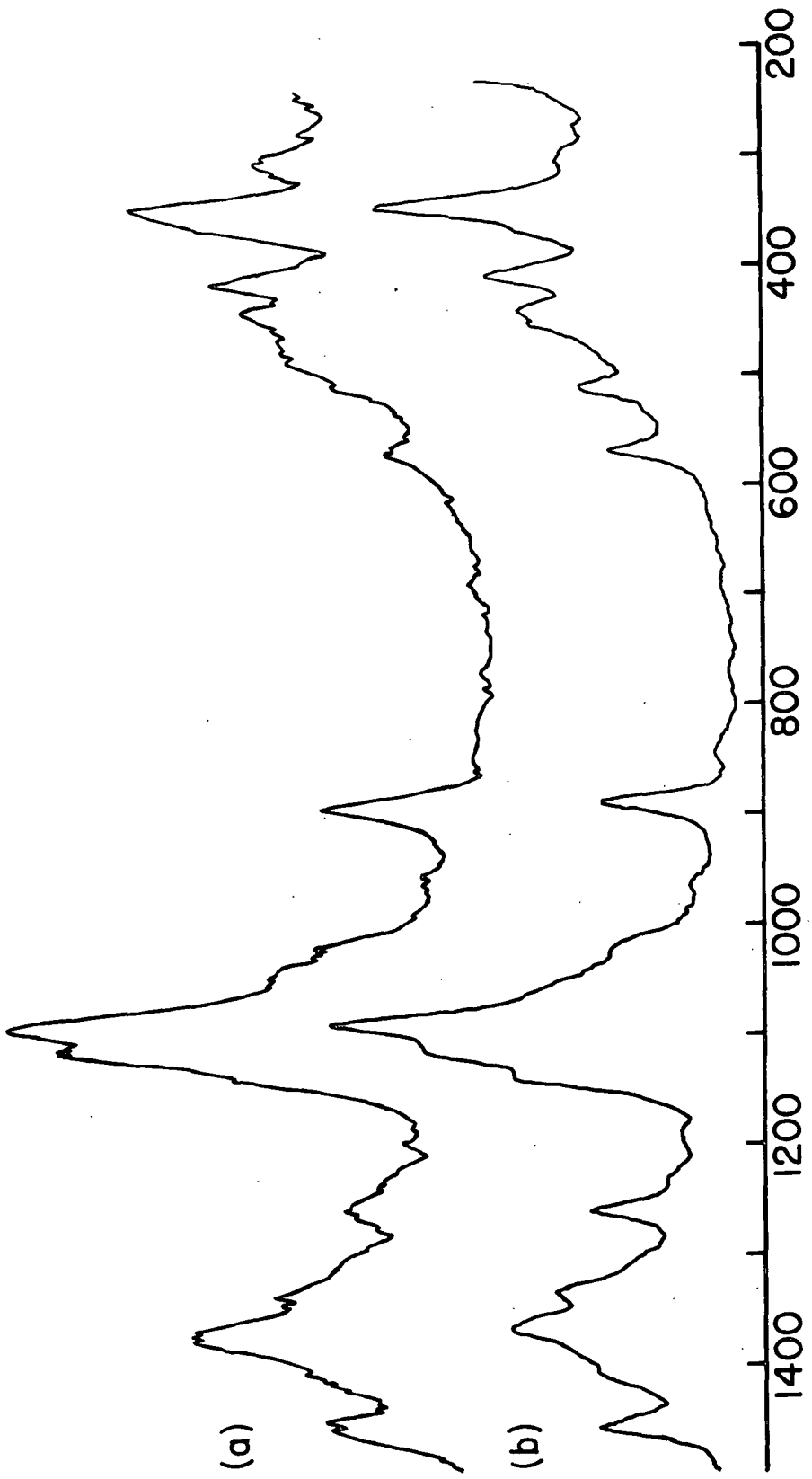


Figure 1. Laser Raman Spectra of (a) Regenerated Cellulose from DMSO/PF Solvent and (b) a Highly Crystalline Cellulose II

OBJECTIVES OF THESIS

The objectives of this thesis were twofold: first to understand why cellulose dissolves in the DMSO/PF solvent system and second, to investigate homogeneous cellulose etherification in the DMSO/PF solvent.

The first part of the research program was designed to explore further the plausible mechanisms of cellulose dissolution in the DMSO/PF solvent. Based on what is known about other solvents, two main mechanisms for the dissolution can be proposed — interaction with a hydrogen bonded component complex or formation of an uncharged cellulose derivative. Experimental programs were designed to elucidate which mechanism(s) was operable in the DMSO/PF solvent.

The second portion of the research program was designed to obtain: (1) homogeneous etherification of cellulose in DMSO/PF, (2) control over the specific etherification by modification of reaction conditions, and (3) substituent group distribution data which would reflect the hydroxyl group reactivities in the organic solvent. Carboxymethylation and methylation were the etherifications studied since considerable heterogeneous reaction data were available on these systems.

RESULTS AND DISCUSSION

GENERAL

This research program is divided into two main areas of investigation: (1) the cellulose-DMSO/PF solvent interaction, and (2) the homogeneous etherification of cellulose in the DMSO/PF solvent.

CELLULOSE DISSOLUTION IN DMSO/PF

This investigation was begun at a point where little was known about the solvent except that it could dissolve cellulose. In attempting to answer the question of why cellulose dissolves in this system, I considered two possible mechanisms. One involves the solvent components forming a complex which was capable of dissolving cellulose. Such a complex may well be involved in the methylamine-DMSO system which dissolves cellulose (20). The other functions by way of derivatization of the cellulosic hydroxyl groups, producing a cellulose derivative which was soluble in the medium.

SEARCH FOR A DMSO/PF COMPLEX

Raman analysis was based upon the assumption that if any DMSO/PF complexes were formed during interaction, the resulting DMSO bands would be significantly altered. For example, if a sulfur-oxygen-formaldehyde interaction was involved, the S=O stretch region (1050 cm^{-1}) would reflect this change. Similarly, if the methyl groups were associated with formaldehyde or paraformaldehyde in some way, one would expect the C-H bands to undergo a shift in maxima or relative intensity.

Raman spectroscopic analysis was conducted on various DMSO/PF solutions (void of any cellulose) which had been prepared in an open vessel following

the basic cellulose dissolution procedure. Initial PF concentrations ranged from 10-25%. Since it was evident from observing the open vessel dissolution procedure that much of the formaldehyde was being lost to the atmosphere, a closed system adaptation of the procedure was employed. Again a series of four DMSO/PF solutions (without cellulose) were prepared using the closed vessel procedure, with initial PF concentrations of 3-15%.

The Raman spectra showed major bands at 675, 705, 1050, 2910, and 2995 cm^{-1} which were identical to the bands seen in a spectrum of pure DMSO. In the event that we were masking some subtle changes in the C-H bands of the DMSO, deuterated DMSO-d_6 was employed in similar sample preparations. As before, no changes were evident in the deuterated DMSO spectrum after PF addition and subsequent heating.

Although the possibility of a DMSO/PF complex was not eliminated by these results, we can conclude that it seemed unlikely that such complexes were the prime reason for dissolution.

CLOSED SYSTEM DISSOLUTION

Since the prior experiments did not indicate the presence of a DMSO-formaldehyde complex, the question remained: Could such a complex exist in low concentrations? For this reason it becomes important to know how much formaldehyde was in solution. If the concentration of formaldehyde in DMSO was critical to the dissolution procedure, then a closed system process could be employed to maximize the concentration. With this in mind, cellulose dissolution with DMSO/PF in a closed system was conducted. The primary goal was to determine the lower limiting PF concentration required for cellulose dissolution.

The vessel was a teflon-lined steel bomb equipped with a magnetic stirring apparatus and pressure gage. Figure 12 (Experimental section) illustrates the basic assembly.

Using this apparatus, a closed system dissolution of cellulose was achieved. When the initial charges of PF were varied, it was possible to determine the lower limit of PF necessary for cellulose dissolution. These data are given in Table I.

TABLE I

CLOSED SYSTEM DISSOLUTION OF CELLULOSE[a]

Trials	PF, g	% PF[b]	Observations	Mole Ratio, CH_2O:Angl
I	1.0	2.3	No dissolution	27:1
II	1.25	2.8	Partial dissolution	34:1
III	1.35	3.1	Complete dissolution	37:1
IV	1.5	3.4	Complete dissolution	41:1

[a]Cellulose was standard ICCA No. 1 pulp (DP_n 2300) 0.2 g in 40 ml (43.8 g) DMSO. Dissolution time constant 2 1/2 hr, 120°C.

[b]% PF based upon weight of DMSO and cellulose (44.0 g).

As expected, these results illustrate less PF was required to achieve dissolution of cellulose in the closed system as compared to the open procedure which required ca. 5% PF.

In an effort to estimate the amount of PF in solution (DMSO), the closed system cellulose dissolution was duplicated using the lower PF

requirement (3%) while the pressure was recorded throughout the procedure. Since the contribution to the total vapor pressure from DMSO at 120°C is slight (80 mm), the recorded pressure after 2 hours was taken as a measure of the vapor pressure of formaldehyde. Using the ideal gas law relationships, a quantitative approximation of the formaldehyde in the vapor state could be obtained. Subtraction of this amount from the initial PF charge gave the quantity of formaldehyde in solution. Data are presented in Table II. One major source of error was the volatilization of PF which was added to the reactor that was at 120°C; some loss of formaldehyde was evident before the reactor lid could be secured.

TABLE II

ESTIMATION OF FORMALDEHYDE IN SOLUTION (DMSO/PF)[a]

Trials	PF, g	% PF[b]	Recorded Pressure, psig	% PF in Vapor[c]	% PF in Solution (by Difference)	Mole Ratio, CH_2O:Angl in Solution
I	1.35	3.1	10	2.6	0.5	5.1:1
II	1.35	3.1	9	2.5	0.6	6.2:1
III	1.38	3.1	10.5	2.7	0.4	5.4:1

[a]Cellulose used was standard ICCA No. 1 pulp (DP_n 2300) 0.2 g in 40 ml (43.8 g) DMSO. Dissolution time was constant 2 1/2 hr at 120°C.

[b]% PF based upon weight of DMSO and cellulose (44.0 g).

[c]Calculated PF in the vapor employed the relationship PV = nRT where P was recorded, V = 745 ml and T = 393°K (120°C) based upon the assumption that by the time the reactor lid was secured there existed 1 atmosphere of CH_2O.

The results from these three duplicate runs in which cellulose was dissolved indicates that the DMSO contains ca. 0.5% PF. NMR analysis of the DMSO/PF solution (without cellulose) substantiated this value and illustrated the molecular species present to be predominantly formaldehyde hydrate, dimer

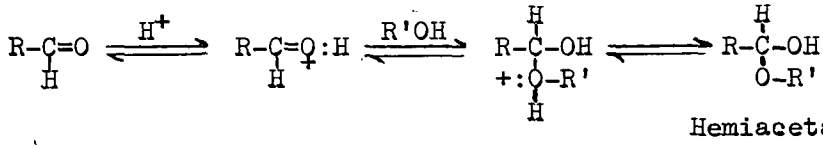
and trimer (38). Now that it is certain most of the formaldehyde leaves as a vapor, the closed system procedure appears an ideal way to accomplish large scale cellulose dissolution with a minimum of formaldehyde.

The preceding experimental approaches, while not disproving the existence of a possible DMSO-formaldehyde complex, certainly cast doubt upon it as being the main reason for cellulose dissolution in the new solvent.

CELLULOSE-PARAFORMALDEHYDE INTERACTION

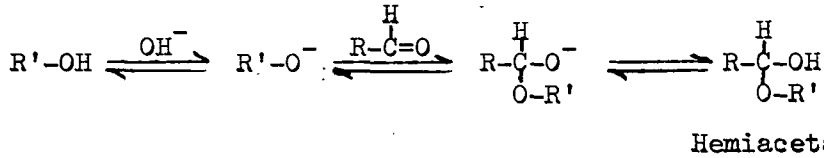
Another potential mechanism for cellulose dissolution involves formation of a soluble derivative. DMSO, while not being capable of dissolving cellulose, does possess the ability to swell cellulose (40). The other solvent component, paraformaldehyde (PF), appears more likely to possess the potential of reacting with the cellulose. Since it is after the PF decomposes to formaldehyde that cellulose dissolution is observed, it is likely that formaldehyde (and not PF) is the reactive species.

Such a proposed reaction between cellulose and formaldehyde could be an example of the general alcohol-carbonyl addition reaction. Aldehydes, in the presence of acid or base catalysts, add one mole of alcohol to form hemiacetals (41). The acid-catalyzed reaction proceeds via nucleophilic attack at the protonated carbonyl.



(4)

Similarly, base-catalyzed reactions involve the attack of the alcohol anion.



(5)

While cellulose dissolution takes place in an aprotic solvent (DMSO), small amounts of water (<1%) are present and could contribute to catalysis. Although one would expect cross-linking of this system (cellulose-formaldehyde) in acid conditions (42), acid was not present. Viscometric analysis of cellulose which had been dissolved, regenerated, dissolved, and regenerated again, indicated no detectable amount of cross-links (39).

It has been reported that PF can readily undergo depolymerization by carbanions in DMSO at room temperature, thus providing a convenient way of preparing methylol derivatives of compounds not otherwise easily obtained (43). Similar to the hydrates, hemiacetals are very unstable and often exist only in solution. Isolation is often facilitated by electron-withdrawing groups present on the α-carbon (41). There is very little information concerning the methylol or hemiacetal derivative of cellulose. It has been postulated as an intermediate in proposed cross-linking reactions which might either react further in the presence of acid to produce cross-links or decompose upon treatment with water (44). Although these intermediates have not been isolated, statements have been made concerning their instability in water (45,46).

NMR analysis of an analogous system containing formaldehyde and methanol illustrated the gradual conversion of methanol to the hemiacetal methylol methanol (38). Based upon this evidence, it was concluded that formaldehyde could interact with alcohols in the presence of DMSO to form hemiacetals. Apparently, the solvent system for cellulose involving chloral involves the same type of reaction leading to hemiacetal formation (22). Additional analysis of the DMSO/PF solvent (NMR) indicated that under conditions in which cellulose dissolves, relatively short polyoxymethylene chains are present (formaldehyde hydrate, dimer and trimer). In contrast, when predominately longer chain PF is present, no cellulose dissolution takes place (38).

The next question was, could methylol cellulose, if it existed, be isolated from the cellulose-DMSO/PF solution?

ISOLATION OF METHYLOL CELLULOSE FROM DMSO/PF SOLUTION

A sample of the cellulose-DMSO/PF solution was frozen and evacuated on a Brunswick freeze-dry apparatus. [The first demonstration of isolation of a solid in this manner was by Dimick (47).] Within three days a white fibrous material was obtained. In order to remove as much DMSO as possible, samples were freeze-dried up to thirteen days. All samples appeared physically identical.

Stability

A sample of the freeze-dried material was added to DMSO at room temperature and immediately dissolved without stirring; thus the freeze-dried sample could not be cellulose.

Numerous tests of the solubility of samples freeze-dried for three to thirteen days indicated all were soluble in DMSO. Solubility of the samples was also tested in: dimethyl formamide, sulfolane, nitromethane, and acetonitrile. The isolated material was found to be insoluble in all these solvents.

Methylol cellulose, a hemiacetal, has been proposed to be unstable in water (45,46). This was easily confirmed; the isolated material did not dissolve in water but appeared to generate tiny bubbles within the porous structure. After a short time, the sample was allowed to air dry. A check of its solubility in DMSO now revealed it was insoluble.

Laser Raman spectroscopic analysis of the freeze-dried material revealed several significant differences from regenerated cellulose. First, it was apparent that DMSO was still associated with the product since the characteristic bands at 675, 705 and 2995 cm^{-1} were very evident. Perhaps the most striking difference in the spectrum, compared to that of cellulose, was the medium to strong doublet observed at 910 and 950 cm^{-1}. While unsubstituted cellulose II possesses a strong singlet at 900 cm^{-1}, cellulose derivatives produce a broad doublet in the C-H deformation region around 900 cm^{-1}, the exact position of which depends upon the specific derivative. Comparison of Raman spectra of methyl, hydroxyethyl, and hydroxypropyl cellulose revealed such characteristic bands (48). Similar characteristic absorption bands are found in IR analysis of cellulose derivatives (49). From these bands it is easy to recognize a cellulose derivative.

In Fig. 2 are the Raman spectra of the freeze-dried material (as a pellet) and methyl cellulose. As indicated by the broad doublet, the isolated material is indeed a cellulose derivative.

An IR analysis of the same materials (KBr pellet prepared under dry nitrogen) revealed subtle differences in the 900 cm^{-1} region compared with those observed in the Raman spectra. (Spectra are reproduced in Appendix I, Fig. 15.) For example, the sharp shoulder seen in regenerated cellulose at 900 cm^{-1} has been replaced by two slight inflections at 910 and 950 cm^{-1} in the freeze-dried sample.

