

非水系溶剤中の セルロスの 反應^{*2}

石 津 敦^{*3}

Cellulose Reaction in Non-aqueous Solvents^{*2}

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It is well known that partially crystallized structure of cellulose generally makes it difficult to prepare highly substituted cellulose derivatives. Successive findings of non-aq. cellulose solvents in the last two decades stirred me to prepare such derivatives, which could be expected to have some unique characteristics. Today I'd like to present you the results of our studies on the preparation of highly and homogeneously substituted cellulose derivatives by the use of non-aq. solvents.

The outline of my presentation is shown in Fig. 1. In the beginning non-aq. cellulose solvents will be introduced.

Fig. 1 Cellulose Reactions in Non-aqueous Solvents,

by A. Isogai, T. Ishii, A. Ishizu & J. Nakano

1. Non-aqueous solvents
2. Esterification
Acid-stable products obtained by acetylation in chloral/pyridine/DMF
3. Etherification
Tri-O-benzyl cellulose
Thermotropic properties
4. Halogenation
Chlorodeoxycellulose (d.s. = 1.3)

In the part of esterification an acetate of chloral-containing cellulose which is a new acid-stable material will be introduced. In the part of etherification the success in the preparation of tri-O-benzyl celluloses which have thermally unique properties will be discussed. In the last part the success in the preparation of highly substituted chlorodeoxycellulose will be discussed.

In the first place, I'd like to introduce to you non-aq. cellulose solvents briefly. Fig. 2 shows three examples of single component solvents: hydrazine, amine oxides, one example of which is *N*-methyl-morpholine oxide, and *N*-ethylpyridinium chloride. All these reagents require heating for dissolution of cellulose. According to Dr. Hergert cellulose acts as a base toward the last reagent, whereas it acts as an acid toward the first two reagents. The last two reagents mixed with aprotic solvents also can be used for dissolution of cellulose.

Fig. 2 shows main examples of multicomponent solvents, too. The first one was found out by W. Fowler et al. during their studies on oxidation of cellulose with N_2O_4 . The dissolution of cellulose in this solvent was explained by R. Schweiger to be due to the formation of cellulose nitrite ester being soluble in polar aprotic solvents. The second solvent was invented by Japanese researchers, K. Hata et al and the dissolution of cellulose was explained by Nakao to be due to the formation of complexes such as shown in the Fig. Namely, in the formula (A) a charged complex of SO_2 with amines interact with hydroxyl groups of cellulose, and in the formula (B) SO_2 and an amine

*1 Received Aug. 15, 1982.

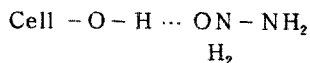
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Fig. 2 Non-aqueous Cellulose Solvent Systems

A. Single Component Solvents

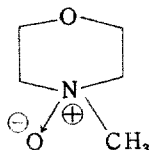
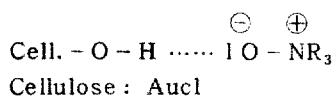
1. Hydrazine [M.H. Litt (1976)]



2. Amine Oxides

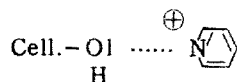
4 - methylmorpholine N - oxide

[D.L. Johnson (1970)]

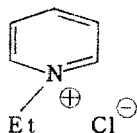


3. N - Ethylpyridinium chloride

[E. Huseman (1969)]



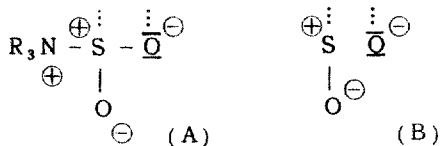
Cellulose : base



B. Multicomponent solvents

1. N₂O₄/Polar aprotic solvent

[W. Fowler et al. (1947)]

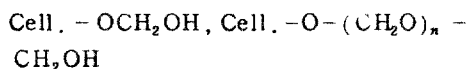
2. SO₂/amine/polar solvent

[K. Hata et al. (1968) :

O. Nakao (1974)]

3. Paraformaldehyde / DMSO

[D. C. Johnson et al. (1976)]



4. Chloral / Polar solvent

[K. H. Meyer et al. (1950)]

Chloral / Pyridine / Polar solvent

[L. P. Clermont et al. (1974)]

interact with a hydroxyl group separately. The formation of these complexes serves to the destruction of cellulose crystals. With the third solvent, heating at 130°C is necessary for the dissolution of cellulose. D.C. Johnson, the inventor of this solvent, reported that formaldehyde formed from paraformaldehyde by heating reacts with cellulose to produce monomethylol derivative of cellulose soluble in DMSO. He reported later that when gaseous formaldehyde is used, aprotic solvents other than DMSO can be used also, and heating is unnecessary. Furthermore, he proved the presence of polymethylol substituents, too.

K. H. Meyer et al found out that the combination of chloral and polar solvents dissolves cellulose. It takes a long time for this solvent to dissolve cellulose. It takes a long time for this solvent to dissolve cellulose. L. P. Clermont et al. found out that the addition of pyridine accelerates the dissolution of cellulose. We have studied the dissolution mechanism in this solvent. I'd like to explain you the result here briefly.

