Preparation of Tri-*O*-Substituted Cellulose Ethers by the Use of a Nonaqueous Cellulose Solvent

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Synopsis

The previously reported method for the preparation of tri-*O*-benzylcellulose was applied to the preparation of various tri-*O*-substituted cellulose ethers. By this method, in which a mixture consisting of SO_2, diethylamine (DEA), and dimethylsulfoxide (DMSO) and powdered sodium hydroxide were used as a cellulose solvent and a base, respectively, many tri-*O*-arylmethylcelluloses could be prepared from the corresponding chlorides. Cellulose ethers containing double bonds such as tri-*O*-allyl-, tri-*O*-methallyl- , and tri-*O*-2-butenylcellulose were also prepared from the corresponding chlorides under a milder condition than that used for the preparation of tri-*O*-arylmethylcelluloses. Reaction factors accelerating complete etherification were discussed.

INTRODUCTION

Recently many kinds of nonaqueous cellulose solvents have been found, and many fundamental and practical works about them have been reported.[1] In the previous paper,[2] the authors reported that tri-*O*-benzylcellulose could be prepared almost quantitatively with powdered NaOH and benzyl chloride in one of nonaqueous cellulose solvents, SO_2–DEA–DMSO. This derivative was found to show the characteristics of thermotropic liquid crystal during the course of cooling after melting.

In this paper, the procedure used for the preparation of tri-*O*-benzylcellulose was applied to the preparation of other tri-*O*-substituted cellulose ethers, which cannot be prepared easily by etherification of alkalicellulose with halides. Many kinds of tri-*O*-substituted cellulose ethers could be prepared without repetition of etherification by this method. On the other hand, some kinds of reagents could not give the corresponding tri-*O*-substituted cellulose ethers even under severe reaction conditions. Thus, the factors controlling complete etherifications were discussed. All these tri-*O*-substituted cellulose ethers were characterized by infrared (IR) spectra, optical rotations, ^{13}C-NMR spectra, and melting points.

EXPERIMENTAL

Materials. A cellulose sample used was Avicel (commercial cellulose powder manufactured by Asahi Chemical Ind. Co., Ltd., $\overline{DP}_v = 250$). Cellulose was used after dried at 105°C for more than 3 h. The superior grade DMSO was dried over molecular sieve 3A. Another solvents and reagents of reagent grade were used without further purification.

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Preparation of Cellulose Solutions. Cellulose/SO_2–DEA–DMSO solutions were prepared as described in the previous paper.[2]

Preparation of Tri-*O*-Arylmethylcelluloses. Tri-*O*-*p*-methylbenzyl-, tri-*O*-*o*,*p*-dimethylbenzyl-, tri-*O*-*p*-isopropylbenzyl-, tri-*O*-*p*-methoxybenzyl-, tri-*O*-*p*-chlorobenzylcellulose and tri-*O*-α-naphthylmethylcellulose were prepared by the same method as described in the previous paper.[2] In the case of tri-*O*-*p*-bromobenzylcellulose, all *p*-bromobenzyl bromide was added at one time, and the reaction mixture was slowly heated to 60°C and kept at this temperature for 3 h.

Tri-*O*-substituted cellulose ethers were isolated and purified according to the procedure used for tri-*O*-benzylcellulose, but tri-*O*-*p*-isopropylbenzyl- and tri-*O*-α-naphthylmethylcellulose were purified finally by a Sephadex LH-20 column. Characteristics of these tri-*O*-arylmethylcelluloses were summarized in Table I. Complete etherifications were ascertained by the absence of the absorption around 3400 cm^{-1} due to hydroxyl groups in IR spectra.