On the basis of the previous experimental results, it was concluded that this isolated material was methylol cellulose. Evidence substantiating the existence of the methylol derivative came from the fact that formaldehyde (not PF) was critical to the dissolution process, and from the NMR analysis

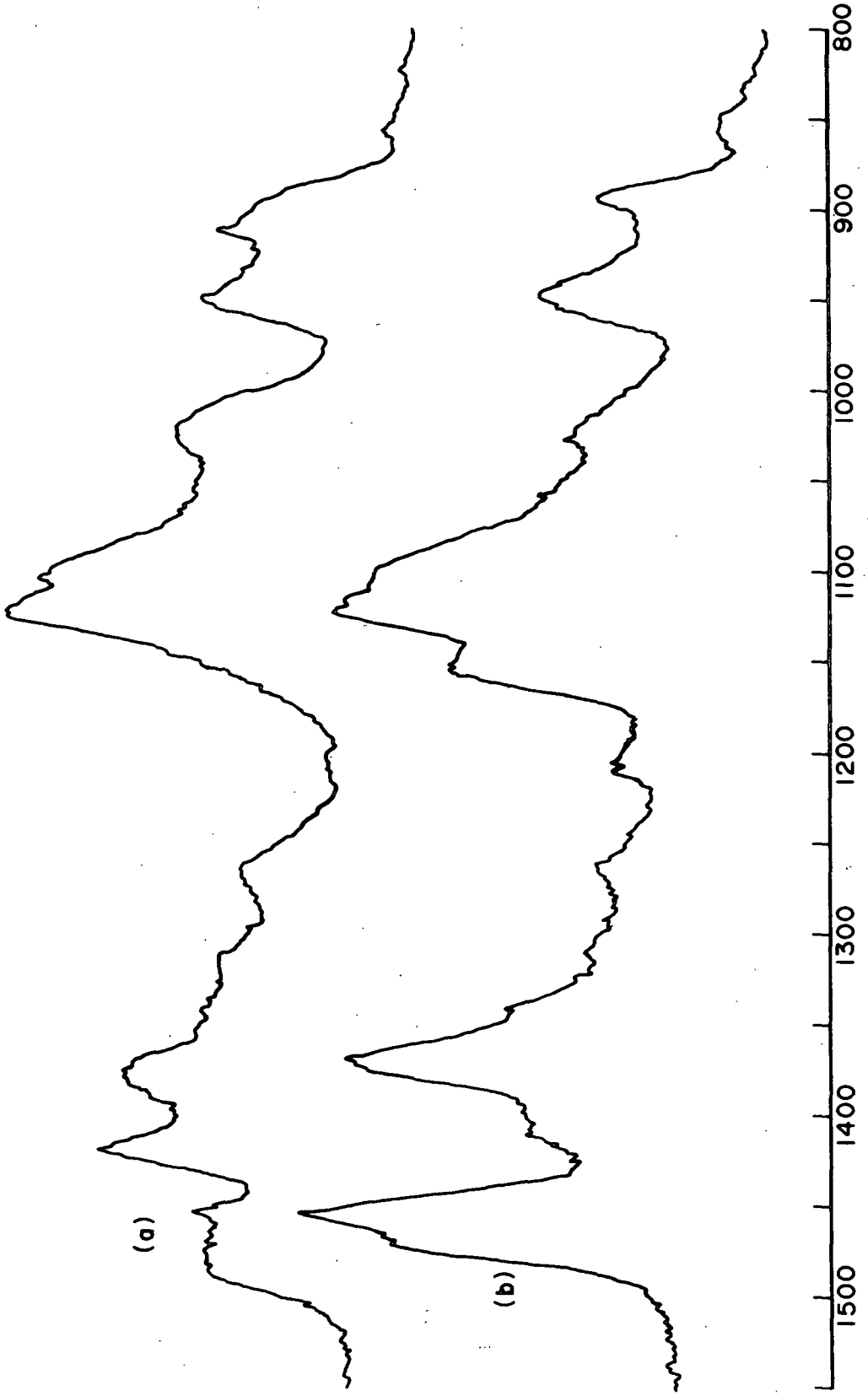


Figure 2. Laser Raman Spectra (1550-800 cm^{-1}) of (a) Methylol Cellulose and (b) Methyl Cellulose

illustrating the likelihood of this formaldehyde-cellulose interaction in DMSO (38).

The author envisions the cellulose-dissolving procedure as follows:

1. Swelling of the cellulose in DMSO.
2. Thermal decomposition of PF to formaldehyde.
3. Penetration of the swollen cellulose by formaldehyde.
4. Reaction of formaldehyde and the cellulose hydroxyls to produce the hemiacetal (methylol) units.
5. Stabilization of this hemiacetal by DMSO association through hydrogen bonding.
6. Dissolution of the hemiacetal cellulose (methylol cellulose) in DMSO.

Degree of Substitution of Methylol Cellulose (MOLC)

Methylol cellulose (MOLC) was observed to be unstable in water, resulting in the liberation of formaldehyde. This is a characteristic of similar hemiacetals (50). Since we had shown spectroscopically that the product of cellulose regenerated in water or alcohol did not contain any detectable methylol units, the quantitative measure of the formaldehyde liberated upon methylol removal in water was possible. This analysis would determine the number of methylol groups on the cellulose.

In order to check the validity of such a formaldehyde measurement, the freeze-dried MOLC was dissolved in DMSO-d_6 and analyzed by NMR. This sensitive analysis would illustrate the presence of any free formaldehyde (δ 9.54) not bound to the cellulose as a methylol group. The spectrum indicated the freeze-dried sample (seven days) did not possess any free formaldehyde but as before contained considerable DMSO seemingly incapable of being removed.

Figure 3 illustrates the NMR spectrum of MOLC showing the proton resonance absorptions for the various proton environments. Table III includes the assignments of the various peaks.

TABLE III

ASSIGNMENT OF PROTON NMR SIGNALS
FOR METHYLOL CELLULOSE IN DMSO-d_6

	Ppm, δ
DMSO-d_6	2.50
HOD	3.30
-$\underline{CH_2}$-O-	4.20-4.90
-CH_2-$\underline{OH}$	5.60-6.10

The absence of the signal at δ 9.54 (inset trace), observed in the DMSO/PF solvent solution and corresponding to the formaldehyde proton resonance, indicates the formaldehyde in the isolated material (MOLC) is bound as the methylol group. It further indicates formaldehyde is not liberated when MOLC is redissolved in DMSO.

The quantitative analysis for formaldehyde was accomplished using the standard sodium sulfite method (51). This procedure uses the quantitative reaction between formaldehyde and sodium sulfite which liberates sodium hydroxide upon the formation of the formaldehyde-bisulfite addition product.

$$CH_2{=}O + Na_2SO_3 + H_2O \longrightarrow NaOH + CH_2(NaSO_3)OH \qquad (6)$$

The alkali formed can then be titrated, quantitatively measuring the formaldehyde in the aqueous solution.

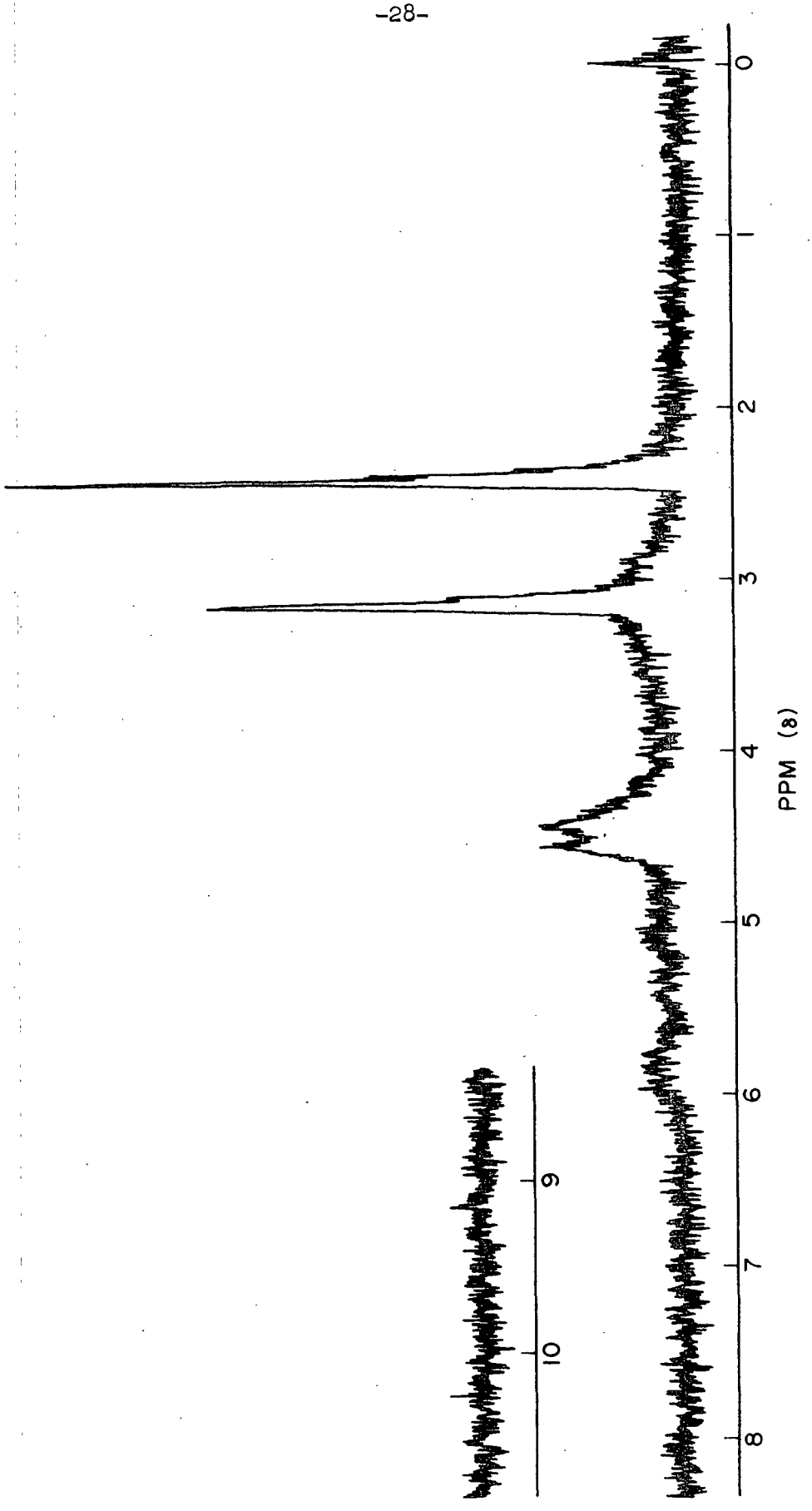


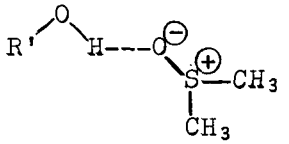
Figure 3. Nuclear Magnetic Resonance Spectra of Methylol Cellulose Dissolved in DMSO-d_6

Duplicate samples of different MOLC preparations (varying in concentration) were analyzed in the above manner. The data are given in Table VII, Appendix II.

Results were consistent and indicated approximately one methylol group per anhydroglucose unit. Actual molar ratios of formaldehyde to anhydroglucose gave a molar substitution (MS) range of 1.05 to 1.16.

Formation of methylol cellulose is shown in Fig. 4. Reasons for positioning the methylol group at the C-6 hydroxyl will be apparent in the following section.

In all of the freeze-dried isolations of MOLC, complete removal of DMSO has been difficult if not impossible. This may well relate to the function of DMSO in the solvent. Its proposed function is twofold: (1) it is a swelling agent which may initially enhance the cellulose accessibility to the formaldehyde, and (2) it should stabilize the methylol (hemiacetal) groups as they are formed through hydrogen bonding, thus imparting stability to the cellulose-DMSO/PF solution and MOLC as long as water uptake is prevented. Such hydrogen bonding between alcohols and DMSO (III) is well established and is of considerable utility in interpretating NMR spectra (52).



(III)

The amount of DMSO associated with the isolated MOLC was estimated, using NMR spectra comparison, to be 16%. This corresponds approximately to a molar ratio of MOLC (glucose unit):DMSO of 2:1.

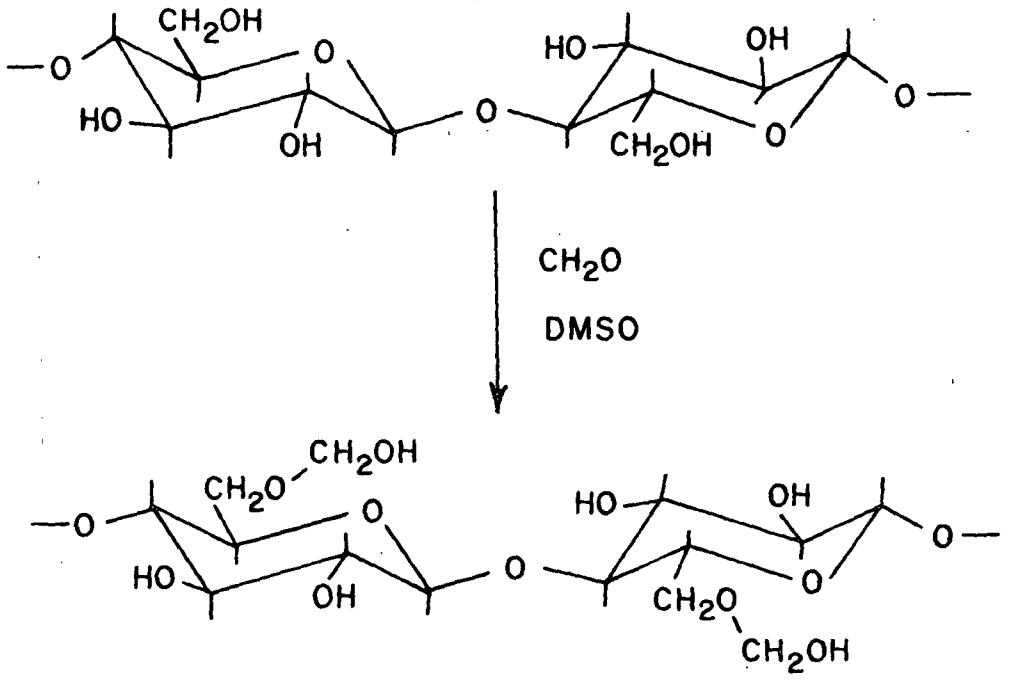
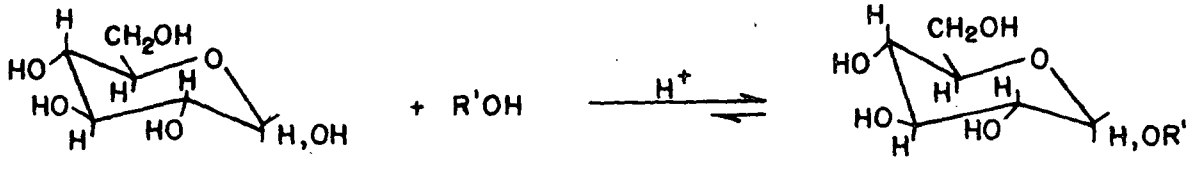


Figure 4. Mechanism of Cellulose Dissolution in DMSO/PF: Formation of Methylol Cellulose

Reactivity of Methylol Cellulose (MOLC)

With few exceptions, the hemiacetal hydroxyl group of monosaccharides is generally thought to be the most reactive. This hydroxyl group can be easily derivatized to form an acetal (glycoside). A simple illustration of the acetalation (glycosidation) of glucose would be the Fischer glycosidation employing an acid catalyst and an alcohol.



Glucopyranose Glucopyranoside

As can be inferred from this general reaction of monosaccharides, the hemiacetal hydroxyl group of the MOLC will probably be more reactive than either the C-2 and C-3 secondary hydroxyls or the C-6 primary hydroxyl groups. Very early in this investigation, it was noted that cellulose, dissolved in DMSO/PF, appeared to react with chloroacetic acid in the presence of triethylamine catalyst. The product obtained, while being DMSO-soluble, was also water-soluble and was thought to be carboxymethyl cellulose (CMC). An IR analysis of this material after precipitation into ethanol revealed the presence of weak carbonyl absorption characteristic of a reference sample of low DS CMC. Figure 5 shows the spectra of this product and commercial low DS (0.3) CMC.

Water solutions of this material were found to be stable for only 1-2 hours, after which precipitation occurred. While hydrolysis of CMC should produce several carboxymethyl glucose components, acid hydrolysis of this material followed by GLC analysis showed only glucose with no significant amounts of carboxymethyl glucose.

The seemingly contradictory nature of these results fits well with the proposed hemiacetal theory of cellulose dissolution. One could easily envision the reaction with the hemiacetal hydroxyl group producing the acetal, carboxymethylmethylol cellulose. This acetal would possess the characteristics of water solubility that CMC has and upon isolation in ethanol would retain sufficient acetal to produce carbonyl absorption indicative of low DS CMC. In addition, during acid hydrolysis, the acetal-methylol links would hydrolyze, leaving only glucose to be detected. However, one observation still requires clarification: why was this acetal soluble and stable in aqueous solution only 1-2 hours?