Chloral had been postulated to react with hydroxyl groups of cellulose to produce chloral hemiacetal analogous to the reaction between alcohols and chloral (Fig. 3). However, the presence of polychloral hemiacetal substituents had been also suggested. In order to prove chloral hemiacetal structure, cellulose dissolved in a mixture of chloral, pyridine and DMF was acetylated with AC₂O at 60°C for 4 hr. The acetate was recovered by pouring the reaction product into water. Since unreacted chloral hemiacetal substituents are unstable to water, the acetate obtained was expected to have the structure shown at the lower part of the right side. If this structure is true, the d.s. of acetyl group must be equal to that of chloral group. The chemical analyses revealed that this expectation holds good. In the other structure having polychloral hemiacetal substituents, the d.s. of acetyl group can hardly coincide with the d.s. of chloral. When these two d.s. become equal by chance, there must be acetyl groups linked directly to glucose residues. However, the presence of such acetyl groups could not be

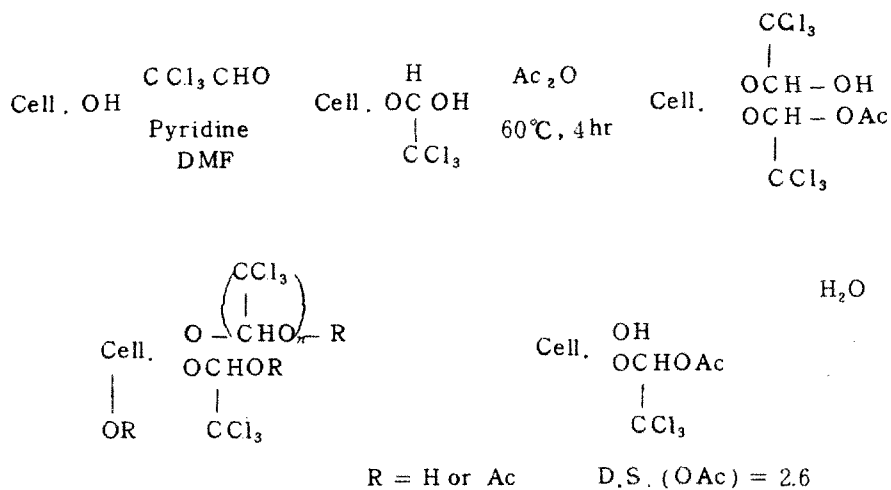


Fig. 3 Dissolution mechanism in chloral and DMF

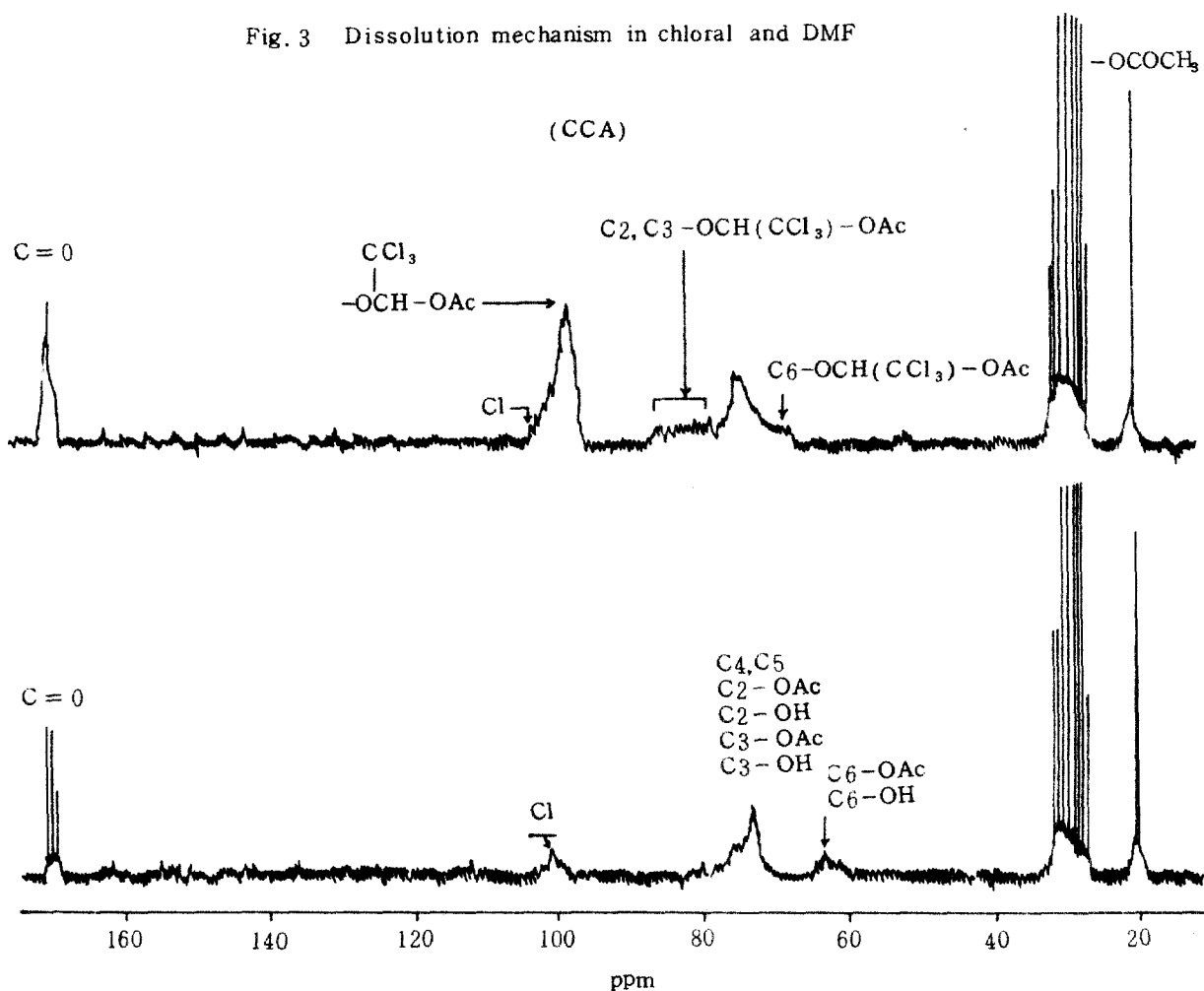


Fig. 4 C-*n.m.r.* spectra of modified cellulose acetate prepared with acetic anhydride (CCA) and of commercial cellulose acetate (CAc). Measured in deuterio-acetone

proved by C-13 n.m.r. (Fig. 4): The spectrum of commercial cellulose acetate has two signals around at 65 ppm due to C-6 having OH and OAc groups. These two peaks cannot be detected in the acetate of chloral-containing cellulose. Instead of these two peaks, this acetate has a signal due to C-6 having a monochloral hemiacetal acetate groups.

This result proved that the acetate has mainly the structure written at the lower part of the right side in Fig. 3. It can be concluded, therefore, cellulose dissolved in chloral-containing solvents has the monochloral hemiacetal structure and has no free hydroxyl groups of original cellulose. The latter conclusion is based on the fact that acetylation of alcoholic hydroxyl groups proceeds much faster than the acetylation of hydroxyl groups of chloral hemiacetals. If free hydroxyl groups were present, they must have been detected as the acetate linked directly to glucose residues by C-13 n.m.r.