Preparation of Tri-*O*-Substituted Cellulose Ethers Containing Double Bonds. Tri-*O*-allyl-, tri-*O*-methallyl-, and tri-*O*-butenylcellulose were prepared by a modified procedure of the tri-*O*-arylmethylcelluloses preparation described above. Namely, powdered NaOH of 37.5 mol/glucose residue was added to a cellulose solution at room temperature, and the suspension was stirred for 1–2 h under nitrogen atmosphere. Then allyl, methallyl, or 2-butenyl chloride of 37.5 mol/glucose residue was added dropwise without partition at room temperature with vigorous stirring. The reaction mixture was heated to 70°C and kept at the same temperature for

TABLE I
Analytical Results of Tri-*O*-Arylmethylcelluloses

Cellulose ethers (formula)		Elementary analysis	Optical rotation[a] (°)	Melting point (°C)
Tri-*O*-benzylcellulose ($C_{27}H_{28}O_5$)	Found:	C : 74.6%; H : 6.5%	+17	ca. 200
	Calcd:	C : 75.0%; H : 6.6%		
Tri-*O*-*p*-methylbenzyl-cellulose ($C_{30}H_{34}O_5$)	Found:	C : 75.9%; H : 7.1%	+22	ca. 170
	Calcd:	C : 76.0%; H : 7.2%		
Tri-*O*-*o*,*p*-dimethylbenzyl-cellulose ($C_{33}H_{36}O_5$)	Found:	C : 77.2%; H : 6.8%	+20	ca. 160
	Cacld:	C : 77.3%; H : 7.0%		
Tri-*O*-*p*-isopropylbenzyl-cellulose ($C_{36}H_{46}O_5$)	Found:	C : 77.3%; H : 8.1%	+17	ca. 125
	Calcd:	C : 77.4%; H : 8.2%		
Tri-*O*-*p*-methoxybenzyl-cellulose ($C_{30}H_{34}O_8$)	Found:	C : 69.0%; H : 6.5%	+20	ca. 140
	Calcd:	C : 68.8%; H : 6.6%		
Tri-*O*-*p*-chlorobenzyl-cellulose ($C_{27}H_{25}O_5Cl_3$)	Found:	C : 67.6%; H : 4.5%; Cl : 17.5%	+22	ca. 180
	Calcd:	C : 60.5%; H : 4.7%; Cl : 19.9%		
Tri-*O*-*p*-bromobenzyl-cellulose ($C_{27}H_{25}O_5Br_3$)	Found:	C : 48.4%; H : 3.7%; Br : 35.4%	+20	ca. 160
	Calcd:	C : 48.5%; H : 3.7%; Br : 35.8%		
Tri-*O*-α-naphthylmethyl-cellulose ($C_{39}H_{37}O_5$)	Found:	C : 79.8%; H : 5.8%	−64	ca. 135
	Calcd:	C : 80.0%; H : 6.3%		

[a] Optical rotation, $[\alpha]_D^{20}$ (C 1.0, chloroform).

4 h under nitrogen atmosphere. The reaction products were isolated and purified by the same procedure used for tri-*O*-benzylcellulose soon after etherification in order not to deteriorate those quality by oxidation. Tri-*O*-allyl-, tri-*O*-methallyl-, and tri-*O*-2-butenylcellulose could be prepared almost quantitatively. They must be stored under nitrogen atmosphere at the temperature below 0°C in order to avoid oxidation.

Analyses of Ethers. Degree of substitution (DS) of cellulose ethers was determined by elementary analyses, hydroxyl absorptions in IR spectra, and/or the determination of functional groups. Contents of halogens and double bonds were determined by the microcombution method[3] and by the Wijs method,[4] respectively. IR spectra were measured by the KBr disk technique and the deposited film technique prepared from chloroform solution, using a Shimazu IR-400 Spectrophotometer. ^{1}H-NMR spectra were measured for the determination of DS of carboxymethylcellulose[5] by the use of MH 100 Type Spectrometer (Japan Electro Optics Laboratory JEOL). ^{13}C-NMR spectra were measured using JEOL FX 100 Type Spectrometer and the measuring conditions were as follows: 8000 points, 6000 Hz, pulse delay 0.5 sec, and Fydac accumulation method. Optical rotations were measured, using Jasco SIP-4 Digital Polarimeter. Melting points were determined using a Yanaco micro melting point apparatus.

RESULTS AND DISCUSSION

Preparation of Tri-O-Arylmethylcelluloses

As cellulose ethers are more stable under various chemical conditions than other derivatives such as esters and carbamates, they have been used widely as variously functionalized celluloses. Cellulose ethers are usually prepared by reactions of alkalicellulose with alkyl halides or epoxides. Generally, however, the preparation of highly substituted cellulose ethers, soluble in many organic solvents, is hardly attained.