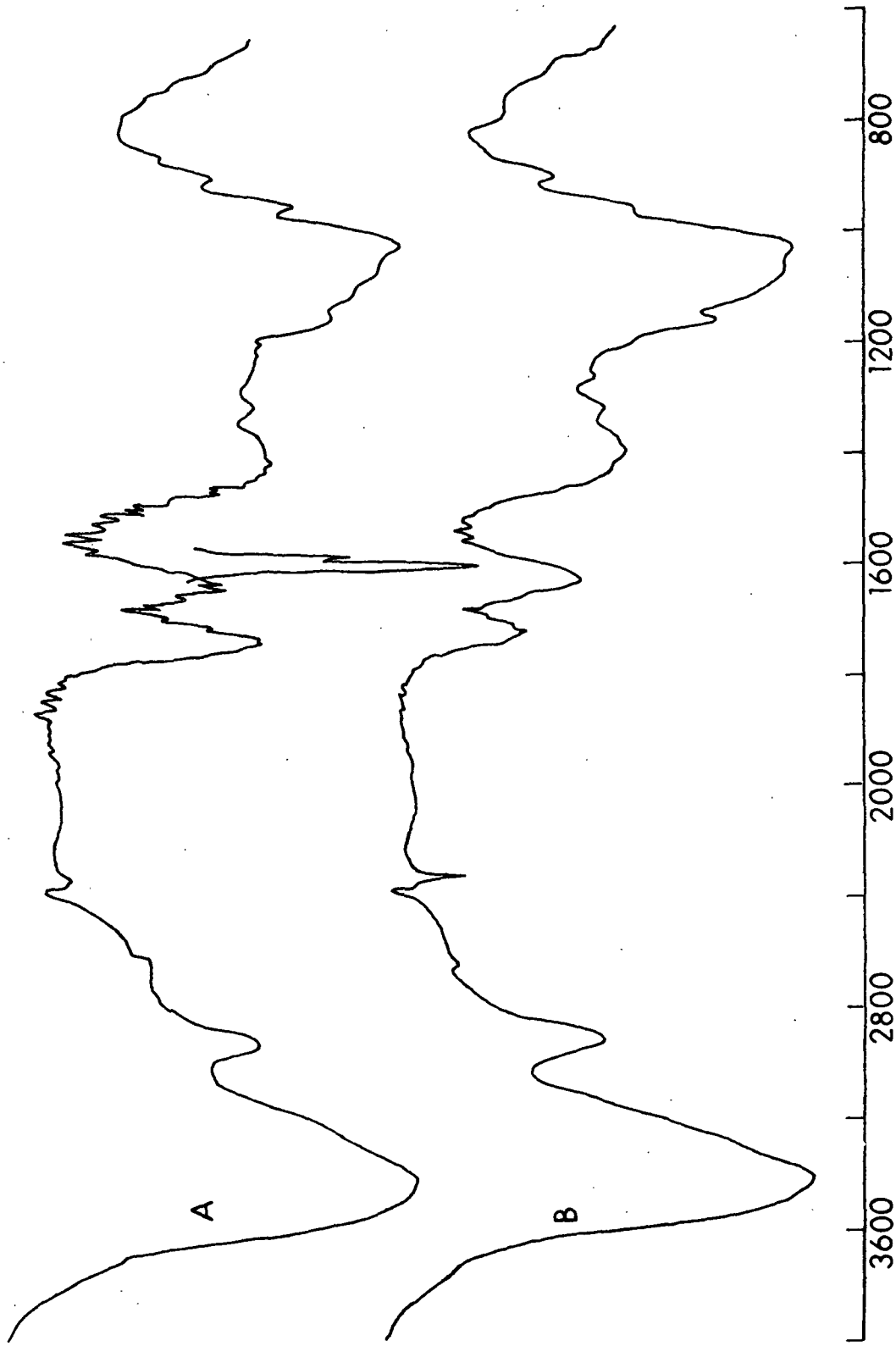
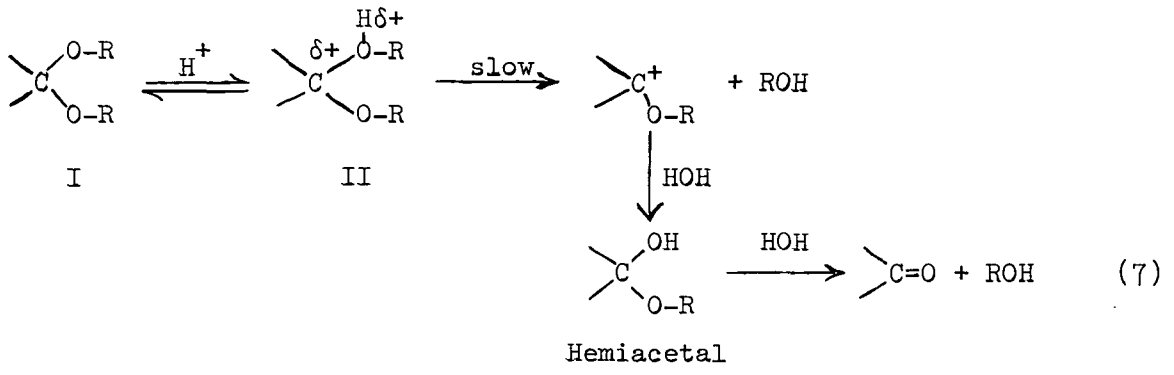


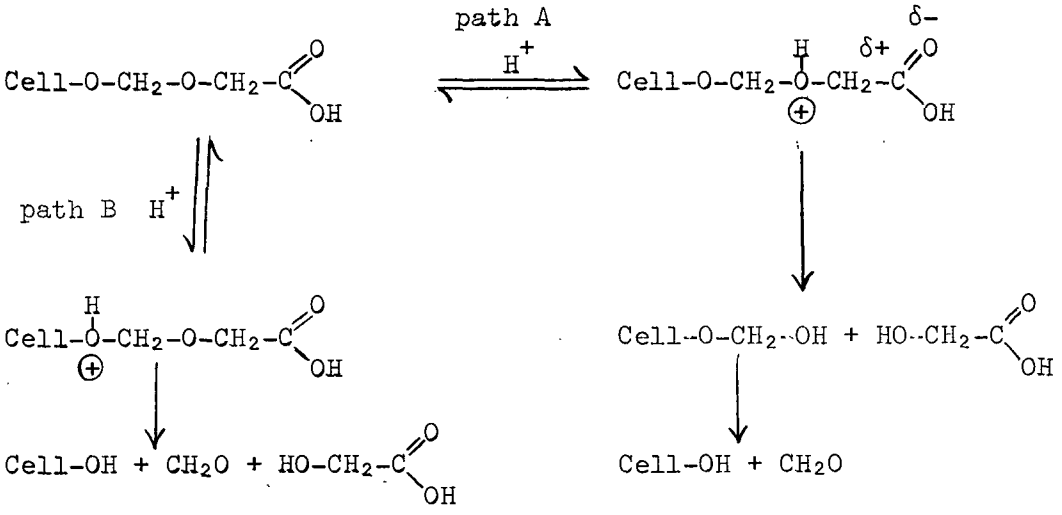
Figure 5. Infrared Spectra of (A) Commercial 0.3 DS Carboxymethyl Cellulose (Acid Form) and (B) Carboxymethylmethylol Cellulose (Acid Form) Prepared in DMSO/PF at 20°C

Acetals can be hydrolyzed in aqueous acid solutions according to the pathway shown below (53). Such hydrolyses are generally subject to specific hydronium ion catalysis which supports the mechanism shown.



(7)

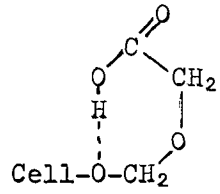
The relative apparent ease with which formals hydrolyze markedly depends upon the substituent character. Correlation of this reactivity with substitution indicated that the dependence is due to polar effects on the protonation of the substrate and formation of the carbonium ion (54). Of the following two hypothetical pathways leading to the hydrolysis of the acetal carboxymethylmethylol cellulose, path A is more compatible with the ease of hydrolysis.



(8)

The instability of the carbonium ion formed via path A could well be affected by the carboxyl substituent, thus accelerating the hydrolysis.

Also, with carboxy substituents, intramolecular catalysis may be important. This has been shown to be a viable pathway of acetal and ester hydrolysis (55). By analogy, the carboxymethylmethylol cellulose system may hydrolyze as shown.



$$+ HOH \longrightarrow Cell\text{-}OH + CH_2{=}O + HO\text{-}CH_2COOH \qquad (9)$$

Carboxymethylmethylol cellulose

Either of the preceding postulated mechanisms [Equations (8, path A) and (9)] could account for the observed accelerated hydrolysis.

CELLULOSE ETHERIFICATION IN THE DMSO/PF SOLVENT SYSTEM

CARBOXYMETHYLATION

Preparation

As we observed in the previous section, the mild carboxymethylation of cellulose-DMSO/PF in solution with chloroacetic acid and triethylamine did not produce etherification. Rather, acetalation occurred on the methylol (hemiacetal) hydroxyl group. In view of these results it was felt that a stronger nucleophile was needed to bring about the desired etherification.

The carboxymethylation of cellulose in DMSO/PF solution was accomplished using sodium hydride and methyl bromoacetate. Of the strong nucleophiles available, sodium hydride was chosen since it was DMSO soluble. Methyl bromoacetate was employed because of its increased reactivity to chloroacetic reagents.

The first step in the carboxymethylation of cellulose in DMSO/PF was that with sodium hydride [Equation (10)]. This formed the reactive species sodium cellulose alcoholate. Analogous to Equation (10) the hemiacetal

$$\text{Cell-OH} + \text{NaH} \longrightarrow \text{Cell-O}^{-}\text{Na}^{+} + \text{H}_2 \qquad (10)$$

(methylol) hydroxyl groups may undergo reaction to either remove the methylol group forming the alcoholate, or form the methylolate.

$$\text{Cell-O-CH}_2\text{-OH} + \text{NaH} \quad (\text{MOLC}) \;\begin{cases} \longrightarrow \text{Cell-O}^{-}\text{Na}^{+} + \text{CH}_2\text{O} \\ \longrightarrow \text{Cell-O-CH}_2\text{-O}^{-}\text{Na}^{+} \end{cases} \qquad (11)$$

Later discussion (p. 43) of the reaction results will illustrate the role of the methylol groups during etherification.

During the course of the reaction with sodium hydride it was observed that the reaction solution became gel-like in nature. This was probably due to the formation of the alkali methylol cellulose.

It has been reported that both acids and sodium salts of CMC (DS 0.8) are insoluble in DMSO (56). Since preparation and analysis of methyl ester CMC (DS 0.7) revealed it to be DMSO soluble, attempts were made to prepare the CMC methyl ester in DMSO/PF by employing methyl bromoacetate as the carboxymethylating reagent. The resulting CMC methyl ester (DMSO soluble) would allow continued homogeneity of the reaction.

Once the alkali methylol cellulose was prepared, the methyl bromoacetate was added. Within an hour, the gel appeared to dissolve and the reaction mixture became homogeneous again. However, as the etherification proceeded

(16-19 hr) a precipitate gradually formed, which was apparently the sodium salt of CMC. Since CMC methyl ester is DMSO soluble, demethylation must have occurred. Two possible reactions may be responsible for this loss of methyl ester. Either the water in the system reacts with sodium hydride to form the hydroxide, resulting in saponification of the ester, or the dimethyl sulfoxide anion (dimsyl) produced by DMSO-sodium hydride interaction has caused the removal of the methyl ester. The precipitated material was analyzed by IR following purification steps necessary to remove excess sodium hydride and methyl bromoacetate. Upon work-up and dialysis (Experimental section) an acidic CMC was isolated.

The carboxymethylation reactions were performed at 19.50, and 80°C. The 19°C reaction was the lowest temperature found compatible with the DMSO which freezes at 18°C. Reaction at 80°C appeared much too drastic as evidenced by the odorous degradation products.

Of interest concerning the carboxymethylation of cellulose in DMSO/PF is the variety of reactions that can occur. Figure 6 illustrates some of these reactions where the isolated product is the free acid. Etherification of the cellulosic hydroxyl groups, acetalation of the methylol groups, or removal of the methylol prior to subsequent etherification of the hydroxyl group can occur.

The preference for acetal formation rather than ether formation using chloroacetic acid, triethylamine and MOLC suggested that the acetals could be used to block the methylol groups and thereby allow only etherification of the cellulosic hydroxyl groups. Such a reaction was tried using methyl chloroacetate as the reagent since excess reagent could be removed by freeze-drying. Reaction was allowed to proceed with methyl chloroacetate

22 hours. The carboxymethylmethylol cellulose methyl ester was isolated by freeze-drying and identified by IR analysis. Analysis of the IR spectrum revealed the presence of carbonyl absorption (1745 cm^{-1}), characteristic of the carboxymethyl methyl ester substituent.

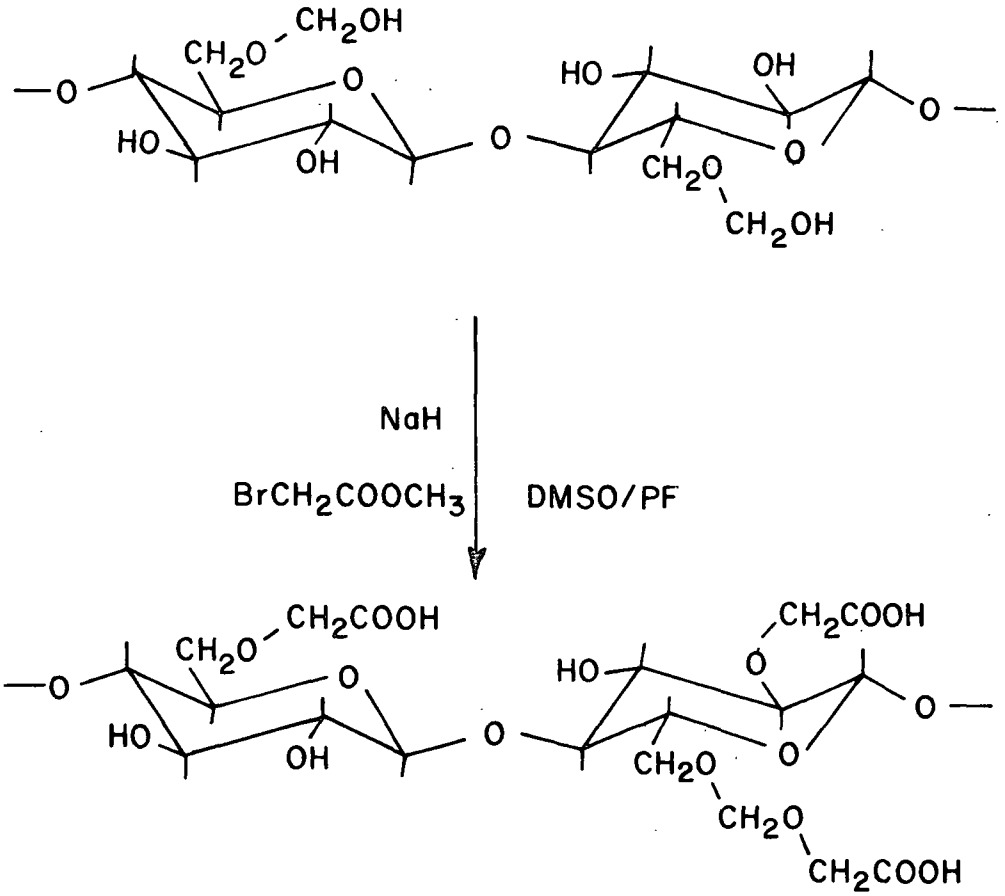


Figure 6. Illustration of the Carboxymethylation of Methylol Cellulose (Cellulose Dissolved in DMSO/PF)

With the methylol hydroxyls stabilized as the carboxymethylmethylol cellulose methyl ester, subsequent etherification employing sodium hydride and methyl bromoacetate was accomplished.

Analysis

Prior to the actual quantitative analysis, the three hydrolysis components of low DS CMC were synthesized. Although the GLC retention times of each prepared component (2-O-CMgl, 3-O-CMgl and 6-O-CMgl) were equivalent to that of the analogous CMC hydrolysis component, mass spectrometry provided confirmation

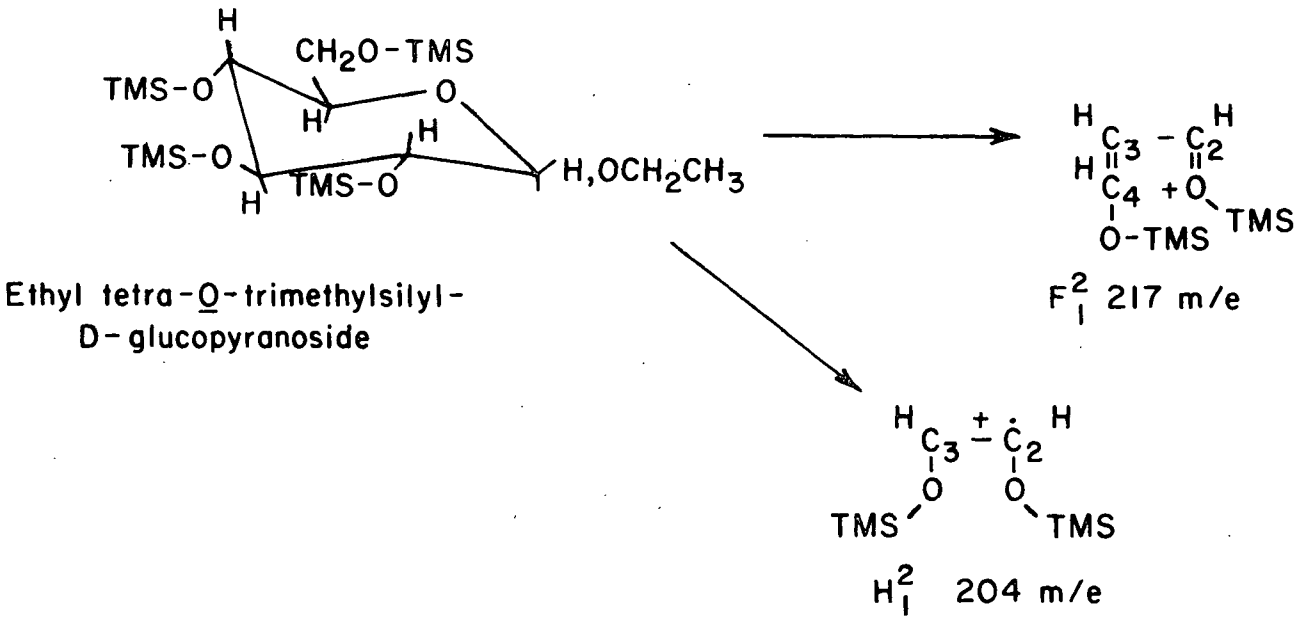
of the respective structures. Mass spectra were obtained for the three mono-substituted components of CMC hydrolysis as well as the authentic synthesis samples. This technique has been used by Ramnas and Samuelson (57) in their work with hydroxyethyl cellulose.

It has been shown experimentally in mass spectrometry (MS) analysis that the main fragmentation paths for the trimethylsilyl (TMS) derivatives of aldohexopyranoses and many of the substituted aldohexopyranoses are the same; that is, the character of the fragmentation of the pyranoid ring is only slightly affected by the nature of the substituents on the oxygen atoms (58-61). Therefore, the mass spectrum for one substituted glucose can be correlated with that of a different substituted glucose. For example, the mass spectral characteristics of 6-O-hydroxyethyl-D-glucopyranose or 6-O-methyl-D-glucopyranose may be used as a reference for the identification of the analogous 6-O-carboxymethyl-D-glucopyranose component.

In order to use the mass spectral data a slight change in the derivatization was necessary. This change involved the formation of ethyl esters/glycosides in order to eliminate the mass equality of the TMS ethers and the carboxymethyl methyl ester substituents. Since identification of fragments is based on mass alone, the TMS and carboxymethyl ethyl ester groups could now be distinguished from each other.

Perhaps the most important fragments are the ions designated H_1^2 and F_1^2 (G_1) (62), shown in Equation (12).

Using these main fragmentation routes, the structure of each compound could be determined. The characteristic fragments, when compared with knowns cited in the literature, may be used to determine the position of substitution



(12)

(57,62). From the mass spectral data it was concluded that each prepared component was in fact identical with the corresponding CMC hydrolysis component which had the same retention time. Data are given in Appendix III, Table VIII.

Response factors for the three monosubstituted carboxymethyl glucose components (2-O-CMgl, 3-O-CMgl and 6-O-CMgl) were determined. Table IX in Appendix IV illustrates the calculated response of each component. Analysis of the CMC samples was by GLC and the necessary work-up along with the GLC conditions are given in the Experimental section.

Figure 7 illustrates the hydrolysis products obtained from the analysis of Hercules 0.4 DS CMC by GLC. Quantitative measurement of the individual component peaks provides a means of obtaining substituent distributions of the carboxymethyl groups among the three available hydroxyl groups (C-2, C-3 and C-6). Table IV summarizes the results. These results indicate that the C-2 hydroxyl group is slightly more reactive than the C-6. Although this does not agree with the previously reported position preference of heterogeneously prepared CMC [C-6 preference 2:1:2.5 (27)], the conditions of preparation of this commercial derivative, which influence the substituent distribution, are not known.