Summarizing the previous discussion, there are two mechanisms for the dissolution of cellulose in non-aq. solvents. The first one is the formation of H-bonds or complexes between hydroxyl groups of cellulose and solvent components. The other is the formation of cellulose derivatives soluble in organic solvents. Cellulose nitrite, methylol cellulose and cellulose monochloral hemiacetal are examples.

Now I am going into the very subject of my presentation. Preparation of cellulose esters by the use of non-aq. solvents has been studied by several researchers (Fig. 5). Schweiger succeeded in the preparation of cellulose sulfate from cellulose dissolved in N_2O_4/DMF by the use of SO_3/DMF . He reported this ester exchange reaction takes place selectively at the C-6. When cellulose is dissolved in N_2O_4/DMF , nitric acid is formed together with cellulose nitrite. By warming this solution, Schweiger obtained water-soluble cellulose nitrate with a d.s. of 0.5. Mansson et al. prepared cellulose acetate with a d.s. of less than 2 by acetylation of cellulose nitrite with AC_2O and pyridine. They reported that acetyl groups is mainly introduced into C-2, when the d.s. is low. Huseman et al. succeeded

Fig. 5 Preparation of Cellulose Derivatives by the use of Non-aqueous Solvents.

A. Esterification

1. Sulfation [R.G. Schweiger (197)]
 $Cell. - ONO + SO_3 / DMF \rightarrow$
 $Cell. - OSO_2OH$
2. Nitration [R.G. Schweiger (1974)]
 $Cell. - OH + N_2O_4 / DMF \rightarrow Cell. - ONO$
 $+ HNO_3 \xrightarrow{\Delta} Cell. - ONO_2 (d.s., 0.5)$
3. Acetylation
 $Cell. - ONO + Ac_2O / Pyridine \rightarrow Cell.$
 $- OAc (d.s., \sim 2)$
 [P. Mansson et al. (1980)]
 $Cell. - OH$ in N-Ethylpyridinium chloride
 $Cell. - OAc (d.s., \sim 3)$
 $Ac_2O / Pyridine$
 [E. Huseman et al. (1969)]

in the preparation of cellulose acetates having a d.s. of 3 by acetylation with Ac_2O and pyridine in N-ethylpyridinium chloride. By adjusting the amount of acetylating reagents they could prepare cellulose acetate having a wide variety of d.s. One advantage of preparation of cellulose derivatives by the use of non-aq. solvents is the preparation of products having a desired d.s. in one step.