In the previous paper,[2] the authors revealed that the use of nonaqueous cellulose solvents makes it easy to prepare tri-*O*-benzylcellulose in one step. Clearly, both the decrystallization of cellulose and removal of water from the reaction mixture are favorable for the complete etherification.

In the beginning of this work, various kinds of halides containing aromatic rings were tried to react with cellulose under the same conditions as used for the preparation of tri-*O*-benzylcellulose and tri-*O*-arylmethylcelluloses shown in Table I could be prepared almost quantitatively.

Optical rotations of these derivatives except tri-*O*-α-naphthylmethylcellulose are around 20°, indicating that substituents at aromatic rings have little influence on optical rotations. On the other hand, tri-*O*-α-naphthylmethylcellulose shows a different value from those of the other tri-*O*-arylmethylcelluloses. Bulky naphthylmethyl groups must have stereochemical influence on chiral carbons in the cellulose ether. Physical properties such as melting points, x-ray analyses, and so on will be discussed in the following paper.

IR spectra of these ethers are shown in Figure 1. Each ether has its characteristic bands in the regions of 3100–2800, 1600–1400, and 800–650
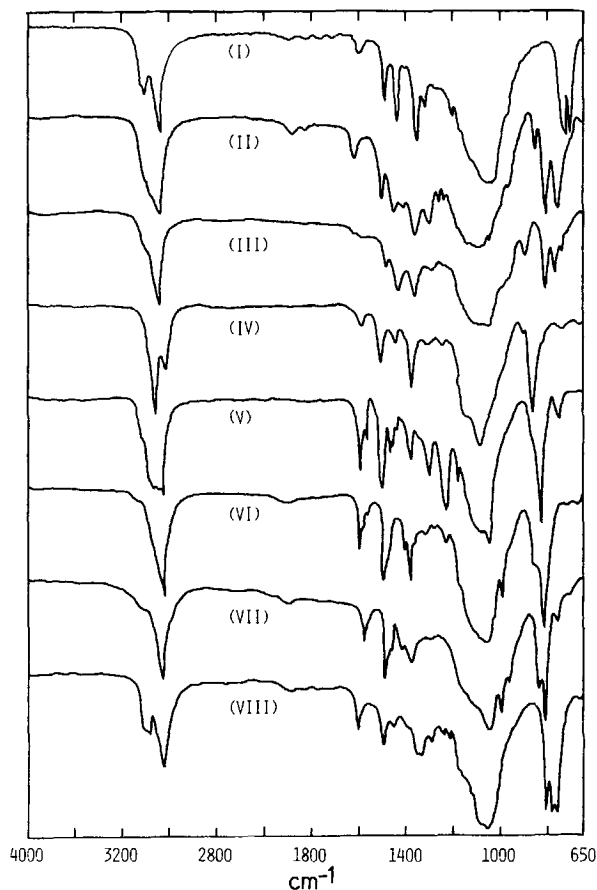
Fig. 1.   Infrared spectra of various tri-*O*-arylmethylcelluloses: (I) tri-*O*-benzylcellulose; (II) tri-*O*-*p*-methylbenzylcellulose; (III) tri-*O*-*o,p*-dimethylbenzylcellulose; (IV) tri-*O*-*p*-isopropylbenzylcellulose; (V) tri-*O*-*p*-methoxybenzylcellulose; (VI) tri-*O*-*p*-chlorobenzylcellulose; (VII) tri-*O*-*p*-bromobenzylcellulose; (VIII) tri-*O*-*α*-naphthylmethylcellulose.

cm^{-1}. These bands are due to C—H stretching vibrations, skeletal vibrations involving carbon to carbon stretching within the aromatic rings, and out-of-plane bending of the aromatic ring C—H bonds, respectively. As the locations and shapes of these characteristic bands are different from each other, IR spectrometry is a convenient way for the identification of these cellulose ethers.