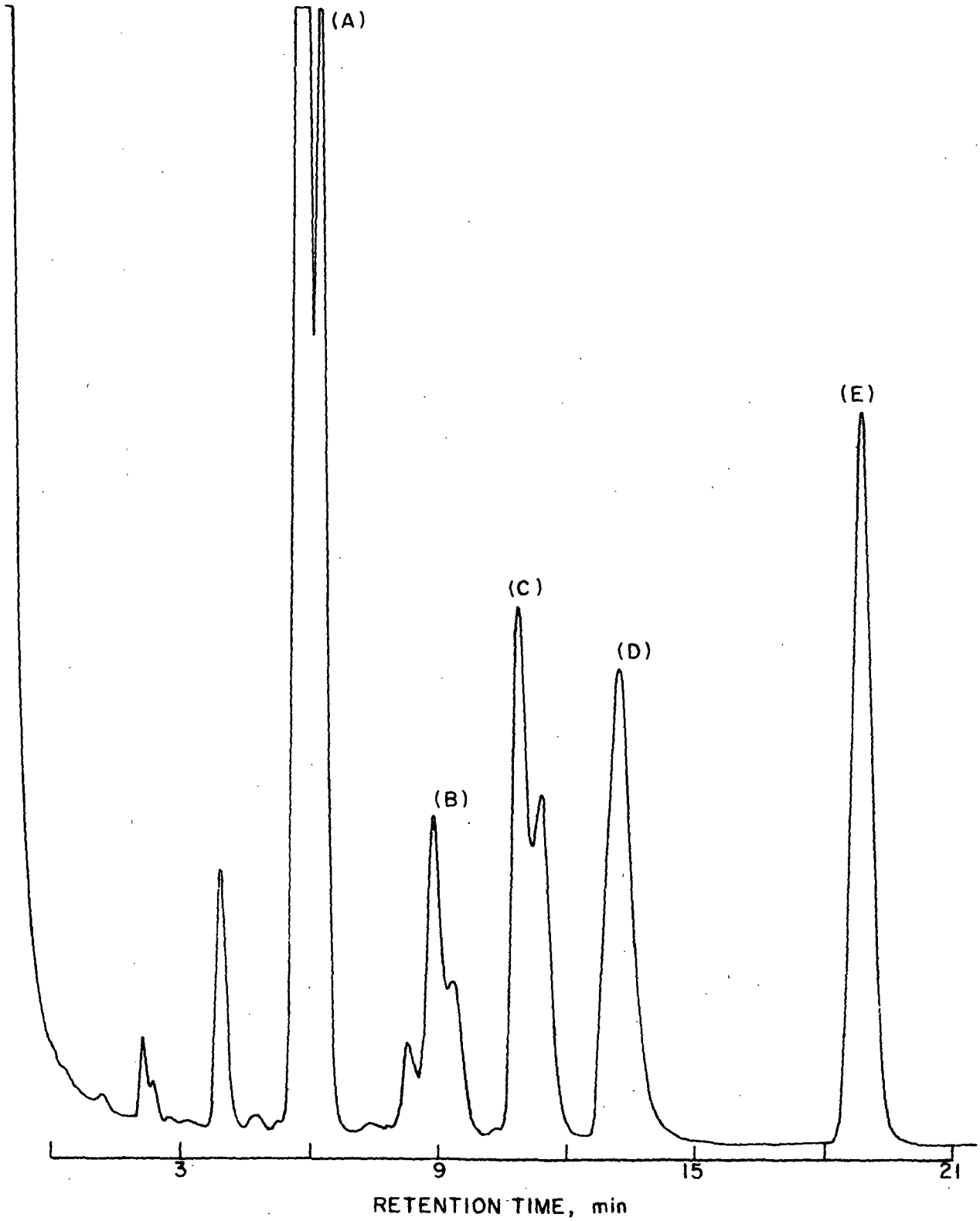


Figure 7. Gas Chromatogram of Hydrolyzate of Commercial 0.4 DS Carboxymethyl Cellulose Showing Peaks for: (A) Glucose, (B) 3-O-CMgl, (C) 2-O-CMgl, (D) 6-O-CMgl all as Methyl Ester/Glycoside TMS Derivatives and (E) Cyclohexyl Glucopyranoside (Std.) as TMS Derivative

TABLE IV

ANALYSIS OF COMMERCIAL CMC

	Experimental DS	Mole Ratios, 2:3:6[a]
Hercules 4M6 (dialyzed)	0.40	1.96:1:1.45
Hercules 4M6 (undialyzed)	0.34	1.90:1:1.64
Hercules 4M6 (dialyzed)	--	2.20:1:1.57
	Average	2.02:1:1.55

[a]Each determination was an average of three analyses.

Analysis of the CMC samples prepared in DMSO/PF is illustrated in Fig. 8. The chromatograms were obtained from the carboxymethylation products of MOLC: (a) at 19°C, (b) at 50°C, and (c) of carboxymethylmethylol cellulose methyl ester (CMMOLC) at 19°C. The quantitative measure of the substituents at each hydroxyl position is converted to molar ratios and can be seen in Table V.

The first series of samples prepared at 19°C all seemed to possess a limiting low DS of around 0.15. This can best be explained in light of the solubility characteristics of CMC. (Acid and salt forms of CMC are insoluble in DMSO, while the methyl ester is soluble.) In an effort to keep the CMC soluble, preparation of the methyl ester of CMC was attempted using methyl bromoacetate. However, this attempt failed as evidenced by the precipitation of the reaction product. Since the CMC did precipitate after approximately the same reaction time, further carboxymethylation was hindered. Thus the extent of carboxymethylation was limited to that DS at which CMC became DMSO insoluble.

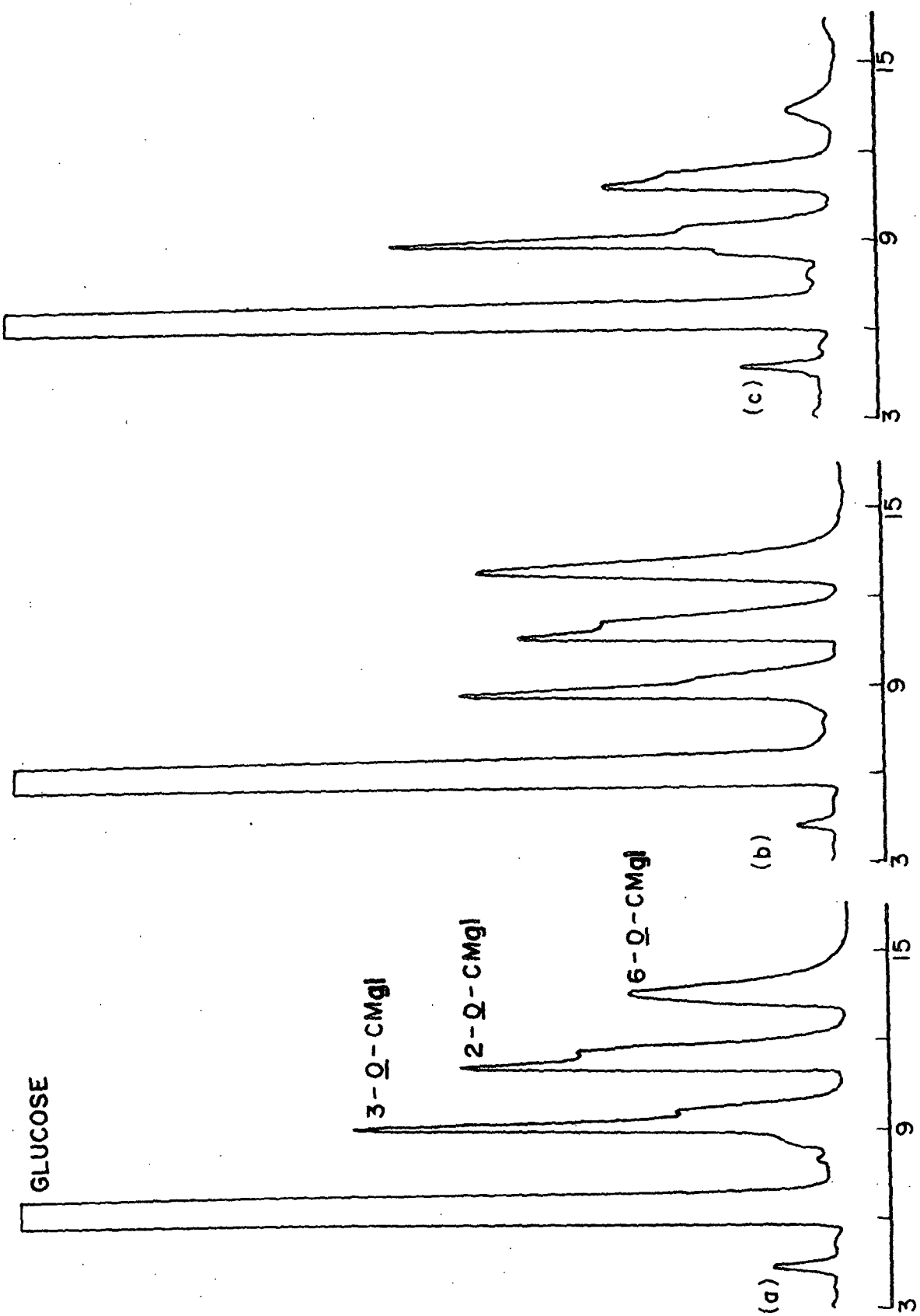


Figure 8. Gas Chromatograms of Hydrolyzates of Carboxymethyl Cellulose Prepared by Carboxymethylation of: (a) Methylol Cellulose at 19°C, (b) Methylol Cellulose at 50°C, and (c) Carboxymethylmethylol Cellulose Methyl Ester at 19°C Showing Peaks for Glucose, 3-O-CMgl, 2-O-CMgl and 6-O-CMgl all as Methyl Ester/Glycoside TMS Derivatives

TABLE V

ANALYSIS OF CMC PREPARED IN DMSO/PF

Carboxymethylation of		Experimental DS		Mole Ratios, 2:3:6[a]
(a) 19°C	MOLC	0.14-0.16		1.67:1.47:1
				1.71:1.55:1
				1.68:1.40:1
			Average	1.69:1.47:1
(b) 50°C	MOLC	0.21		1.07:1:1.21
				1.14:1:1.22
			Average	1.11:1:1.21
(c) 19°C	CMMOLC	(0.1-0.3)[b]		6.51:9.26:1
				6.56:9.51:1
				6.47:9.40:1
			Average	6.52:9.36:1

[a] Each determination is an average of three analyses of a common sample.

[b] This is an estimated range based on comparison with other chromatograms.

The low reactivity of the C-6 primary hydroxyl is evident in the first chromatogram (Fig. 8a). Also, from Table V it can be seen that the C-2 and C-3 secondary hydroxyl groups are at least 1-1/2 times as reactive as the C-6. The reduction in the C-6 carboxymethylation reflects the preferential location of the methylol group at the C-6 oxygen.

Chromatogram (b) illustrates that C-6 substitution increased markedly at the reaction temperature of 50°C, at which almost uniform substitution is realized among the C-2, C-3, and C-6 hydroxyls. These results are best explained by envisioning the removal of some methylol groups at this increased temperature such that more C-6 cellulose hydroxyls are free to react to form the ethers.

Chromatogram (c) in Fig. 8 illustrates the component distribution obtained upon carboxymethylation of the acetal carboxymethylmethylol cellulose methyl ester (CMMOLC) at 19°C. It can be easily seen that the stabilization of the methylol groups by acetal formation has a drastic effect upon the subsequent C-6 etherification. Since this acetal is not easily cleaved by sodium hydride, the etherification was directed primarily to the C-2 and C-3 hydroxyls which are not methylolated to a substantial degree.

This observation of selective etherification provides evidence that the methylol groups responsible for cellulose dissolution in DMSO/PF are in fact primarily located on the C-6 hydroxyl groups. The observed reduction in C-2 carboxymethylation (Fig. 8c) of the stabilized acetal derivative may indicate limited attachment of methylol groups at the C-2 hydroxyl group. It is interesting to note that in cellulose cross-linking reaction with formaldehyde, the primary hydroxyl group (C-6) has also been reported to be 10-20 times as reactive as the secondary hydroxyls (63).

Besides these data elucidating the position of the methylol groups, these reactions illustrate the feasibility of controlling homogeneous reactions with cellulose in DMSO/PF. Either one can achieve uniform substituent distribution among the 2, 3 and 6 hydroxyls (at 50°C) or restrict the reaction (etherification) to the secondary C-2 and C-3 hydroxyl positions (at 19°C).

For comparison with another solvent, cellulose was dissolved in N-methylmorpholine-N-oxide/DMSO and carboxymethylated according to the same procedure. Difficulty in maintaining the cellulose solution made it necessary to run the reaction at 70°C. This resulted in noticeable DMSO degradation, and the CMC product obtained was discolored. Figure 9

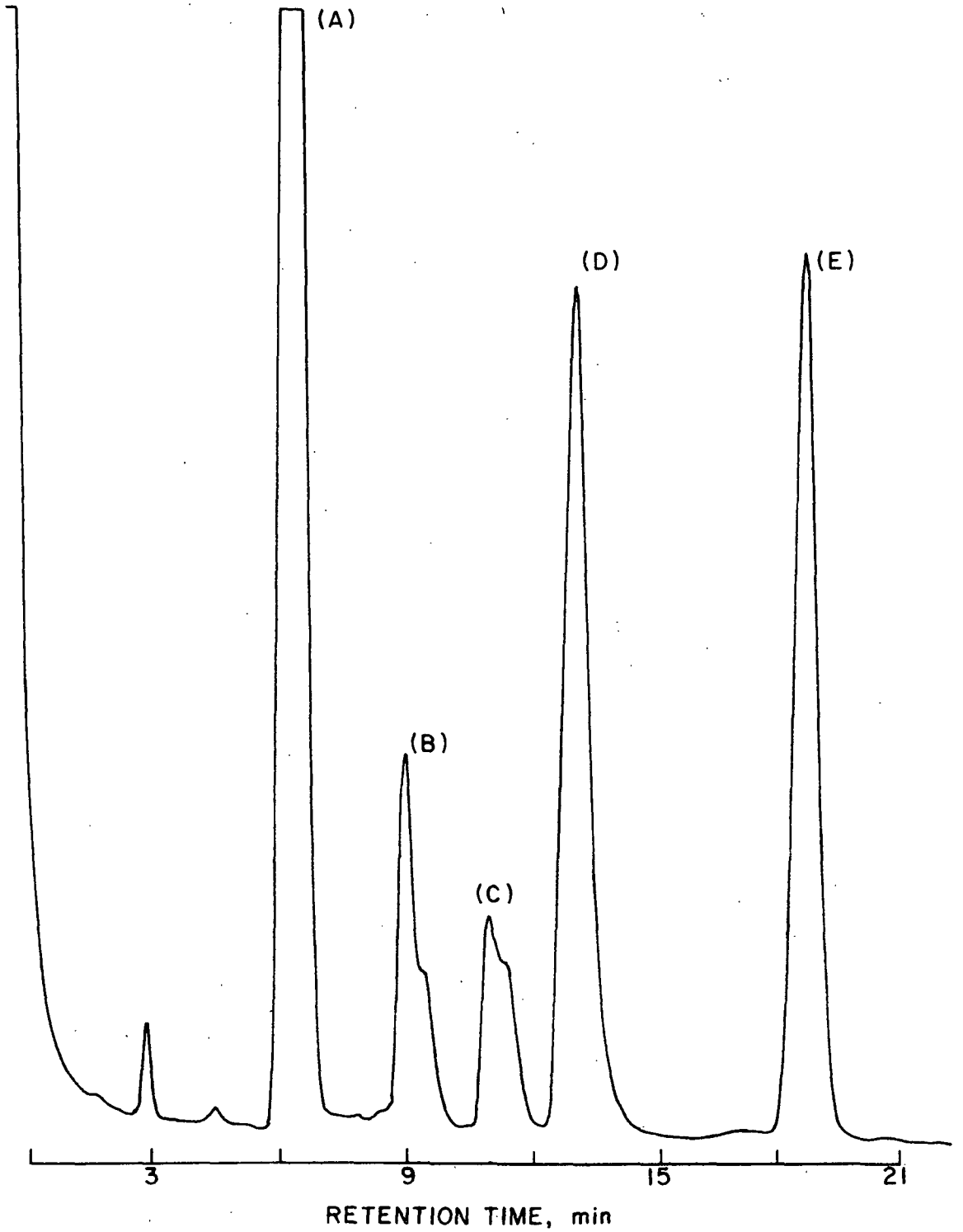


Figure 9. Gas Chromatogram of Hydrolyzate of Carboxymethyl Cellulose Prepared in DMSO/N-Methylmorpholine-N-oxide at 70°C Showing Peaks for: (A) Glucose, (B) 3-O-CMgl, (C) 2-O-CMgl, (D) 6-O-CMgl all as Methyl Ester/Glycoside TMS Derivatives and (E) Cyclohexyl Glucopyranoside (Std.) as TMS Derivative

illustrates the GLC obtained upon hydrolysis and analysis of this material, while Table VI shows the calculated substituent distributions as mole ratios.

TABLE VI

ANALYSIS OF CMC PREPARED IN N-METHYLMORPHOLINE-N-OXIDE/DMSO

	Experimental DS	Mole Ratios, 2:3:6
CMC (70°C) dialyzed	0.45	1:1.4:4.0 1:1.4:3.9

These results show etherification of the C-6 hydroxyl was favored to an even greater extent in DMSO than in water; the distribution in heterogeneous aqueous reactions was 2:1:2.5 (27). Cellulose-amine oxide interaction, responsible for the solvent action here, apparently influences the relative reactivity of the hydroxyl groups.

METHYLATION

Preparation

Further support for the conclusions drawn from the carboxymethylation study was sought by a related study of methylation. Preparation of the methyl cellulose followed closely the carboxymethylation procedure in that sodium hydride was necessary. Subsequent methyl iodide addition accomplished methylation of the cellulose in DMSO/PF (MOLC).