As discussed earlier, cellulose monochloral hemiacetal was acetylated in order to study the dissolution mechanism. This acetylation is also one example of homogeneous reactions. The distribution of acetyl groups in the acetate of cellulose chloral hemiacetal was examined according to the scheme shown in the Fig. 6. Methylation of cellulose monochloral hemiacetal acetate with CH_2N_2 in the presence of BF_3 etherate and subsequent saponification with $NaOCH_3$ yielded partially methylated cellulose. Thus, hydroxyl groups and monochloral hemiacetal acetate groups were converted into methoxyl groups and hydroxyl groups, respectively. This product was further hydrolyzed and then reduced with $NaBH_4$. Partially methylated glucitols thus produced were analyzed by g.l.c as acetates. (Fig. 7). Based on peak areas, the extents of acetylation of chloral hemiacetals at C-2, C-3 and C-6

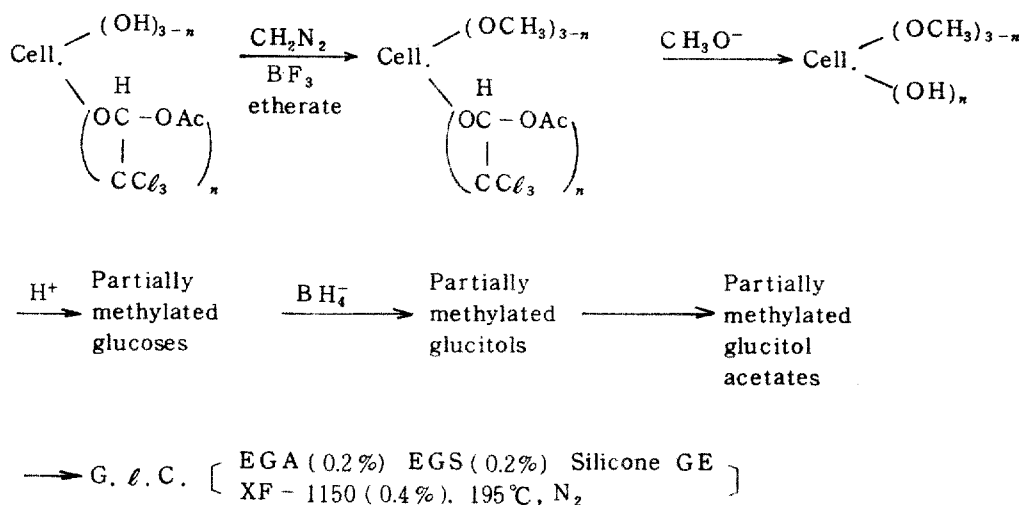


Fig. 6 Examination of acetyl group's distribution in the acetate of cellulose chloral hemiacetal.

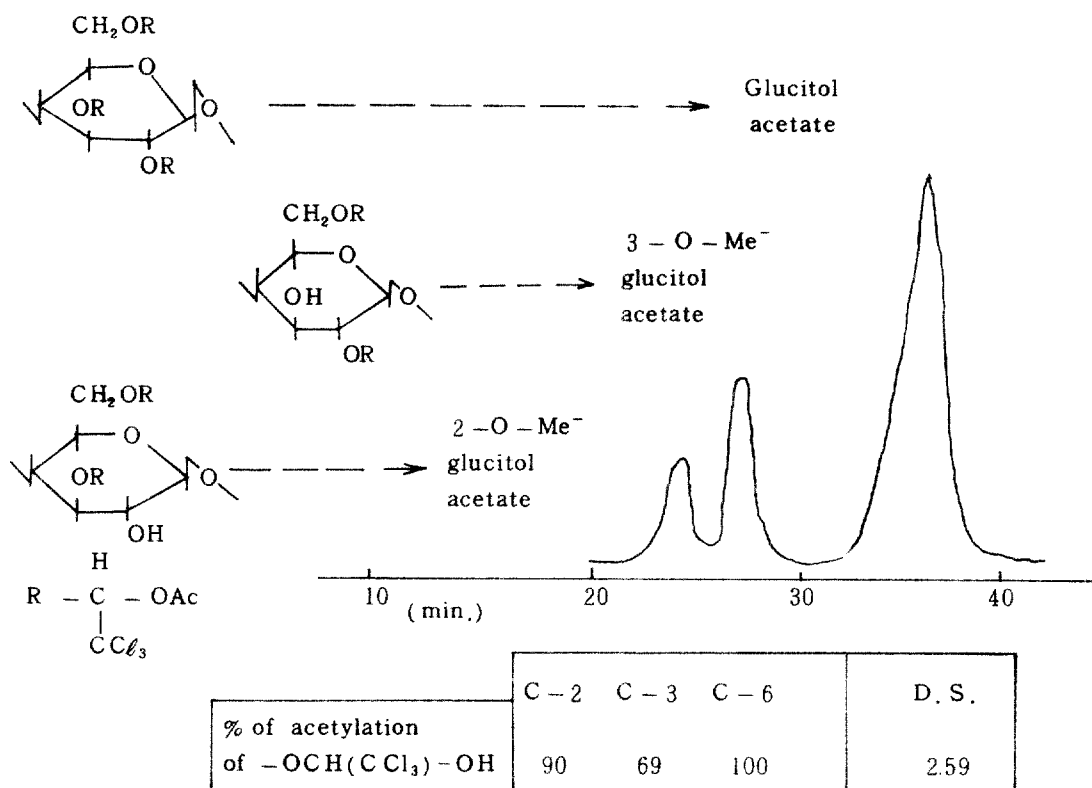


Fig. 7 The extent of acetylation of chloral hemiacetal at each carbon.

were calculated as 90, 69 and 100 %, respectively. As hemiacetal hydroxyl groups are separated from glucose residues by a chloral group, the reactivities of all hydroxyl groups were expected to be equal.