These tri-*O*-arylmethylcelluloses were further characterized by ^{13}C-NMR (Fig. 2). C-6, C-2 (or C-3), and C-3 (or C-2) of each arylmethylated glucose residues are found to be located around 68.0, 82.0, and 83.2 ppm, respectively. Two peaks in the region of 70–75 ppm are due to benzyl carbons linked to O-6, and O-2 and O-3. The peaks due to C-4 and C-5 may overlap with the benzyl or $CDCl_3$ carbons. The chemical shift due to C-1 in every tri-*O*-arylmethylcelluloses appear around 102 ppm, as a single peak. Aromatic carbons have various chemical shifts, depending on substituents on aromatic rings. All signals in the range of 108–160 ppm were assigned to each aromatic carbon on the basis of calculations of empirical substituent increments in aromatic compounds. For example, chemical shifts of C1, C2
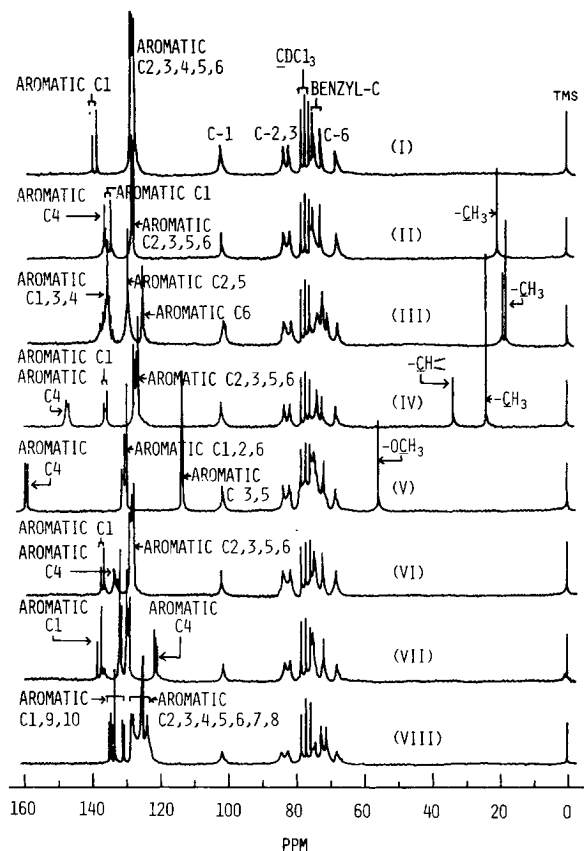
Fig. 2.   ¹³C-NMR spectra of tri-O-arylmethylcelluloses: (I) tri-O-benzylcellulose; (II) tri-O-p-methylbenzylcellulose; (III) tri-O-o,p-dimethylbenzylcellulose; (IV) tri-O-p-isopropylbenzylcellulose; (V) tri-O-p-methoxybenzylcellulose; (VI) tri-O-p-chlorobenzylcellulose; (VII) tri-O-p-bromobenzylcellulose; (VIII) tri-O-α-naphthylmethylcellulose.

(C6), C3 (C5), and C4 in tri-O-p-methylbenzylcellulose are calculated to be 136, 128.7, 128.4, and 137.3 ppm, respectively, and these values coincide well with the measured values of 135.6–136.6, 128.9, 129.9, and 136.9 ppm, respectively.

Preparation of Tri-O-Allyl- and Its Related Cellulose Ethers

Allylation of cellulose is a very important etherification, because its double bond is a reactive functional group. Timell[6] succeeded in the preparation of tri-O-allylcellulose by treating alkalicellulose seven times with allyl bromide in an aqueous medium during a week, but his product was not soluble in any kind of organic solvents. Yoshimura[7] have made systematic studies on allylation of cellulose. He has developed a preparative method of allylcellulose completely soluble in some organic solvents by using a kneader, and reported that allylation of cellulose leveled off at the DS of ca. 2.0. Furthermore, he reported that allylcellulose was very unstable because of facile oxidation of α-carbons in allyl groups followed by crosslinking reac-

tions of produced radicals. Tri-*O*-allylcellulose prepared by Timell must have been denatured and insolubilized by the severe preparative conditions.