Contrary to the carboxymethylation where DMSO insolubility of the derivative (CMC) limited further reaction (etherification), methylation proceeded homogeneously. After the initial formation of the alkali cellulose (gel-like state) upon sodium hydride interaction, the system clarified as methylation with methyl iodide proceeded. The methyl cellulose remained DMSO soluble throughout the reaction. Since the solubility of the reaction

product was not a limiting factor, the DS could be controlled. By varying the reaction time and the number of sodium hydride/methyl iodide treatments, methyl cellulose samples of varying DS levels (low to very high) could be obtained.

In the normal process of methylation of polysaccharides a number of separate methylation steps are employed along with purification between each methylation. Using the procedure for methylating cellulose in DMSO/PF, a degree of uniqueness was illustrated since low to high DS material could be obtained with the same reagents in a multistep addition without intermediate purification.

An illustration of the progression of this reaction can be seen in the IR analysis of various samples taken during the 72 hour 20°C methylation, Fig. 10. One can see from the spectra how the hydroxyl region of absorption (3425 cm^{-1}) gradually decreases, accompanied by a corresponding increase in methyl absorption (2924 cm^{-1}). The relatively low degree of methylation at the C-6 oxygen (discussed below) may be reflected in the changing shape of the OH band in early stages of methylation since C-6 hydroxyl absorption is found at a lower frequency than that of C-3 (64).

Hydrolysis and subsequent GLC analysis of the methylated cellulose allowed detection of the various methyl glucose components. The location of methyl groups in the partially methylated samples was determined and analyzed to see if the pattern of substitution was the same as observed in carboxymethylation.

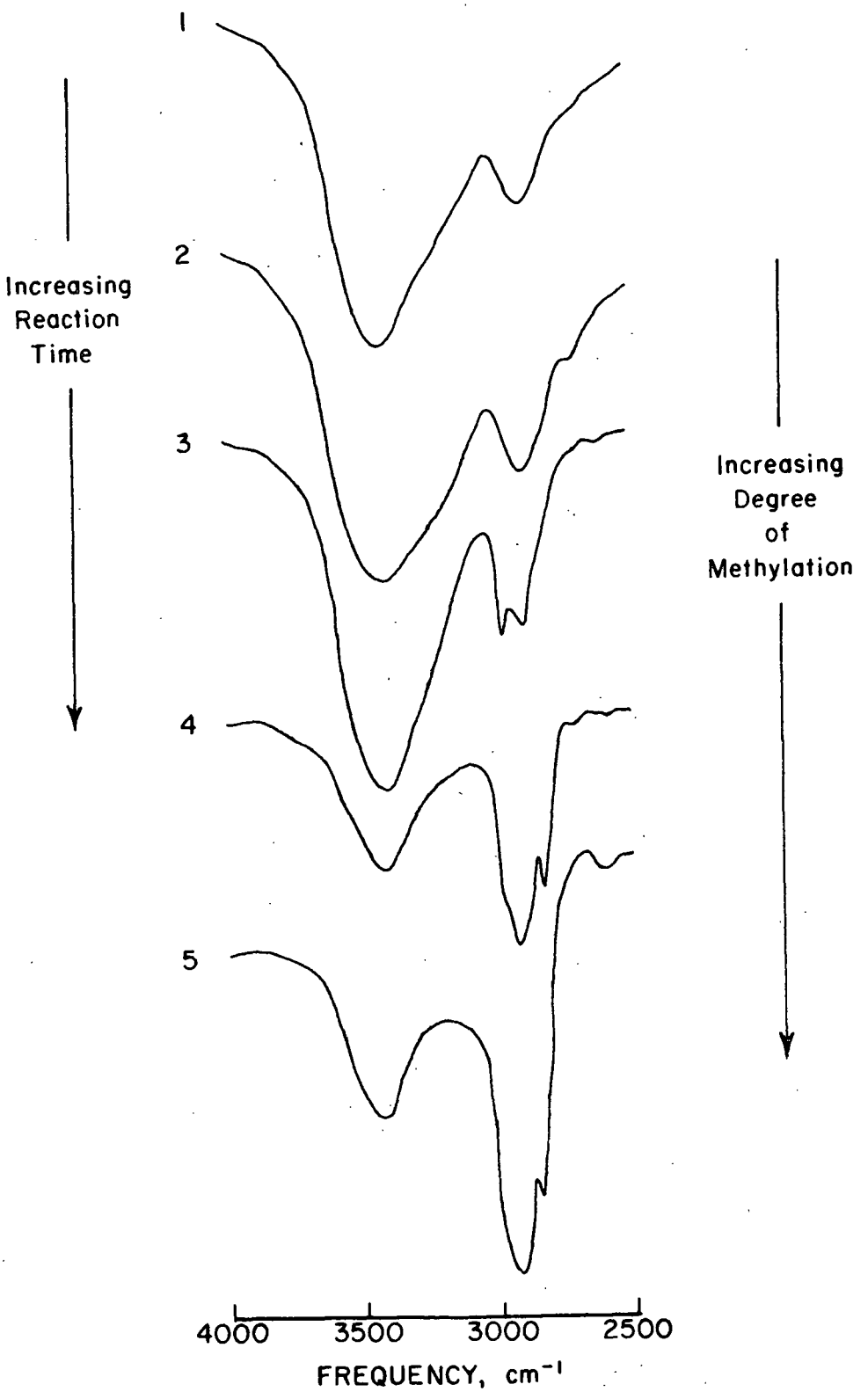


Figure 10. Infrared Spectra (4000-2500 cm^{-1}) of Methyl Cellulose (Low to High DS) Prepared in DMSO/PF. Spectra 1, 3, and 5 Correspond to Chromatograms (a), (b), and (c), Respectively, of Figure 11

Analysis

Although the response factors for the various methyl glucose ethers were not determined, quantitative analysis and comparison with the carboxymethyl system was based upon the relative component GLC peak areas. Since the response of the three monosubstituted carboxymethyl glucose components was very similar, it was assumed that the three monosubstituted derivatives were likewise similar in their chromatographic behavior.

In an effort to look at a low DS methyl cellulose, which would be comparable to the CMC prepared in DMSO/PF, a sample was taken very early during the multistep methylation. Workup consisted of purification, hydrolysis, methyl glycosidation, and trimethylsilylation prior to the GLC analysis.

The series of chromatograms shown in Fig. 11 follow the methylation from low (<1) DS (a) to high (>2) DS (c). The methylation is seen to proceed primarily on the C-2 and C-3 hydroxyl group positions; finally, in the later stages the methylol group is removed to allow formation of the C-6 methyl ether, producing the termination product 2,3,6-tri-O-methyl-glucopyranose.

These results further support the contention that the positional preference of the methylol group is indeed at the C-6 hydroxyl position; also since a high DS product can be achieved, this further illustrates the potential for removal of the methylol groups.

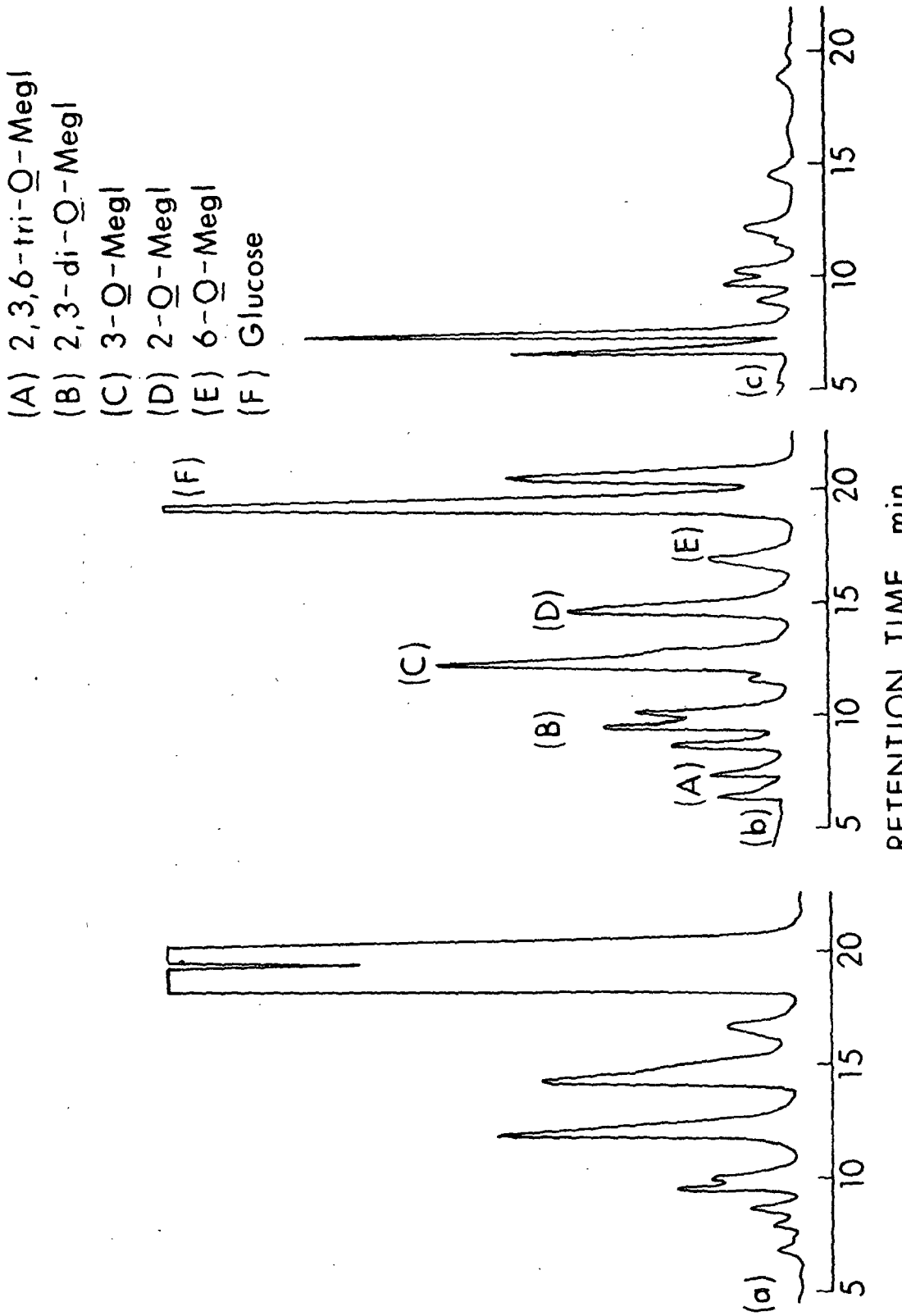


Figure 11. Gas Chromatograms of Various Hydrolyzed Methyl Cellulose Samples Prepared in DMSO/PF at 20°C. Chromatogram (a) Sample DS <1, (b) DS >1, and (c) DS >2

CONCLUSIONS

The dissolution of cellulose in the DMSO/PF solvent system was experimentally shown to be due to formation of the methylol cellulose derivative which results from the reaction of formaldehyde with cellulose in DMSO. The methylol cellulose was isolated by lyophilization and characterized by solubility, Raman spectroscopy and formaldehyde content. Both its solubility and the Raman spectrum were characteristic of derivatized cellulose. In addition, the behavior of this isolated material in water was found to be identical to that observed for the cellulose-DMSO/PF solution. From the determination of the formaldehyde content of the methylol cellulose it was shown that approximately one mole of formaldehyde was present in the methylol derivative per mole of anhydroglucose.

Homogeneous etherification of cellulose, employing both carboxymethylation and methylation, was accomplished in the DMSO/PF solvent. Analysis of the cellulose ethers illustrated that the methylol substituent definitely affects the etherification. Partial removal of the methylol groups by an increased reaction temperature (from 19 to 50°C) resulted in an increased C-6 substitution, while stabilization of the methylol by acetal formation directed the etherification to primarily C-2 and C-3 hydroxyl positions. The data supported the assumption that the methylol groups were preferentially located at the primary C-6 hydroxyl position.

The reaction data illustrate the feasibility of controlling the substituent distribution via homogeneous cellulose etherification in the DMSO/PF solvent.

EXPERIMENTAL

GENERAL METHODS

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

Infrared (IR) spectroscopic analyses were accomplished on a Perkin-Elmer Model 700 grating recording spectrophotometer.

Gas-liquid chromatography (GLC) was performed on a Varian Aerograph 1200 gas chromatograph equipped with a hydrogen flame ionization detector. Chromatograms were recorded on a Honeywell Electronic 16 recorder equipped with a Disc integrator. The carrier gas used was prepurified nitrogen from Matheson Gas Products. A 5% SE-30 on 60/80 mesh Chromosorb W column (1/8" × 10' ss) was used for all analyses. The operating conditions varied with the system being analyzed and are given in the Product Analysis section.

Thin-layer chromatography (TLC) was accomplished on silica gel G coated microscope slides. Upon spotting and development, the slides were sprayed with methanolic sulfuric acid (20% w/w) and heated until the spots were visible.

Optical rotations were determined using a Perkin-Elmer 141 recording polarimeter.

Mass spectrometric analysis was performed on a DuPont 21-491 mass spectrometer interfaced with a Varian Model 1400 gas chromatograph equipped with the hydrogen flame ionization detector. Chromatograms were recorded on a Hewlett Packard 7128A system while mass spectral data were recorded on a Century GPO 460 galvanometric recorder.

Laser Raman spectral analyses were performed on a Spex Raman system which employed the 5145A line of a coherent radiation 52 A laser for excitation.

REAGENTS

ANHYDROUS ALCOHOLS (METHANOL AND ETHANOL)

Stock alcohols were purified and fractionally distilled using an 80-cm vigreux column according to the procedure of Lund and Bjerren (65).

DIMETHYL SULFOXIDE (DMSO)

Dimethyl sulfoxide (Eastman Kodak Co.) reagent grade ACS (<0.2% water) did not require any additional purification; however, since moisture absorption was undersirable, the entire contents of the container were used soon after breaking the seal.

PARAFORMALDEHYDE (PF)

This linear polymer of formaldehyde was obtained from Mallinckrodt Chemicals. The grade specified was photographic grade which possessed a DP_n range of 8-12 and a decomposition temperature of <120°C.

SOURCE, PREPARATION AND PURIFICATION OF COMPOUNDS

CELLULOSE

Whatman CF-1 powder was the cellulose source used throughout this thesis. No additional purification was deemed necessary since this long fiber cellulose was prepared for chromatographic use. The number average degree of polymerization (DP_n) as determined by the Analytical Department using TAPPI Standard T 230 was 616.

METHYL β-D-XYLOPYRANOSIDE (MBX)

This compound was purchased from Pfanstiehl Laboratories Inc. The specified physical constants were m.p. 156-158°C, and $[\alpha]_D$ - 65.5°. Literature (66,67): $[\alpha]_D$ - 65.5° and m.p. 156-157°C.

CYCLOHEXYL β-D-GLUCOPYRANOSIDE (CHG)

This compound was obtained from Dr. J. W. Green. The melting point was checked and found to be 133-134°C. Literature (68,69): m.p. 133-137°C, 132.5-134.5°C.

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

This material, obtained from Dr. L. R. Schroeder, was prepared according to the procedure of Glen, et al. (70). The compound was recrystallized from low boiling petroleum ether:acetone (4:1, v/v), and the melting point obtained was 109.7°C. Literature (71): m.p. 110°C.

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

This compound was prepared according to the basic procedure of Shyluk and Timell (72), employing 20 g of the 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose in anhydrous ethylether, sodium or sodium hydride (excess) and methylbromoacetate (12 ml). The product was recrystallized from isopropyl ether; m.p. 104°C. Literature (72): m.p. 104-105°C.

METHYL 3-O-CARBOXYMETHYL-D-GLUCOPYRANOSIDE, METHYL ESTER (3-O-CMgl)

The 3-O-carboxymethyl-1,2:5,6-di-O-isopropylidene-α-O-glucofuranose, methyl ester (7 g) from the previous procedure was treated with 20 ml of

solvent exchanged Amberlite IR-120 ion-exchange resin in 100 ml of anhydrous methanol under reflux conditions. The resin was solvent exchanged with anhydrous methanol to remove the water according to Zgol (73,74). The cleavage of the isopropylidene groups and subsequent formation of the glycoside were followed by TLC using chloroform:methanol (10:1, v/v).

Upon completion of the reaction (24 hr), the methanol solution of the carbohydrate was decanted and the resin washed with methanol (2 × 50 ml). The methanol wash solutions were combined with the original decantant and concentrated to a sirup at 50°C. Attempts to crystallize this product failed; thus a chromatographic purification was employed.

A column 1 m × 25 mm was dry-packed using 153 g of 60-200 mesh chromatographic grade silica gel (Sargent-Welch). After the 3-O-CMgl was dissolved in chloroform, this solution was added to the column. A glass wool plug was inserted and pressed down into contact with the silica gel. The solvent was added, in this case chloroform:methanol (10:1, v/v), and allowed to contact the entire column surface. Once the flow rate was adjusted to 40-45 ml/hr, fractions of 10 ml were collected. The desired fractions were determined by TLC analysis using chloroform:methanol (10:1, v/v).

The 3-O-CMgl, ca. 2.0 g of a sirup was shown to be pure by TLC and GLC analyses; $[\alpha]_D^{25}$ + 63.6° (c 1.45, MeOH).

6-O-ACETYL-BISMETHYLENE-D-GLUCOSE*

This compound was prepared according to the procedure of Hough, et al. (75). Recrystallization from methanol yielded a product having a m.p. 104°C. Literature (75): m.p. 104°C.

*Although the structure of this compound is unknown, it has been used to prepare the analogous 6-O-methyl-D-glucopyranose.

6-O-CARBOXYMETHYL-BISMETHYLENE-D-GLUCOSE, METHYL ESTER

The crystalline compound from the preceding step was deacetylated with 1N methanolic sodium methoxide. The resulting reaction mixture was deionized with Amberlite MB-3 resin prior to concentration *in vacuo* at 50°C. The sirup was then carboxymethylated again following the procedure of Shyluk and Timell (72). Since this compound could not be crystallized, the sirup was taken directly into the following hydrolysis step.

METHYL 6-O-CARBOXYMETHYL-D-GLUCOPYRANOSIDE, METHYL ESTER (6-O-CMgl)

The 6-O-carboxymethyl-bismethylene-D-glucofuranose methyl ester (7 g) was treated with 20 ml of solvent-exchanged IR-120 ion-exchange resin in 100 ml of methanol under reflux. The methylene removal and subsequent glycosidation were monitored by TLC using chloroform:methanol (10:1, v/v). Reaction was complete within 48 hours.