However, the result was against the expectation. Acetylation of these hydroxyl groups, therefore, seem to be sterically different.

The chloral-containing cellulose acetate was found

to be very stable to acid. It remained insoluble in 72 % H_2SO_4 at room temperature even after one year. However, it is unstable to alkali. Clearly this acid-stability is due to the stability of acetyl groups is due to the presence of chloral. Because the chloral group is a strong electron-withdrawing group, it makes the oxygens of ester groups less electron negative and therefore stabilizes the ester from acid catalyzed hydrolysis. On the other hand, glucosidic linkages are stabilized by the bulkiness of chloralhemiacetal acetate substituents. Thus, both the bulkiness and the electron-withdrawing chloral-hemiacetal acetates result in such a high acid-stability of glucosidic linkages.

Acetyl chloride was found to give the same acetate as acetic anhydride. Many kinds of chloral-containing cellulose esters, therefore, may be prepared by the use of a wide variety of acid chlorides. They can be expected to have the same acid-stability as the acetate.

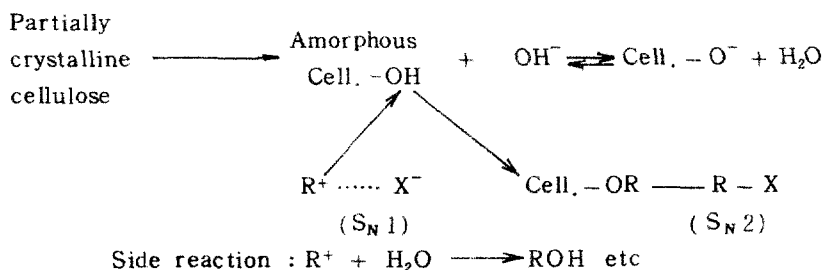
Cellulose ethers are also important cellulose derivatives. Generally cellulose ethers are prepared by the reaction of alkali cellulose with alkyl halides (Fig. 8). In this case cellulose alcoxide anion attack alkyl halide according to the $\text{S}_{\text{N}}2$ mechanism to produce cellulose ethers. In the tritylation, on

the other hand, generally pyridine is used as a base. Pyridine is not strong enough to produce alcoxide anion. Nevertheless, etherification takes place at the hydroxyl group at C-6. This result can be explained by the formation of triphenyl-carbonium cation and the subsequent attack of the hydroxyl group at C-6 by this cation (Sri). The formation of triphenylcarbonium cation is rather easy owing to the presence of three phenyl groups. Also in the case of benzylation, as will be explained later, the formation of benzyl cation were suggested to play an important role.

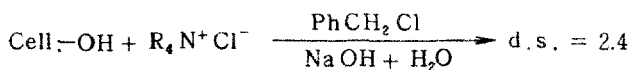
By the way alkali cellulose necessarily contains water, because 17.5 % aqueous solution must be used for its preparation. The presence of water, however, is known to be unfavorable for the preparation of ethers. Therefore, the use of non-aq. cellulose solvents was thought to be ideal for the preparation of cellulose ethers not only because of removal of water but also because of destruction of crystallinity.

The preparation of benzyl celluloses has been tried by us in non-aq. solvents. As this derivative has aromatic substituents, it is a useful intermediate for the preparation of other derivatives. Many researchers has prepared this derivatives, but no

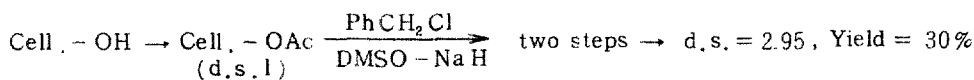
Etherification



Benzylation



(W. H. Daly et al (1979))



(E. Husemann et al (1975))

Fig. 8 Etherification of cellulose.

benzyl cellulose with a d.s. of 3 has been prepared by the heterogeneous reaction. The use of a quaternary ammonium salt as a phase-transfer catalyst gave a rather good result, but the d.s. attained was only 2.4. (Fig. 8). Huseman et al. tried the preparation of tri-*o*-benzyl cellulose from cellulose monoacetate by the use of dimethyl sodium as a base. This reaction was a homogeneous reaction, because the acetate could dissolve in DMSO used as solvent, and a d.s. of 2.95 was obtained after two treatment, but the yield was less than 30%.