In the present work, the authors succeeded in the preparation of tri-*O*-allylcellulose soluble in organic solvents by the use of the SO_2–DEA–DMSO mixture together with powdered NaOH and allyl chloride. Tri-*O*-methallyl- and tri-*O*-2-butenylcellulose also could be prepared similarly almost quantitatively by the use of methallyl chloride and 2-butenyl chloride, respectively. These tri-*O*-substituted cellulose ethers were almost soluble in chloroform, dichloromethane, tetrahydrofuran, benzene, and so on, but completely soluble in these solvents admixed with very small amounts of methanol or ethanol. Figure 3 shows the relation between the amounts of powdered NaOH as a base and DS of methallylcellulose. DS was calculated on the basis of the content of double bonds. This figure indicates that tri-*O*-methallylcellulose could be prepared by the addition of more amounts of powdered NaOH than 12.5 mol/mol hydroxyl group in cellulose, and this value was equal to the case of the preparation of tri-*O*-benzylcellulose.[2] Furthermore, this result indicates that it is possible to control the DS of methallylcellulose by changing the amounts of the base. Figure 4 shows the DS of cellulose ethers versus reaction time at 70°C. As described before, allyl and its related groups are apt to deteriorate. It is necessary, therefore, to shorten the reaction time. This result indicates that it takes 4 h at 70°C to prepare tri-*O*-substituted cellulose ethers containing double bonds. Optical rotations $[\alpha]_{20}^{D}$ of tri-*O*-allyl-, tri-*O*-methallyl-, and tri-*O*-2-butenylcellulose are $+2°$, $+15°$, and $-7°$, respectively (C 1.0, chloroform). IR spectra of these three tri-*O*-substituted cellulose ethers are shown in Figure 5, and the locations of absorptions due to double bonds are well coincide with those in the literature.[8] Namely, $C=C$ stretching vibrations due to $-CH=CH_2$
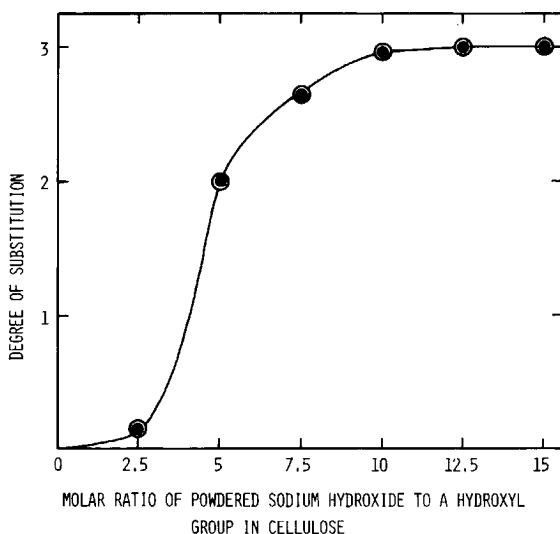

Fig. 3. Degree of substitution of methallylcellulose prepared in SO_2–DEA–DMSO by addition of various amounts of powdered NaOH; methallyl chloride equimolecular to powdered NaOH was added.
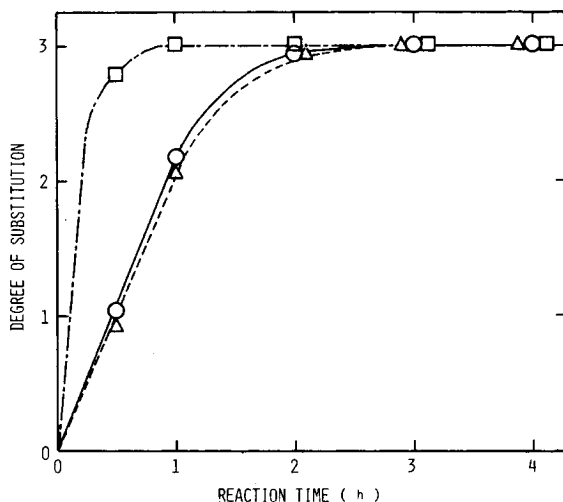
Fig. 4. Reaction between etherifying reagents and powdered NaOH–cellulose suspension at 70°C; molar ratios of powdered NaOH and reagents to a hydroxyl group in cellulose are 12.5, respectively: (○) allylcellulose; (△) methallylcellulose; (□) 2-butenylcellulose.

in tri-*O*-allylcellulose and $C=CH_2$ in tri-*O*-methallylcellulose appear at 1640 and 1650 cm^{-1}, respectively. The bands due to out-of-plane bending of the olefinic C—H bonds in tri-*O*-allyl-, tri-*O*-methallyl-, and tri-*O*-2-butenylcellulose appear at 910, 890, and 960 cm^{-1}, respectively.