After the methanol solution was decanted, the resin was washed with methanol (2 × 50 ml) and the combined methanol solutions concentrated *in vacuo* at 50°C. Like the analogous compound 3-O-CMgl, 6-O-CMgl failed to crystallize.

Purification was accomplished by chromatographic separation on 60-200 mesh Sargent-Welch silica gel using chloroform:methanol (10:1, v/v) as the eluant. The 6-O-CMgl (*ca.* 2.5 g), shown to be pure by TLC and GLC analyses, had $[\alpha]_D^{25}$ + 70.1° (*c* 1.15, MeOH).

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

The 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (26 g) previously obtained was dissolved in 140 ml of methanol to which was added 140 ml of

0.8% aqueous sulfuric acid. This controlled removal of isopropylidene was allowed to proceed 24 hours at 25°C (76).

Upon completion, the acid was neutralized with barium carbonate and the solution filtered. The solution was concentrated *in vacuo* at 50°C, and the product crystallized. Recrystallization from ethyl acetate (three times) yielded 14.3 g of material having a melting point of 159.5°C. Literature (76): m.p. 160°C.

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

The 1,2-O-isopropylidene-α-D-glucofuranose (10 g) was benzylated according to the procedure of Finan and Warren (77). Completion of the reaction was determined by TLC monitoring using isopropyl ether. The resulting compound (liquid) was purified by chromatographic separation on 60-200 mesh Sargent-Welch silica gel using isopropyl ether as the eluant. The pale yellow oil obtained after concentration *in vacuo* at 50°C had $[\alpha]_D^{25}$ - 34.4° (*c* 1, $CHCl_3$). Literature (77): $[\alpha]_D$ - 34.7°.

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

A 15 g portion of the oil obtained in the previous step was treated with 30 ml of solvent-exchanged IR-120 ion-exchange resin in 150 ml of methanol under reflux conditions. The isopropylidene removal and subsequent glycosidation were followed by TLC using isopropyl ether. Upon completion of the reaction (26 hr), the resin was removed and washed with methanol. The combined methanol solutions were concentrated *in vacuo* at 50°C and the resulting sirup was purified by chromatography on 60-200 mesh Sargent-Welch silica gel using isopropyl ether:benzene (10:1, v/v) as the eluant. The pure fractions were combined, concentrated to a sirup and used directly in the following carboxymethylating step.

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

Carboxymethylation of the methyl 3,5,6-tri-O-benzyl-D-glucofuranoside was accomplished following the procedure of Shyluk and Timell (72). When attempts to crystallize this compound failed, it was taken directly into the following reduction step.

METHYL 2-O-CARBOXYMETHYL-D-GLUCOPYRANOSIDE, METHYL ESTER (2-O-CMgl)

The benzylated carboxymethyl glucose derivative (ca. 3 g) obtained from the previous procedure was dissolved in 100 ml tetrahydrofuran:methanol (1:1, v/v) and placed in a Parr bomb along with 300 mg of catalyst. The 10% palladium on charcoal catalyst was prepared by MacLeod according to Mozingo (78,79). The Parr bomb was sealed and 40 psig of hydrogen was administered at 25°C. The contents of the bomb were stirred continuously by a magnetic stirring apparatus.

Removal of the benzyl groups was monitored by TLC using chloroform: methanol (10:1, v/v). After 4 days, 50 ml methanol was added and the temperature raised to 50°C. Within 3 days the reaction (as monitored by TLC) was complete. The contents of the bomb were filtered, the residue washed with methanol, and the combined solution concentrated to ca. 2 g of sirup in vacuo at 50°C.

This sirup was refluxed with 10 ml of solvent-exchange IR-120 ion-exchange resin and 100 ml of methanol for 12 hours. The resin was washed with methanol and the combined solution concentrated in vacuo at 50°C. The resulting sirup was dissolved in chloroform and applied to a silica gel column (60-200 mesh Sargent-Welch chromatographic grade). Elution with

chloroform:methanol (10:1, v/v) accomplished the desired chromatographic separation. The compound, ca. 1 g 2-O-CMgl, shown to be pure by TLC and GLC analyses, had $[\alpha]_D^{25}$ + 33.3° (c 1, MeOH).

METHYL 2,3,-DI-O-BENZOYL-4,6-O-BENZYLIDENE-β-D-GLUCOPYRANOSIDE

This compound, obtained from Dr. Schroeder, was prepared by F. C. Haigh (80,81). The observed melting point was 184°C. Literature (81): m.p. 185°C.

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

Approximately 1 g of the previous starting material was debenzoylated with 50 ml of 1N methanolic sodium methoxide. The reaction proceeded at 25°C and was followed by TLC using chloroform:ethyl acetate (4:1, v/v). Upon completion of the debenzoylation (12 hr), the reaction mixture was poured into water. The methyl 4,6-O-benzylidene-β-D-glucopyranoside crystallized immediately. This crystalline product was washed (3 × 50 ml) with petroleum ether before recrystallization from water. The product (0.5 g) had a melting point of 204-205°C. Literature (82): m.p. 205°C.

METHYL 2-O-METHYL-, 3-O-METHYL-, AND 2,3-DI-O-METHYL-4,6-O-BENZYLIDENE-β-D-GLUCOPYRANOSIDE MIXTURE

The preceding product was methylated by the Kuhn (83) variation of the Purdie procedure using methyl iodide and silver oxide in dimethyl formamide (DMF) according to the procedure of Seib (84). Since a mixture of the three possible products was desired, the reaction was quenched after 10 hours. The silver salts were removed by centrifugation and washed with chloroform. The chloroform wash solutions and the DMF centrifugate were combined and washed with 2% aqueous potassium cyanide. After chloroform extraction of the

combined aqueous phases, the extracts were washed with water and dried over anhydrous sodium sulfate. The dried chloroform solution was concentrated to a sirup *in vacuo* at 50°C. This product was taken directly into the next hydrolysis step.

METHYL 2-O-METHYL-, 3-O-METHYL-, AND 2,3-DI-O-METHYL-β-D-GLUCOPYRANOSIDE MIXTURE

The material (0.4 g) from the preceding stage was treated with 4% HCl/methanol. The methanolic HCl was prepared by dropwise addition of acetyl chloride (7 ml) to anhydrous methanol (100 ml). The reaction was allowed to proceed 12 hours under reflux conditions. After neutralization of the acid with barium carbonate and subsequent removal of the salts by filtration, the methanol solution was concentrated to a sirup *in vacuo* at 50°C.

The sirup was analyzed by GLC and found to contain three components. These components possessed retention times identical with three of the methylcellulose hydrolysis components. A purified sample of 3-O-Megl was obtained from MacLeod (78) and used to differentiate the 3-O-Megl peak in the GLC from the 2-O-Megl and 2,3-di-O-Megl.

PRODUCT ANALYSIS PROCEDURES

CELLULOSE SOLUTION IN DMSO/PF

Open System Procedure

Whatman CF-1 cellulose powder (15 g) was suspended in 473 ml (508 g) of dimethyl sulfoxide (DMSO) in a two-necked reaction vessel (1 liter capacity) fitted with a thermometer. The slurry was stirred while slowly heated to 120°C using a magnetic stirrer/hot plate combination. (Figure 12 illustrates the assembly.) At this point, 30 g of Mallinckrodt Photographic grade

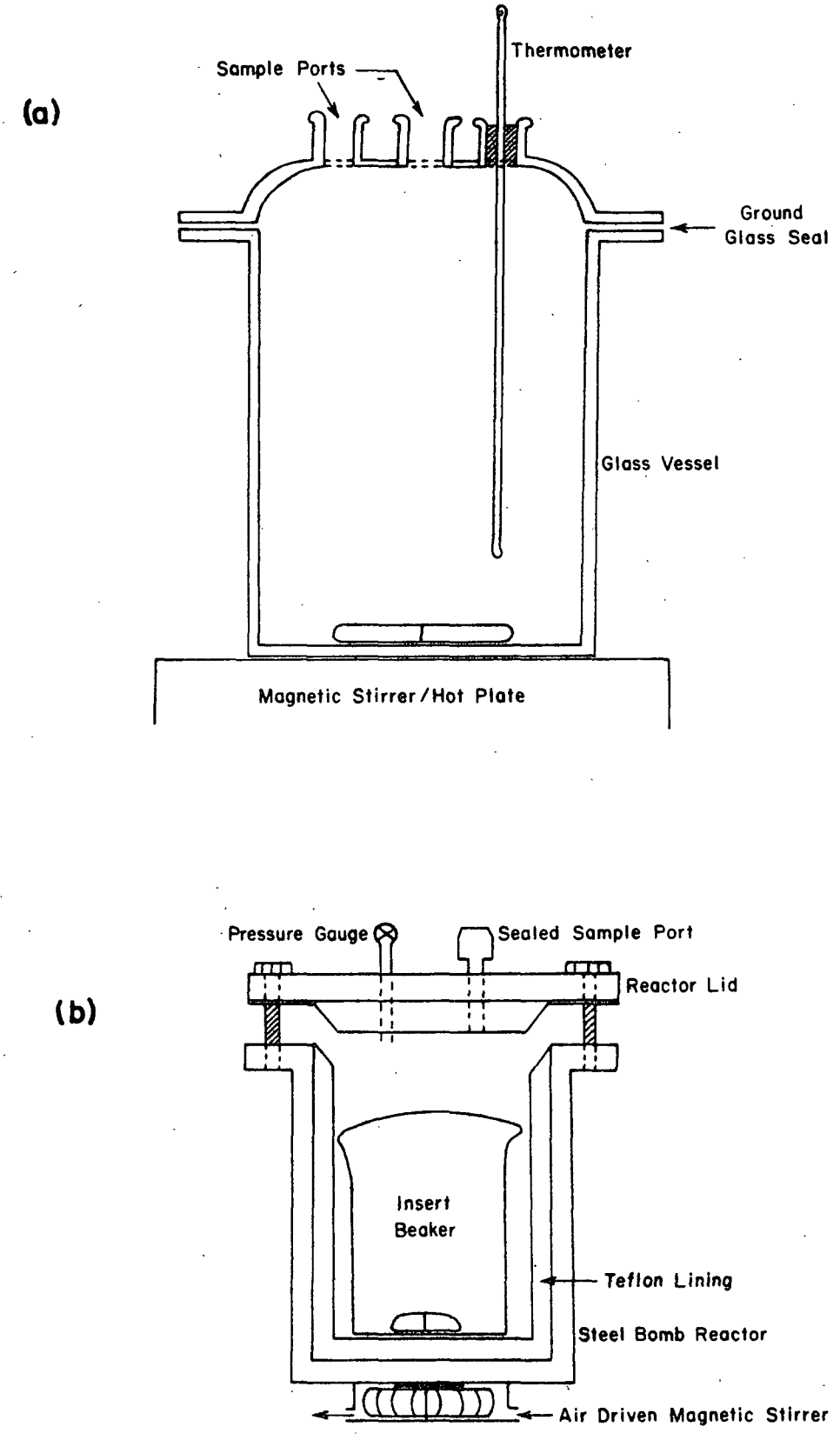


Figure 12. Illustration of the Apparatus Employed in the Dissolution of Cellulose in DMSO/PF: (a) Open System and (b) Closed System

paraformaldehyde (PF) was added. An immediate drop in temperature of the solution was observed, followed by a noticeable generation of formaldehyde gas. This evolution of formaldehyde continued for a few minutes (5-10 min) before noticeable dissolution of the cellulose began. Within 15 minutes after the PF addition all the cellulose appeared dissolved, but there continued to be some formaldehyde evolution. Continued heating for periods as long as 5 hours accomplished the complete decomposition of the paraformaldehyde and the removal of excess formaldehyde. No attempt was made to expedite the removal of excess formaldehyde by higher temperatures or reduced pressures. The solution of cellulose (2.95% w/w) in the DMSO/PF system was cooled and stored in polyethylene bottles for subsequent experimental use.

Closed System Procedure

Closed system dissolution of cellulose was accomplished in a 1 liter capacity steel bomb reactor which had been constructed by Sinkey (85). The reactor was fitted with a glass insert beaker which facilitated stirring and handling of small samples. Figure 12 illustrates this assembly.

At this point the lower half of the reaction vessel was immersed in a circulating glycol bath (120°C) and allowed to reach temperature. DMSO, 40 ml, and 0.2 g cellulose were added to the insert beaker, and the mixture was allowed to reach 120°C. Constant stirring was accomplished by an air-driven magnetic stirring apparatus. When the DMSO-cellulose slurry had reached 120°C, the required PF (1.3 g) was quickly added, the reaction vessel lid secured, and the entire assembly lowered into the bath.

Approximately 2 hours were required for complete cellulose dissolution. The two hour reaction time was necessary to allow temperature recovery of the system after PF addition. When the system again reached 120°C, noticeable formaldehyde generation was indicated by the steady rise in pressure.

After 2 hours, the pressure ceased to increase and the reactor was removed from the bath. The pressure was released, and the reactor lid opened. At this point the insert beaker containing the cellulose solution in DMSO/PF could be removed. This solution was cooled and stored for later use and analysis.

ISOLATION OF METHYLOL CELLULOSE (MOLC)

A sample of the 3% (w/w) cellulose-DMSO/PF solution (25 ml) was frozen in a 100 ml round bottom flask and freeze-dried for 3 days. The white fibrous material (MOLC) contained trace amounts of DMSO which could not be removed by prolonged freeze-drying (ca. 13 days).

MOLC was easily soluble in DMSO at room temperature. However, if allowed to interact with water, the sample (after air drying) was no longer DMSO soluble. Further indications that this freeze-dried product from the cellulose-DMSO/PF solution was indeed a cellulose derivative came from the Raman spectroscopic analysis. This spectral analysis of the MOLC illustrated absorption characteristics which are common to all cellulose derivatives.

Due to its sensitivity to moisture, the MOLC was stored in a vacuum desiccator or in vessels purged with dry N_2 and sealed.

DEGREE OF SUBSTITUTION OF METHYLOL CELLULOSE

Methylol cellulose decomposed in water to liberate formaldehyde. Quantitative determination of the formaldehyde, by the sodium sulfite method, was used to measure the extent of methylol group substitution.

Duplicate samples of the freeze-dried MOLC (0.1-0.2 g) were analyzed for formaldehyde by the procedure of Sadtler (51). The quantitatively

produced sodium hydroxide was titrated with standard sulfuric acid to a thymolphthalein end point. The percentage of formaldehyde in the sample was then related to the molar substitution of methylol groups, and is listed in Appendix II, Table VII.

ANALYSIS OF CMC COMPONENTS BY MASS SPECTROMETRY

Purified samples of each component, 3-O-CMgl, 2-O-CMgl and 6-O-CMgl, were refluxed 24 hours with 4% HCl/ethanol. The ethanolic HCl was prepared by dropwise addition of acetyl chloride (7 ml) to anhydrous ethanol (100 ml). The ethyl O-carboxymethyl glucopyranoside ethyl ester derivatives were trimethylsilylated following the procedure outlined in the Work-up Procedures section (p. 70).

Similarly, commercial Hercules 0.4 DS CMC, after hydrolysis to its substituted glucose components according to Croon and Purves (27), was subjected to the same ethyl esterification/glycosidation prior to trimethylsilylation. The mass spectral data obtained for the synthetically prepared carboxymethyl glucose derivatives was compared with that obtained for the carboxymethyl glucose components isolated from the commercial CMC. Positive comparison of the mass spectrum of each of the hydrolysis components to its corresponding prepared component was viewed as proof of identity.

Since very concentrated samples were required for MS analysis, the pyridine peak resulting from the TRI-SIL became overwhelming. To alleviate this problem the TMS derivatives were dissolved in isopropyl ether. The removal of the original pyridine solvent is discussed in the Work-up Procedures section. The ether solution of the components was then injected into the Varian 1400 gas chromatograph which was interfaced with the MS system.

GLC conditions required for the separation of the carboxymethyl glucose components of CMC were:

Column: 5% SE-30 on 60-80 mesh Chromosorb W (1/8" by 5' ss)

Column temperature: P.R. 150-220°C at 2°C/min

Injection temperature: 250°C

Detector temperature: 272°C

Helium flow rate: 22 psig, 30 ml/min (UHP = 99.999% pure He, Matheson Gas)

Hydrogen pressure: 10 psig

Components once separated by GLC were fed into the mass spectrometer by means of a splitter-proportioning valve. This valve assembly leading to the jet separator was temperature controlled:

Valve interface block: 300°C

Connecting tube: 280°C

Jet separator: 250°C

Other control settings for the MS unit were:

Oven temperature: 120°C

Source temperature: 225°C

Sensitivity: 7.5

Ionization voltage: 7.0 ev

Scan: 10 sec/decade

Chart speed: 4 inches/sec

Pressure during sample introduction: 1.5×10^{-6} Torr

The MS data obtained for the various components of CMC are given in Appendix III.

ETHERIFICATION OF CELLULOSE IN DMSO/PF

Carboxymethylation

One hundred milliliters of the cellulose-DMSO/PF solution, containing ca. 3 g (0.019 mole) cellulose was mechanically stirred at 20°C (or other desired temperature). Solid sodium hydride (6 g, 0.250 mole) was added slowly, and within 1 hour the solution became gel-like in nature. Stirring was continued until the sodium hydride had been allowed to react two hours. At this point, methyl bromoacetate (7 ml, 0.076 mole) was added dropwise over 1-2 hours. Almost immediately a yellow color developed, followed by the apparent dissolution of the gel. The reaction was allowed to proceed 16-20 hours at 20°C.

After the allotted reaction time, a white precipitate could be seen in the reaction solution. A second treatment with sodium hydride and methyl bromoacetate (heterogeneous) had little if any effect upon the DS of the partly etherified cellulose, as shown by IR and GLC analysis; therefore, only one reaction sequence in the carboxymethylation was employed.

Upon completion of the carboxymethylation, the reaction solution contained excess sodium hydride, sodium bromide, methyl bromoacetate, DMSO, and carboxymethyl cellulose (CMC). The sodium hydride was decomposed by pouring the reaction mixture slowly into a vigorously stirred formic acid:water (1:1, v/v) solution (50 ml). This aqueous solution (pH 3-4) of CMC, along with the by-products of reaction, was dialyzed against distilled water using an Amicon apparatus at 12-15 psig nitrogen. The dialysis unit was equipped with a XM50 membrane capable of retaining molecules greater than 50,000 molecular weight. Since the cellulose had a number average DP of 616, the CMC was retained. Dialysis continued until the pH of the solution

was neutral (7), or until at least six volumes of the original solution had been exchanged. In most cases this required 24 hours.