Fig. 9 indicates our scheme for the preparation of tri-*o*-benzyl cellulose. Cellulose was dissolved in either in N_2O_4 /DMSO or SO_2 -DEA-DMSO systems. When powdered NaOH was added, the solution turned into a suspension. Clearly neutralization of acidic components in non-aq. solvents (N_2O_4 and SO_2) with NaOH causes precipitation of cellulose. Then equimolecular amount of benzyl chloride was added in four portions. The numerical values in brackets means the fractions of benzyl chloride added at each time to the total amounts of benzyl chloride used. At the end of reaction chloroform and water were added and tri-*o*-benzyl cellulose was extracted. By repeating the dissolution in chloroform and precipitation with hexane, purification with *n*-hexane) → Tri-*o*-benzyl cellulose (T.B.C.)

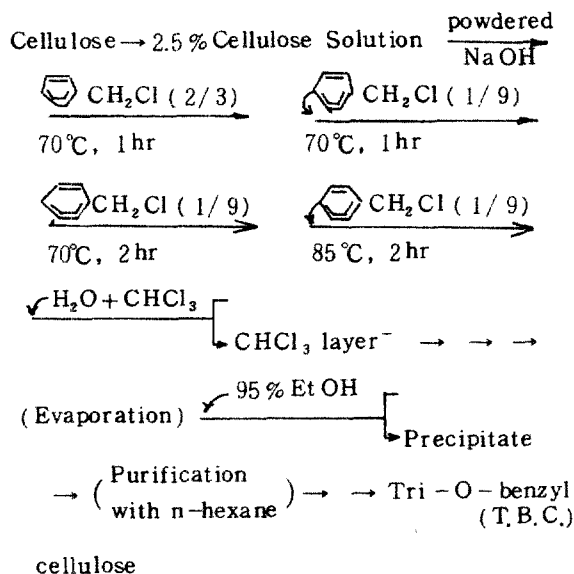


Fig. 9 Scheme for preparation of tri-*o*-benzyl cellulose.

fied tri-*o*-benzyl cellulose could be obtained. The product showed no hydroxyl groups absorption in IR spectrum and has the elementary composition identical with the theoretical one. This results clearly indicates that the precipitation of cellulose caused by addition of NaOH did not prevent cellulose from complete substitution.

Fig. 10 shows the yield of tri-*o*-benzyl cellulose versus molar ratios of NaOH and benzyl chloride to hydroxyl group of cellulose. When N_2O_4 and

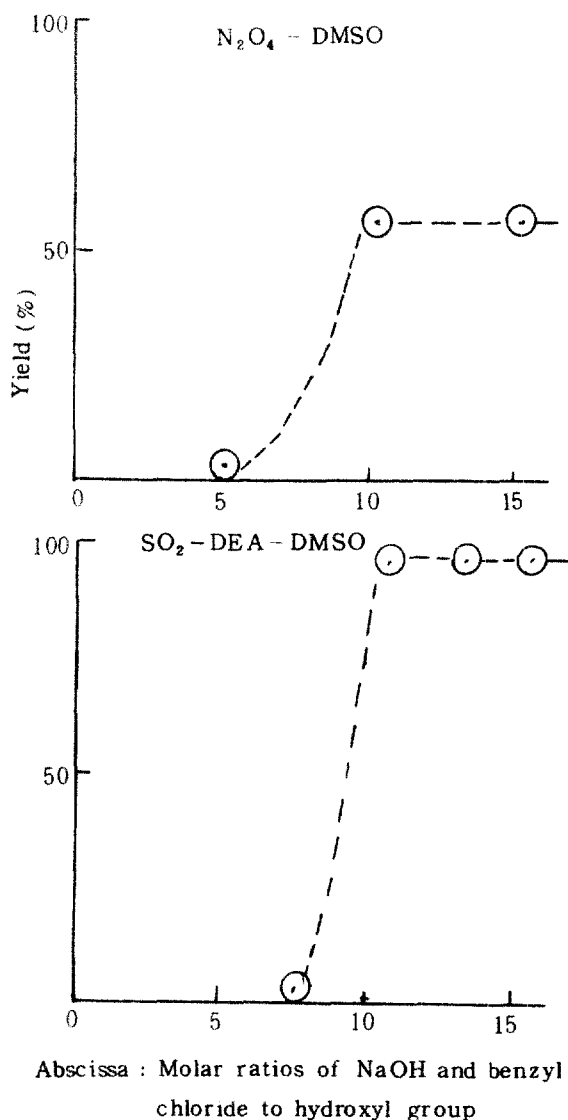
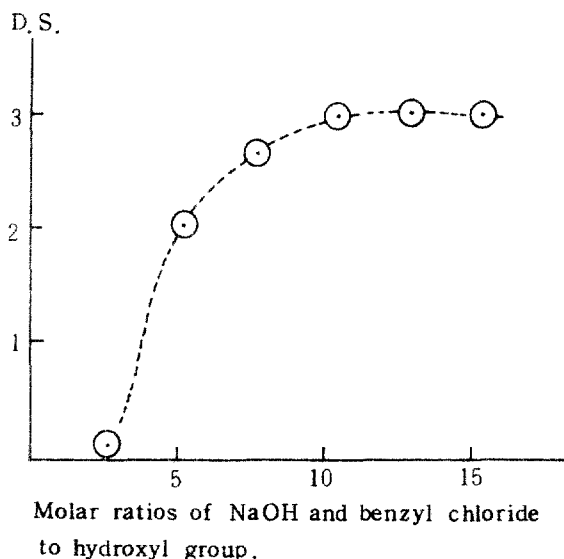


Fig. 10 Yield of Tri-*o*-benzyl cellulose DMSO were used as a reaction medium, the yield of tri-*o*-substituted derivative was 60% at most.