^{13}C-NMR spectra of these three derivatives· are shown in Figure 6. The chemical shifts of C-1,2,3,6 in glucose residues are equal to those of tri-*O*-arylmethylcelluloses described in Figure 2. The chemical shifts of α-carbons in substituents are also equal to those of benzyl carbons in tri-*O*-arylmethylcelluloses. It is well known that allyl ethers are transformed to vinyl ethers by treating with a base–DMSO, such as potassium *t*-butoxide–DMSO system at 100°C for several hours. The results of ^{13}C-NMR, however, denied the occurrence of such transformations during etherifications. Because, for
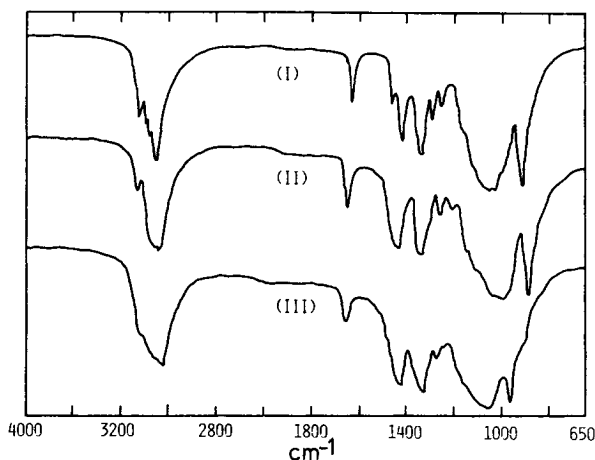

Fig. 5. Infrared spectra of: (I) tri-*O*-allylcellulose; (II) tri-*O*-methallylcellulose; (III) tri-*O*-2-butenylcellulose.
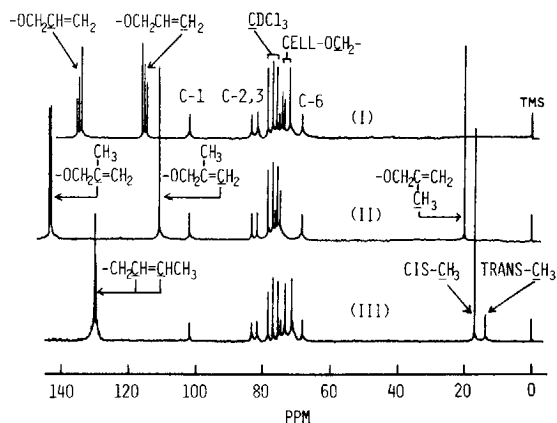
Fig. 6. ^{13}C-NMR spectra of: (I) tri-O-allylcellulose; (II) tri-O-methallylcellulose; (III) tri-O-2-butenylcellulose.

example in the case of tri-O-allylcellulose, the chemical chifts of two allyl carbons containing double bonds are calculated to be 135.7 (—CH=CH$_2$) and 114.6 (—CH=CH$_2$) ppm by the method proposed by Retcofsky and Friedel.[9] On the other hand, the chemical shifts of vinyl ether carbons are calculated to be 143.9 (—O—CH=CH—) and 104.1 (—O—CH=CH—) ppm by the same method.[10] As shown in Figure 6, ^{13}C-NMR spectrum of tri-O-allylcellulose has the peaks of ca. 135 and 116 ppm, and the corresponding peaks to vinyl ether carbons cannot be detected. Also in the case of the other two cellulose ethers containing double bonds, the same conclusions were obtained by the calculation methods.

Factors Causing Complete Etherification

Table II shows the results of etherifications so far examined. Many arylmethyl halides (nos. 13–21) yielded the corresponding tri-O-substituted cellulose ethers (Table I). Among arylmethyl halides, however, benzyl halides substituted with a nitro group (nos. 22, 23, and 26) and a vinyl group (no. 24) yielded large amounts of byproducts unseparable from cellulose derivatives. α-Methylbenzyl chloride (no. 25) also yielded polymeric byproducts, possibly polystyrene. Thus, the DS of cellulose derivatives obtained by the reactions with the reagents nos. 22–26 could not be determined. As described in the previous section, allyl chloride and its related chlorides (nos. 27–30) also yielded tri-O-substituted cellulose ethers. The other chlorides and bromides in Table II (nos. 3–12) did not yield tri-O-substituted ethers.