The purified aqueous solution of CMC was freeze-dried and yielded 2.95 g of product. Infrared (IR) spectral analysis of the material showed a carbonyl absorption at 1730 cm^{-1} indicative of the acid form of CMC. Characteristic IR absorptions previously noted for CMC (acid) are: 1730 carbonyl, very broad undefined 1400 and 890 cm^{-1} bands (86,87). The methyl ester has apparently been removed during carboxymethylation or the acid work-up. The characteristic IR spectrum of CMC (methyl ester) reveals a strong carbonyl absorption at 1745-1750 cm^{-1} along with definitive bands at 1450 and 1380 cm^{-1}. From the IR comparisons of the isolated product with commercial acid form CMC, methyl ester CMC, and salt form CMC, it was evident that the CMC obtained after dialysis and freeze-drying was the acid form.

Methylation

Solid sodium hydride (2 g, 0.083 mole) was added to 50 ml of the cellulose-DMSO/PF solution containing 1.5 g, 0.011 mole of cellulose. Continuous stirring was maintained throughout the reaction. After approximately 2 hours at 19°C, the solution had taken on a gel-like appearance and at this point little or no hydrogen evolution could be detected. The methylating agent, methyl iodide (3 ml, 0.048 mole) was then slowly added. Within a short time the gel appeared to dissolve and the reaction was allowed to proceed for 24 hours.

After this initial 24 hour reaction period, additional sodium hydride (1 g, 0.042 mole) was added. Again, the hydride was allowed to react for at least 2 hours before addition of the methylating agent (2 ml, 0.032 mole). After this addition, a second reaction time of 24 hours was allowed.

Finally, the cellulose in solution was subjected to a third successive treatment with sodium hydride (1 g, 0.042 mole) and methyl iodide (2 ml, 0.032 mole). Total reaction time for the methylation of cellulose in DMSO/PF was 72 hours. Except for the initial sodium hydride treatment (when the gel formed), the reaction was homogeneous.

Methyl cellulose samples of varying degrees of substitution were obtained by simply sampling at different intervals throughout the methylation.

Purification began by pouring the reaction mixture slowly into a formic acid:water (1:1, v/v) solution (100 ml). This step accomplished the decomposition of the excess sodium hydride. The resulting aqueous solution (pH 3-4) of methyl cellulose and by-product contaminants was dialyzed against distilled water using the Amicon dialysis unit at 12-15 psig nitrogen. Again the unit was equipped with a XM50 membrane capable of retaining molecules greater than 50,000 molecular weight. The dialysis was continued until at least six times the original solution volume had been exchanged (ca. 24 hours). In instances where purification of a high DS methyl cellulose was necessary, the derivative precipitated from the aqueous solution as the DMSO was removed. This somewhat hindered the solvent flow and increased the time required for purification.

The purified aqueous solutions of methyl cellulose (only materials having a DS under ca 2.0 were water soluble) were freeze-dried and stored for later analyses.

Carboxymethylmethylol Cellulose Methyl Ester

To 20 ml of cellulose-DMSO/PF solution containing 0.5 g of cellulose, 1 ml of methyl chloroacetate was added. This specific carboxymethylating agent was chosen so that upon freeze-drying excess unreacted reagent could

be removed. The mixture was stirred continuously while 20 drops (ca. 0.25 ml) of triethylamine was added. The reaction was allowed to proceed at 23°C for 22 hours. The reaction product remained DMSO soluble throughout the procedure.

Purification of this material was accomplished by freeze-drying (2-3 days). After redissolving in DMSO, again it was freeze-dried in order to remove traces of reagent (methyl chloroacetate) left after the first freeze-drying.

The white cellulosic material obtained from the two stage freeze-drying purification was analyzed by IR. The carbonyl absorption appeared at 1745 cm^{-1} and the two definitive bands at 1380 and 1440 cm^{-1} were also present, indicative of carboxymethyl methyl ester substituents. In contrast, the carbonyl of the methyl chloroacetate (reagent) absorbs at 1760 cm^{-1} (88).

The carboxymethyl methyl ester substituents were ascertained to be on the methylol groups since no carboxymethyl glucose components could be detected upon hydrolysis and GLC analysis; only glucose was found. The carboxymethylmethylol cellulose methyl ester was redissolved in DMSO and used later in carboxymethylation with sodium hydride and methyl bromoacetate.

Analogous to this preparation, early attempts to carboxymethylate cellulose in DMSO/PF with chloroacetic acid and triethylamine produced a similar product. This material was initially water soluble, but after ca. 1-2 hours precipitated from the aqueous solution. IR analysis found the carbonyl absorption to be at 1730 cm^{-1}, indicating acid form CMC. Analysis via hydrolysis and GLC showed only glucose to be present. This water soluble unstable cellulose derivative was the carboxymethylmethylol cellulose (acetal).

WORK-UP PROCEDURES

All samples of CMC which were quantitatively analyzed by GLC were processed according to the following procedures.

Hydrolysis

Samples of the dried CMC which were to be quantitatively analyzed were hydrolyzed according to the basic procedure of Croon and Purves (27). This hydrolysis employs an initial 2 hour 72% sulfuric acid treatment (25°C) followed by a 4 hour secondary 8% sulfuric acid reflux. Upon completion of the hydrolysis, the solution was cooled and neutralized to pH 7 with barium carbonate. The mixture was digested 1-2 hours at 80°C to remove the carbonic acid formed during neutralization. The insoluble barium salts were removed by filtration, and the resulting aqueous solution of the carboxymethyl glucose components was concentrated to dryness *in vacuo* at 50°C. This residue was taken directly into the next step.

Esterification/Glycosidation

The material from the preceding step was dissolved in 4% HCl/methanol, which was prepared by the slow addition of acetyl chloride (7 ml) to anhydrous methanol (100 ml). When the particular sample was to be used for glucose analysis, the internal standard, methyl β-D-xylopyranoside (MBX), was added at this point. The solution was then refluxed for 24 hours, after which the HCl was neutralized to pH 7 with barium carbonate.

At this stage, when the sample was to be used for carboxymethyl glucose component analysis, the cyclohexyl β-D-glucopyranoside (CHG) internal standard was added. After the sample was thoroughly mixed, the barium salts were allowed to settle out. An aliquot of the supernatant was taken and

concentrated to dryness *in vacuo* at 50°C. This residue was then trimethylsilylated.

Trimethylsilylation

The samples were trimethylsilylated by the addition of TRI-SIL (Pierce Chemicals) reagent to the dry sample from the previous step (89). For every 5-10 mg of carbohydrate, 1 ml of TRI-SIL was required. The sample containing the TRI-SIL was heated for 5-10 minutes at 50°C to facilitate sample dissolution in the TRI-SIL solvent (pyridine). The reaction was allowed to proceed at 25°C for at least 12 hours. Continuous mixing was accomplished by mechanical shaking.

Direct analysis of the trimethylsilyl (TMS) derivatives in pyridine was found to be satisfactory in most cases. However, in the analysis for glucose where MBX was used as the internal standard, an ether solution of the TMS derivatives was used. This ether solution reduced the pyridine "tailing" which often interfered with the internal standard MBX peak. Analysis of the TMS derivatives in pyridine or ether solution produced similar quantitative results.

To remove the pyridine, the sample was concentrated to dryness *in vacuo* at 50°C. Addition of 1-2 ml of toluene followed by further concentration *in vacuo* removed the residual pyridine as an azeotrope. The toluene additions and subsequent evaporation steps were performed at least three times or until no odor of pyridine could be detected. To the dried sample was then added the desired volume of anhydrous isopropyl ether. After being warmed slightly to insure complete dissolution of the TMS derivatives, the sample was ready for quantitative GLC analysis. Duplicate samples of CMC were subjected to this work-up procedure prior to analysis.

Quantitative analysis of methyl cellulose (MC) samples was not based on the response of known compounds but rather on relative component peak heights. Therefore, MC samples were processed through the preceding work-up without addition of internal standard.

DETERMINATION OF COMPONENTS

All quantitative product analysis of the CMC and MC samples was accomplished by GLC of the TMS derivatives. Component identification in all work was based upon GLC retention times of known prepared compounds. The authenticity of the known prepared components was established by mass spectrometric analysis.

Retention times (R_f) of the known components used as references are given in Appendix IV, Tables IX and X.

GLC CONDITIONS

The column used for GLC analysis has been described in the General Methods section (p. 52). Conditions for analyzing the hydrolysis components of carboxymethyl cellulose (as TMS derivatives) were:

Column temperature: P.R. 210-250°C at 1°C/min

Injector temperature: 250°C

Detector temperature: 270°C

Nitrogen flow rate: 13 ml/min

Hydrogen pressure: 10 psig

A typical chromatogram of the analysis of low DS (0.7) CMC (from Hercules, Inc.) illustrates peaks for (A) unsubstituted glucose, (B) 3-O-CMgl, (C) 2-O-CMgl, (D) 6-O-CMgl and di- and trisubstituted components in

in Fig. 13. Carboxymethyl compounds were detected as the TMS derivatives of the methyl esters and methyl glucopyranosides.

For the analysis of methyl cellulose (MC), the GLC conditions used were:

Column temperature: P.R. 170-210°C at 1°C/min

Injector temperature: 250°C

Detector temperature: 270°C

Nitrogen flow rate: 15 ml/min

Hydrogen pressure: 10 psig

The chromatogram in Fig. 14 illustrates the GLC analysis of low DS (0.2) methyl cellulose showing peaks for (A) 2,3,-di-O-Megl, (B) 3-O-Megl, (C) 2-O-Megl, (D) 6-O-Megl and (E) unsubstituted glucose. Components were detected as the TMS derivatives of the methyl ethers and methyl glucopyranosides. Identification of those compounds illustrated was by retention time comparison with known compounds.

DETERMINATION OF RESPONSE FACTORS

Known mixtures of the possible components of low DS CMC were prepared and processed through the work-up procedure, with exception of the hydrolysis step. Since the quantitative analysis was to be done in two parts, the response factors for glucose and carboxymethyl glucose components were determined separately.

The response of glucose was measured against that of methyl β-xylopyranoside (MBX) while the response of the three carboxymethyl glucose components were referenced to cyclohexyl β-D-glucopyranoside (CHG). Solutions containing various ratios of glucose to MBX were analyzed by GLC. Similarly,

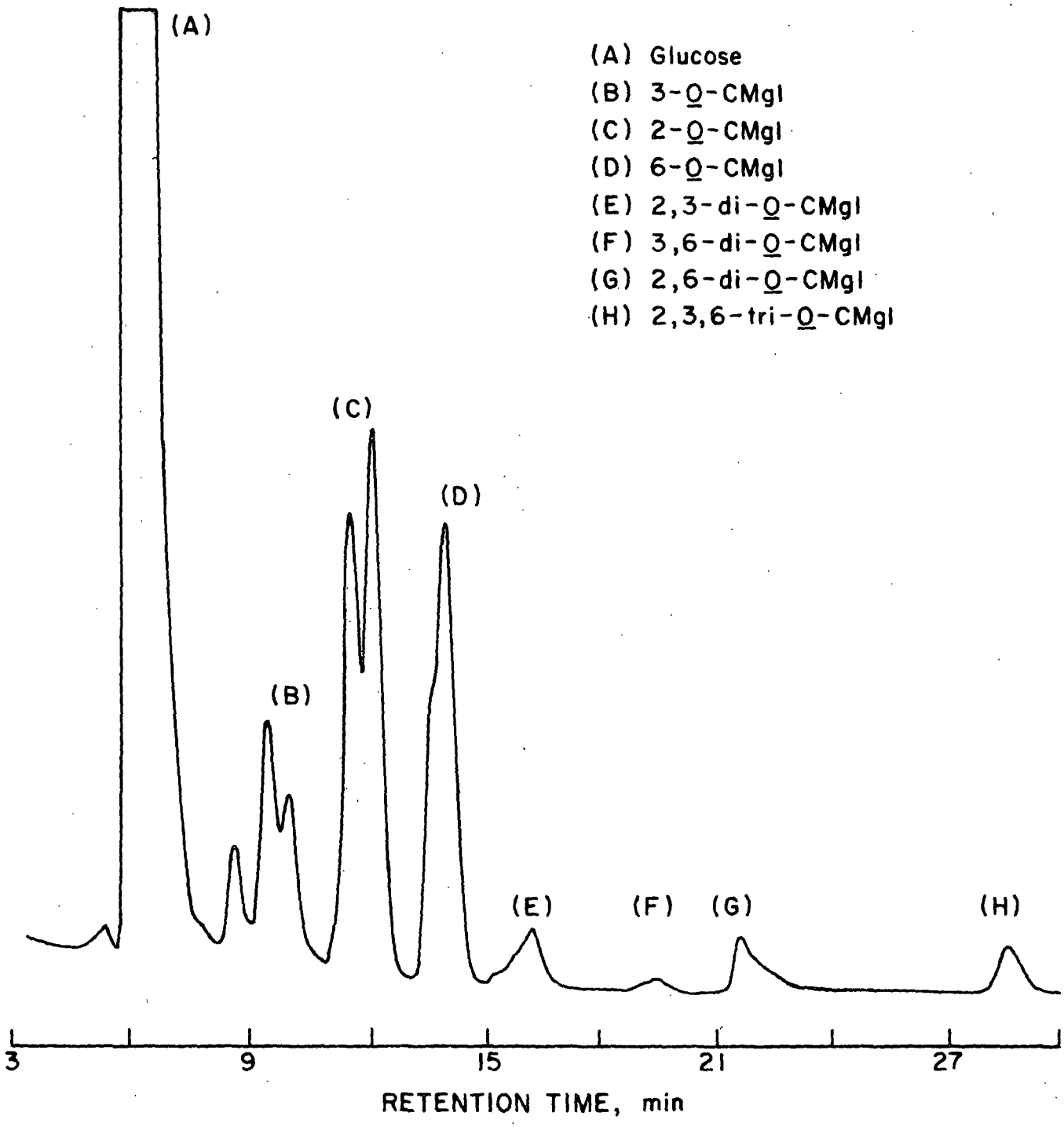


Figure 13. Gas Chromatogram of Hydrolyzate of Commercial 0.7 DS Carboxymethyl Cellulose Illustrating the Separation of all Possible Components as the Methyl Ester/Glycoside TMS Derivatives

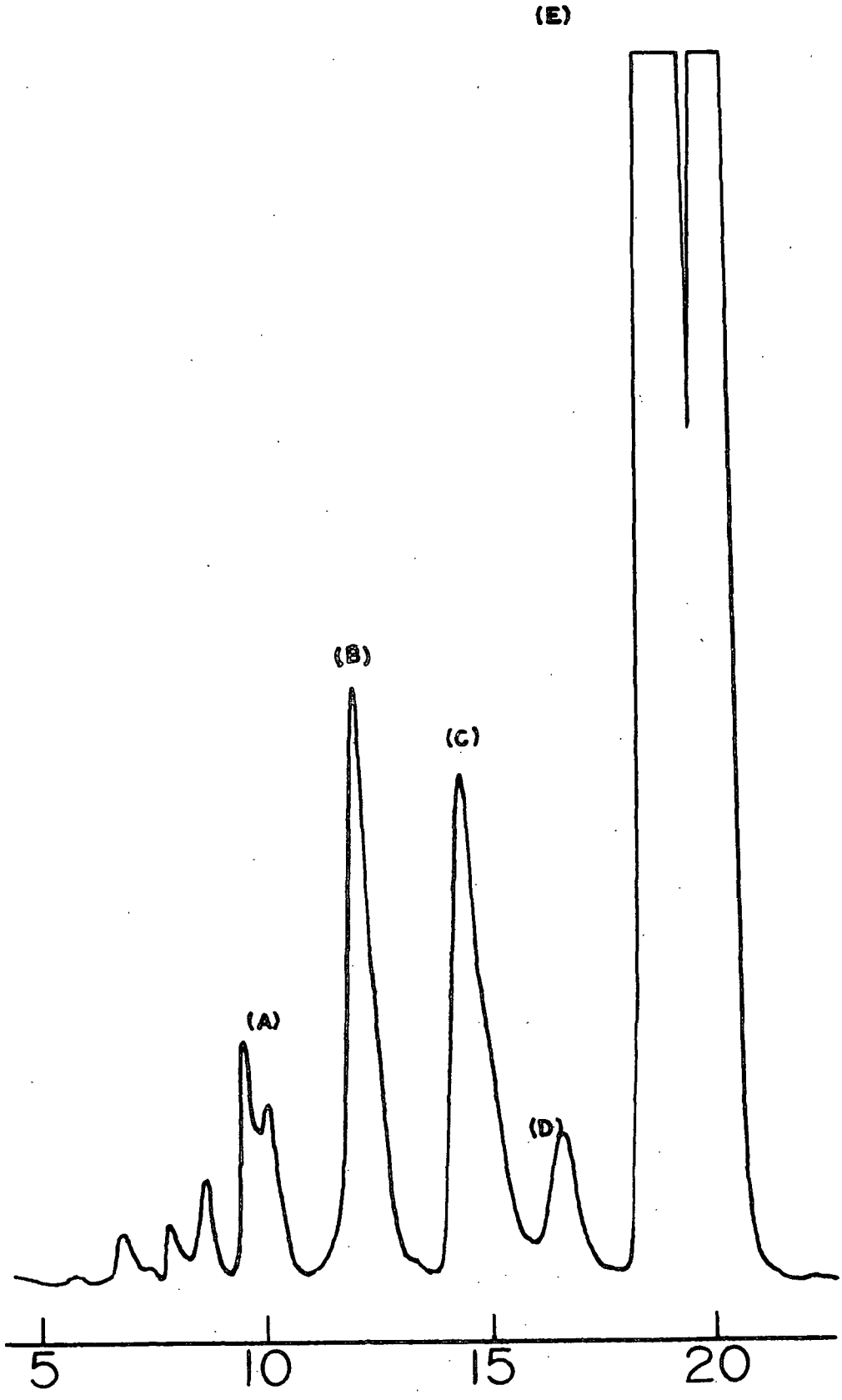


Figure 14. Gas Chromatogram of Hydrolyzate of Methyl Cellulose (Low DS <1) Prepared in DMSO/PF at 20°C Showing Peaks for (A) 2,3-di-O-Megl, (B) 3-O-Megl, (C) 2-O-Megl, (D) 6-O-Megl and (E) Glucose all as Methyl Glycoside TMS Derivatives

solutions of varying amounts of 3-O-CMgl, 2-O-CMgl, 6-O-CMgl and CHG were prepared and analyzed by GLC.