The IR spectrum of CHCl_3 -insoluble fraction showed the presence of carbonyl, carboxyl groups or nitrate group. They must be formed by the effect of N_2O_4 at 70°C . On the other hand, when a mixture of SO_2 , diethylamine and DMSO was used



as a reaction medium, tri-O-benzylcellulose was obtained quantitatively, if enough reagent was used.

The graph in the left side of Fig. 11 shows the dependence of d.s. on the amounts of reagents used. As shown in this graph, the d.s. of benzyl

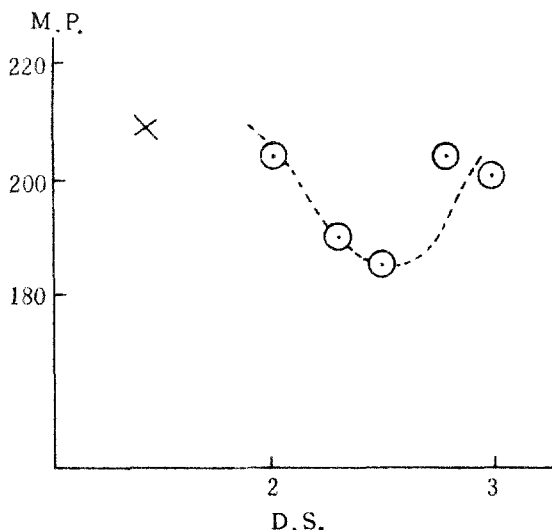


Fig. 11 Dependence of d.s. on the amount of reagents and of m.p. on d.s. of benzyl cellulose

cellulose can be controlled by adjusting the amount of reagents. In this experiment commercial hydrocellulose (Avicel) was used. It is noteworthy that benzyl cellulose having d.s. higher than 2 was found to have m.p. as shown in the right side graph. Among these samples tri-O-benzyl Avicel showed characteristics of thermotropic liquid crystal during the course of cooling after melt. The weight average MW and the number average MW of this sample measured by g.p.c. were 129 and 31, respectively. These low MW values are due to the fact that Avicel was used as starting material and some degradation may also take place during the preparation. On the other hand, tri-O-benzyl cellulose prepared from linter has no m.p. Therefore, M.W. as well as d.s. are important for the appearance of m.p. and characteristics of liquid crystal. This characteristic has been found for water solutions of hydroxypropylcellulose. But characteristics of thermotropic liquid crystal have not been found out for any cellulose derivatives.









Table 1 shows the results of etherification of

Avicel with various alkyl halides. All substituted benzyl chlorides except p-nitrobenzyl chloride could produce tri-O-substituted cellulose ethers. However, alkyl chlorides having no aromatic rings such as t-butyl chloride and α -chloroacetic acid could not produce tri-O-substituted ethers.

Among tri-O-substituted ethers of Avicel in the Table, only benzyl ether and p-methyl benzyl ether showed characteristics of thermotropic liquid crystal during the course of cooling after melt. M.p. of p-methyl benzyl ether is lower than that of benzyl ether. This suggests that benzyl ether having a longer alkyl chain instead of methyl group might have this characteristic at lower temperature than p-methyl benzyl ether.

Etherifications so far performed in non-aq. solution were summarized in Fig. 12. Tritylation could be carried out quantitatively at C-6 in a mixture of SO_2 , DEA and DMSO by the use of pyridine as a catalyst. In this reaction carbonium cation is thought to attack the oxygen atom of hydroxyl groups, as explained previously. Methylation was

Table 1. Alkylation of avicel

Alkyl chloride	Tri-O-substitution	m.p. (°C)	M.P.
 CH ₂ Cl	○	200	← ~200°C
Cl  CH ₂ Cl	○	190	-
CH ₃  CH ₂ Cl	○	169	← ~160°C
CH ₃ O  CH ₂ Cl	○	140	-
 CH ₂ Cl	○	143	-
	○	103	-
O ₂ N  CH ₂ Cl	△	-	-
	○	98	-
t-Bu Cl	×	-	-

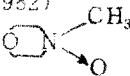
M.P.: mesophase properties. (液晶)

performed in N-ethylpyridinium chloride by the use of dimethyl sodium as a base. Although this methylation yielded a product with high methoxy content, the extent of methylation was not complete.