These examples indicate that only chlorides and bromides which can produce benzyl or allyl cations have abilities to yield tri-O-substituted cellulose ethers. These cations can be easily formed by heating, because carbocations in these cations can be stabilized by the conjugation with a phenyl group or a double bond. Carbocations can attack hydroxyl groups polarized to some extent by the presence of NaOH. t-Butyl chloride (no. 3), which seem to produce the stable carbocation, was not so effective because the steric factor and/or side reactions such as elimination reactions producing

TABLE II

Etherification of Cellulose by the Use of SO_2–SEA–DMSO System as a Cellulose Solvent

No.	Reagent	DS	No.	Reagent	DS
1	$(CH_3)_2SO_4$	2.2	17	p-$CH_3OC_6H_4CH_2Cl$	3.0
2	CH_3I	2.3	18	p-$ClC_6H_4CH_2Cl$	3.0
3	$(CH_3)_3CCl$	1.0	19	p-$BrC_6H_4CH_2Cl$	3.0
4	$CH_3(CH_2)_3Cl$	1.0	20	p-$BrC_6H_4CH_2Br$	3.0
5	$ClCH_2COONa$	1.6	21	α-naphthylCH_2Cl	3.0
6	H_2NCOCH_2Cl	1.0[a]	22	p-$O_2NC_6H_4CH_2Cl$	—[c]
7	$Et_2NCH_2CH_2Cl \cdot HCl$	0.5	23	m-$O_2NC_6H_4CH_2Cl$	—[c]
8	$(CH_3O)_2CH_2CH_2Cl$	0.5	24	p-$CH_2{=}CHC_6H_4CH_2Cl$	—[c]
9	$CH_3COOCH_2CH_2Cl$	1.0[b]	25	$C_6H_5CH(CH_3)Cl$	—[c]
10	CH_3OCOCH_2Cl	1.0[a]	26	p-$O_2NC_6H_4CH_2Br$	—[c]
11	$C_6H_5CH_2CH_2Cl$	0.5	27	$CH_2{=}CHCH_2Cl$	3.0
12	$C_6H_5CH_2CH_2Br$	0.5	28	$CH_2{=}C(CH_3)CH_2Cl$	3.0
13	$C_6H_5CH_2Cl$	3.0	29	$CH_3CH{=}CHCH_2Cl$	3.0
14	$pCH_3C_6H_4CH_2Cl$	3.0	30	$C_6H_5CH{=}CHCH_2Cl$	3.0
15	o,p-$(CH_3)_2C_6H_3CH_2Cl$	3.0	31	$CH_2{=}CHCH_2Br$	—[d]
16	p-$(CH_3)_2CHC_6H_4CH_2Cl$	3.0	32	$C_6H_5COCH_2Br$	—[d]

[a] Partial carboxymethylation occurred.
[b] Partial hydroxyethylation occurred.
[c] By-products were produced.
[d] Gelation occurred.

2-methypropylene restrict the etherifications. Naturally allyl bromide (no. 31) was expected to yield a tri-*O*-substituted ether, but the addition of this reagent as well as phenacyl bromide (no. 32) caused heat evolution accompanied by the gelation of reaction mixture. The reaction condition used here might have been too severe for these reactive bromides.

Tri-*O*-carboxymethylcellulose could not be prepared with sodium chloroacetate even under severe conditions. Neither dimethylsulfate (no. 1) nor methyl iodide (no. 2) yielded tri-*O*-methylcellulose.

CONCLUSION

Two types of tri-*O*-substituted cellulose ethers could be prepared by the use of powdered NaOH as a base and SO_2–DEA–DMSO as a cellulose solvent: (1) tri-*O*-arylmethylcelluloses; (2) tri-*O*-allyl and its related cellulose ethers.

The reagents yielding tri-*O*-substituted cellulose ethers under the condition used were found to have the structures which can yield resonance-stabilized carbocations: substituted benzyl or substituted allyl cations.

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