The areas of the component peaks were calculated from the Disc integrator tracings after employing suitable corrections for base-line drift. From these area measurements, the response factors for each component relative to the internal standard could be determined. The response factors for the carboxymethyl cellulose system are given in Appendix IV.

Quantitative data, that is, the amount of each component present in a CMC sample, was determined from the GLC results using the previously calculated response factors and the standard equation (13)

$$M_x = f_{s/x} \cdot M_s \cdot (\text{Area } x/\text{Area } s), \qquad (13)$$

where M_x = moles of component x in the CMC sample

$f_{s/x}$ = response factor for component x relative to the internal standard s

M_s = moles of internal standard s

Area x = peak area of component x

Area s = peak area of internal standard s

The DS and the relative molar ratios of each component of CMC were then determined from the quantitative data.

NOMENCLATURE

Angl	anhydroglucose
°C	degrees Centigrade
C	grams per 100 ml solution
ca.	about
CHG	cyclohexyl β-D-glucopyranoside
CMC	carboxymethyl cellulose
2-O-CMgl	methyl 2-O-methyl-D-glucopyranoside, methyl ester
CMMOLC	carboxymethylmethylol cellulose, methyl ester
concn.	concentration
DMSO	dimethyl sulfoxide
DS	degree of substitution
DP	degree of polymerization
ft	feet
g	gram
GLC	gas-liquid chromatography
hr	hour
IR	infrared
Lit.	literature
MBG	methyl β-D-glucopyranoside
MBX	methyl β-D-xylopyranoside
MC	methyl cellulose
2-O-Megl	methyl 2-O-methyl-D-glucopyranoside
mg	milligram
min	minute
ml	milliliter
mmole	millimole

MOLC	methylol cellulose
MS	mass spectrometry
NMR	nuclear magnetic resonance
%	percent
P.R.	programmed rate
r.b.	round bottom
R_f	retention time (min)
ss	stainless steel
t	time
TLC	thin-layer chromatography
TMS	trimethylsilyl
v	volume

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APPENDIX I

INFRARED SPECTRA OF CELLULOSE AND METHYLOL CELLULOSE

This appendix contains the IR spectra of methylol cellulose (MOLC) and of Whatman CF-1 powdered cellulose (Fig. 15). Samples were prepared under dry nitrogen using the potassium bromide pellet preparation procedure.

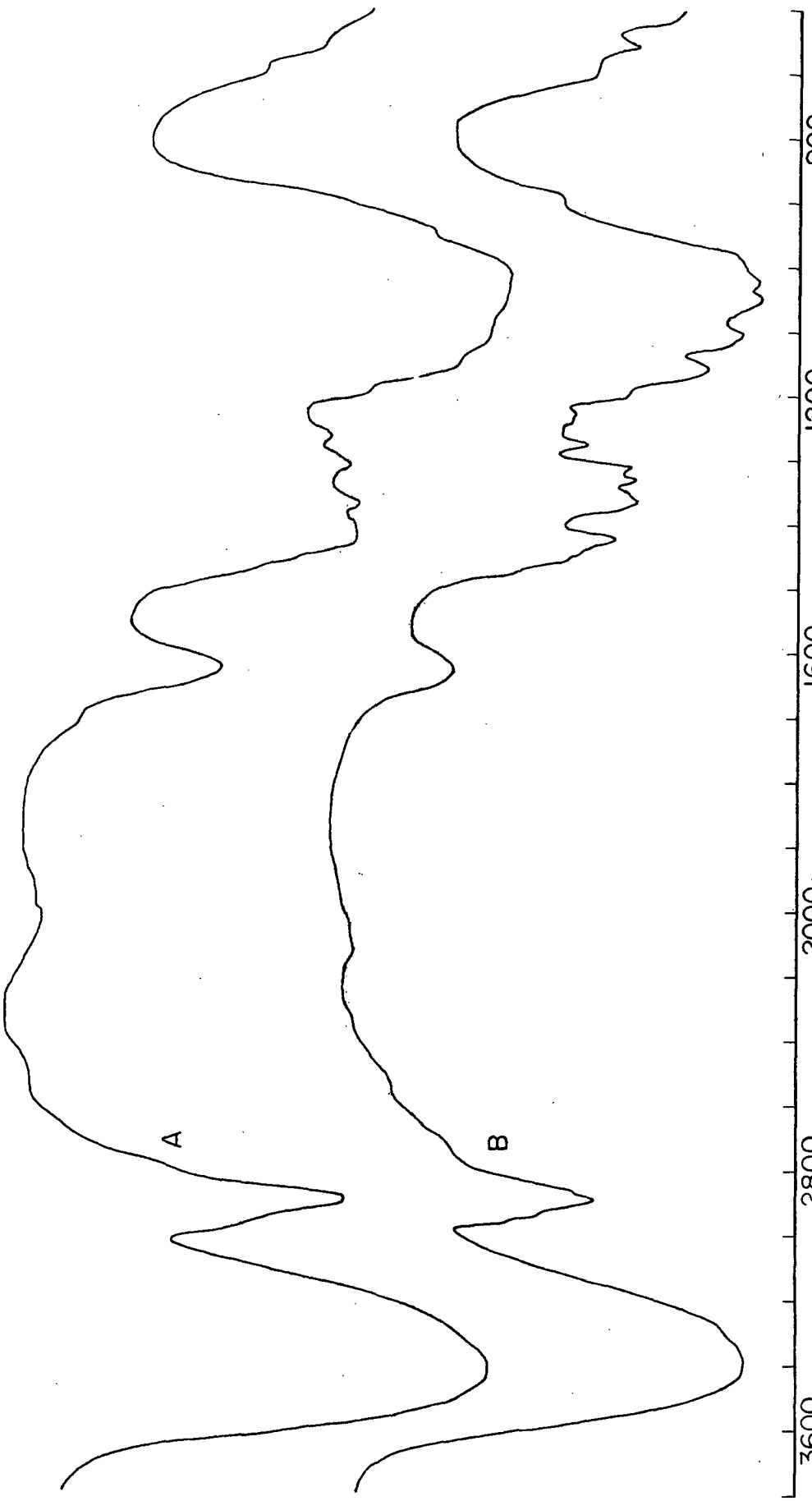


Figure 15. Infrared Spectra of A) Methylol Cellulose and B) Whatman CF-1 Cellulose

APPENDIX III

MASS SPECTRA OF O-CARBOXYMETHYL GLUCOSE DERIVATIVES

This appendix contains the mass spectral data generated by analysis of CMC hydrolysis components and prepared components (Table VIII). Included is a brief discussion of the origin of the important fragments for each component.

TABLE VIII

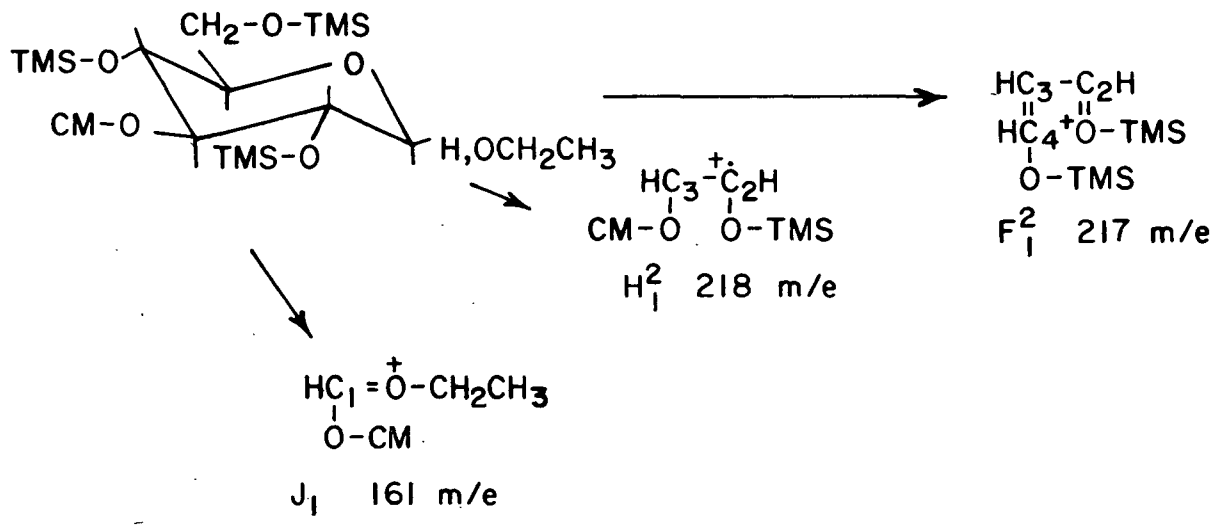
MASS SPECTRAL DATA FOR MONOSUBSTITUTED COMPONENTS ALL AS ETHYL O-CARBOXYMETHYL-O-TRIMETHYLSILYL-D-GLUCOPYRANOSIDE ETHYL ESTERS

m/e	Glucose	A[a]	CMC Hydrolysis 3-O-CMgl	Preparation 3-O-CMgl	CMC Hydrolysis 2-O-CMgl	Preparation 2-O-CMgl	CMC Hydrolysis 6-O-CMgl	Preparation 6-O-CMgl
			Relative Abundance Based Upon Peak Height					
73	77	100	86	81	53	47	56	55
103	10	--	13	13	7	7	12	6
118	5	13	13	13	7	6	--	--
129	7	--	13	10	3	3	8	6
131	--	--	20	7	4	4	--	--
133	7	--	20	12	9	7	--	--
147	44	45	20	11	20	24	26	28
161	--	--	93	84	23	21	9	6
204	100	95	20	4	14	15	100	100
205	25	10	--	--	7	8	29	27
206	15	--	--	--	--	--	11	2
217	23	13	80	63	16	24	23	17
218	3	3	100	100	100	100	11	6
219	3	5	20	25	28	17	20	16
220	--	--	--	--	11	6	--	--
231	--	--	--	--	13	13	--	--

[a] This trace component found in all cellulose ether hydrolyzates was not identified.

MAIN FRAGMENTATION PATHWAYS OF THE CARBOXYMETHYL COMPONENTS

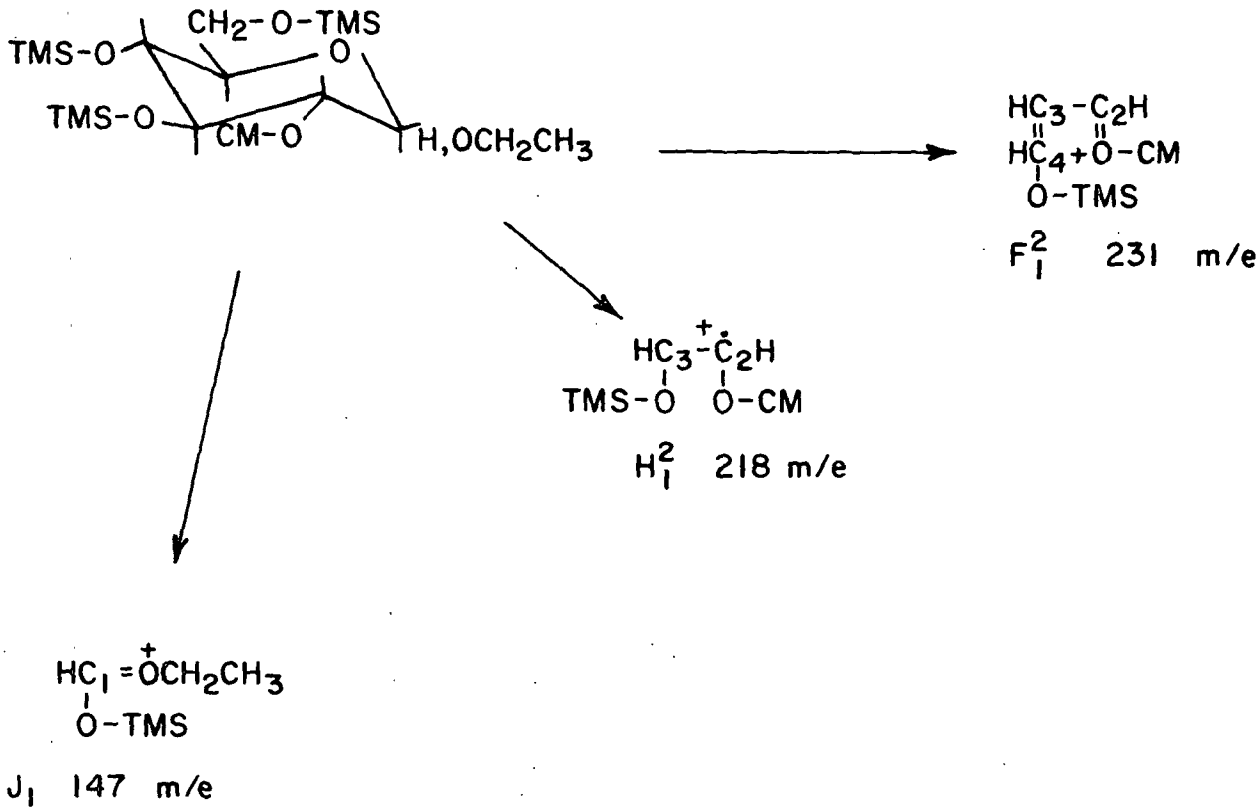
3-O-CMgl COMPONENT



Summary

A substituent at C-3 produces a very intense H_1^2 218 m/e peak. Characteristic of such substitution is a relatively strong F_1^2 217 m/e peak when compared with that produced by C-2 and C-6 substitution (58,62). Since the loss of C-3 substitution is favored, a relatively strong 161 m/e ion J_1 is observed.

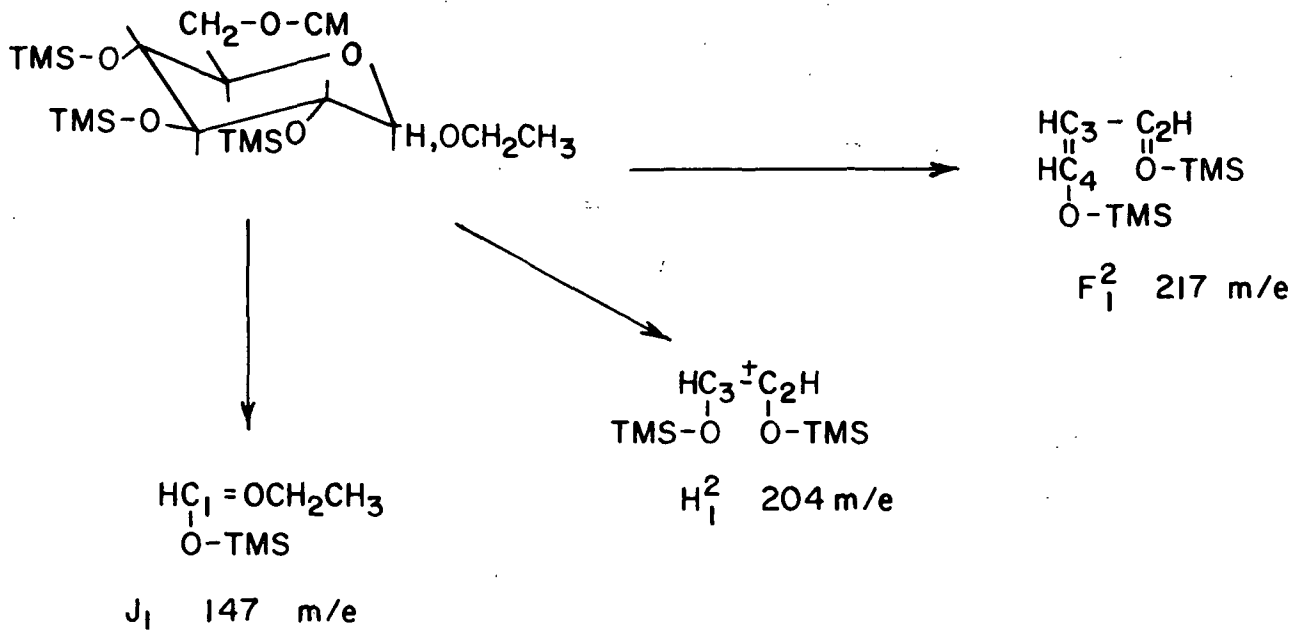
2-O-CMgl COMPONENT



Summary

A substituent at C-2 produces the F_1^2 231 m/e ion. In this case the J_1 fragment ion is at 147 m/e instead of 161 m/e as was the case with 3-O-CMgl.

6-O-CMgl COMPONENT



Summary

Substitution at C-6 would result in a very intense H_1^2 204 m/e ion similar to unsubstituted glucose since no rearrangement is required.

APPENDIX IV

RETENTION TIMES AND RESPONSE FACTORS REQUIRED FOR CMC ANALYSIS

This appendix contains the retention times and GLC response factors for the CMC and methyl cellulose hydrolysis components which were required for quantitative analysis. All response factors were determined relative to the appropriate internal standard using the trimethylsilyl (TMS) derivatives. Work-up procedures for the quantitative analysis along with the GLC conditions employed are given in the Experimental section. (See Tables IX and X.)

TABLE IX

RETENTION TIMES AND RESPONSE FACTORS OF CMC HYDROLYSIS COMPONENTS ALL AS METHYL O-CARBOXYMETHYL-O-TRIMETHYLSILYL-D-GLUCOPYRANOSIDE METHYL ESTERS

Compound	Time, min	Response[a]	Internal Standard
MBX	4.5	1.00	--
Glucose	9.0	1.12	MBX
3-O-CMgl	10.5	0.58	CHG
2-O-CMgl	12.6	0.56	CHG
6-O-CMgl	15.0	0.56	CHG
CHG	20.5	1.00	--

[a]Response factors ($f_{s/x}$) were calculated from Equation (14) where the terms have been previously defined [Equation (13)].

$$f_{s/x} = M_x/M_s \cdot (\text{Area } s/\text{Area } x) \qquad (14)$$

TABLE X

RETENTION TIMES OF METHYL CELLULOSE HYDROLYSIS COMPONENTS ALL AS METHYL O-METHYL-O-TRIMETHYLSILYL-D-GLUCOPYRANOSIDES

Compound	Retention Times, min
2,3,6-Tri-O-Megl	7.5
2,3-Di-O-Megl	10.0
3-O-Megl	12.5
2-O-Megl	15.0
6-O-Megl	17.0
Glucose	19.5