In our experiment NaOH was used as a base and tri-O-benzyl derivatives could be obtained. In this case, as shown in the Table 1, benzyl chlorides having electron-donating substituents on aromatic rings produced tri-O-benzyl cellulose ethers quantitatively. That is to say, the factor which assists the formation of benzyl cation promotes the formation of tri-O-substituted ethers.

On the other hand neither tri-O-carboxymethyl ether nor tri-O-t-butyl ether could be prepared in our experiment. These results suggest that the formation of both cellulose alkoxide anion and

Etherification

1. Cell. -OH + Ph₃C Cl (Pyridine) / SO₂ - DEA - DMSO (I. Hagiwara et al. (1981))
2. Cell. -OH + PhCH₂Cl (NaOH) / SO₂ - DEA - DMSO (A. Isogai et al. (1982))
3. Cell. -OH + RX (CH₂SOCH₃) /  / PF - DMSO (M.D. Nicholson et al. (1977))

Halogenation (D. Horton et al. (1973))

Cell. -OH in CED - DMF → Prep. → (Washing with AcOH & DMF) → MsCl / DMF → Cell. Cl (d.s. = 0.83)

Fig. 12 Examples of etherification and halogenation of cellulose in non-aq. solvents.

benzyl cation might be necessary for the complete etherification.

Benzyl celluloses are interesting derivatives from the physical property point of view, because they have m.p. and some of them have characteristics of tropic liquid crystal. Benzyl cellulose is interesting derivatives also from the chemical point of view. Because it can be used as an intermediate for the preparation of chemically modified cellulose having special functionalities. In our laboratory we are studying both physical and chemical natures of this derivatives.

Another interesting cellulose derivative is halodeoxy cellulose. Horton et al. prepared chlorodeoxy cellulose with a d.s. of 0.83. In their procedure shown in Fig. 12, cellulose dissolved in cupri-ethylenediamine was precipitated with DMF. The precipitate was washed with DMF containing acetic acid and then with anhydrous DMF to remove CED and water. Cellulose swelled in DMF was treated with methanesulfonyl chloride (MsCl) and chlorodeoxy cellulose having a d.s. of 0.83 was obtained.

We have prepared a highly substituted chlorodeoxy cellulose by the use of non-aq. cellulose solvent in one step. Fig. 13 shows our result. In this

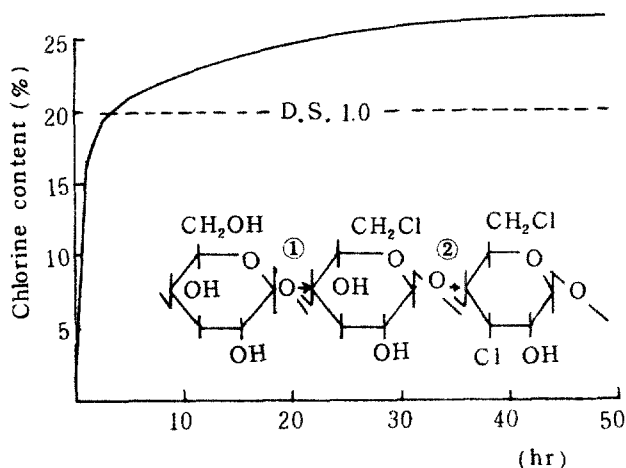


Fig. 13 Chlorination of cellulose with mesyl chloride at 75°C in DMF - Chloral.

experiment hardwood dissolving sulfate pulp was dissolved in a mixture of chloral and DMF and chlorinated at 75°C with MsCl . As shown in the Fig., the chlorine content increased rapidly up to 16% during the first one hour and then slowly up to 24% during 48 hr. These values correspond to the d.s. of 0.8 and 1.3, respectively.

In order to study the position of Cl introduction, chlorodeoxycellulose was hydrolyzed with H_2SO_4 and sugars produced were analyzed as TMS derivatives by g.l.c. This analyses revealed that chlorination

takes place selectively at C-6 to yield 6-chloroglucose residues. After almost of all primary hydroxyl groups are replaced by chlorine atoms, secondary hydroxyl groups at C-3 are subjected to substitution accompanied by the Walden inversion to yield 3,6-di-chloro allose residues. No sugars substituted at C-2 were detected. It is well known that chlorine substituents in sugars can be replaced by amino groups after treatment with ammonia. Thus, it is possible to prepare a polymer containing 6-amino-6-deoxy- and / or 3,6-diamino-3,6-dideoxy sugar residues from this chlorodeoxycellulose. Many other anions can substitute chlorine atoms. Such derivatizations from chlorodeoxycellulose are one of subjects in my laboratory.

In summary the use of non-aq. cellulose solvents made it possible to prepare cellulose derivatives, which can not be prepared by heterogeneous reactions, and to prepare them in good yields. These derivatives, for instance, chloral-containing acetate and tri-O-benzyl celluloses were found to have physically unique characteristics. The use of non-aq. cellulose solvents, furthermore, made it possible to prepare homogeneously cellulose derivatives having the desired d.s. in one step. We succeeded in preparing chemically reactive, highly substituted benzyl cellulose and chlorodeoxycellulose.