Polymer Bulletin 45, 381–388 (2000)

Polymer Bulletin
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Phase transition of thermosensitive amphiphilic cellulose esters bearing olig(oxyethylene)s

Qui Zhou[1], Lina Zhang[1] (✉), Masahiko Minoda[2], Takeaki Miyamoto[2]

[1] Department of Chemistry, Wuhan University, Wuhan 430072, China
[2] Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan
e-mail: lnzhang@public.wh.hb.cn, Fax: 86-27-87686402

Received: 29 August 2000/Revised version: 16 October 2000/Accepted: 31 October 2000

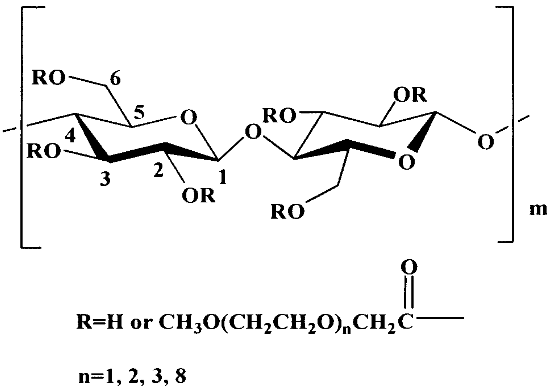
Summary

A series of cellulose esters bearing olig(oxyethylene)s with different degree of substitution (DS) and different length of the oxyethylene chain were synthesized by a homogeneous reaction of cellulose with corresponding monofunctional acid chloride in a 10% LiCl-dimethyl acetoamide (DMAc) solution. The effect of total DS value on the solubility of the derivatives in aqueous solution was investigated. It was found that the lower limit DS value for both water-soluble and amphiphilic derivatives decreases with increasing length of oxyethylene chains. The amphiphilic derivatives, which are soluble in both water and chloroform, precipitate out of aqueous solution on heating without gel forming, such a phase transition behavior was studied in terms of DS value, length of oxyethylene and concentration. The precipitation temperature (T_p) of the amphiphilic derivatives is range from 54°C to 96°C. It decreases with increasing the total DS value, and increases with an increase in the length of oxyethylene chains. The T_p value of the derivatives was found to be almost independent in the concentration range of 1-15 wt %, however the T_p value increases sharply with decreasing polymer concentration when the concentration is lower than 1 wt%.

Introduction

Thermosensitive polymers have been studies extensively over the past decade [1]. The applications of water-soluble amphiphilic polymers with thermosensitivity are currently expanding to the various fields including polymeric surfactants, rheology modifiers, drug carriers, polymer blend compatibilizers, and phase transfer catalysts. Amphiphilic comb-shaped polymers branched with poly(ethylene oxide) (PEO), a water-soluble polymer, are of special interest because of their useful properties, such as solubility in both aqueous and organic solvents, non-ionic character, biocompatibility and metal complex ability [2-4]. More recently, a new class of biodegradable thermosensitive polymers from poly(organophosphazenes) with methoxy-poly(ethylene glycol) and amino acid esters as side groups were synthesized [5], these thermosensitive polymer solutions exhibit a lower critical solution temperature (LCST), defined as the critical temperature at which a polymer solution undergoes phase transition from a soluble to an insoluble state with increasing temperature. The main mechanism of a thermally induced phase transition of aqueous polymer solutions is a drastic change in the hydrophilic-hydrophobic balance of the polymer. Understanding of these properties of the thermo-sensitive polymers is essential for the wide application such as membranes, drug delivery systems, cell culture, isolation of biomolecules, and enzyme activity control.

Plant cellulose is the richest natural polymer on the earth, where thousands and hundred millions ton of cellulose occur per year [6]. Recently, cellulose has been reevaluated as functional material because of unique reactivates and molecular characteristics such as hydrophilic, chiral and semi-rigid etc. [7]. Of the nonionic cellulose derivatives, methylcellulose (MC) [8] hydroxyethyl cellulose (HEC) and hydroxypropyl cellulose (HPC) [9] are water-soluble ether derivatives with thermosensitivity. Although the chemical stability of cellulose ester is lower than that of ether derivatives, esterification of cellulose is the most simple and economical reaction. However, amphiphilic comb-shaped ester derivative with thermosensitivity from cellulose has been scarcely reported. In this work, comb-shaped, thermosensitive amphiphilic cellulose ester derivatives bearing side groups of oligo(oxyethylene)s ($-COCH_2(OCH_2CH_2)_n-OCH_3$) were synthesized by a homogeneous reaction of cellulose with corresponding monofunctional acid chloride in a 10% LiCl-DMAc solution. The reaction characteristics and the solubility of the resulting derivatives (Figure 1) were examined. The phase transition behavior of the resulting derivatives was studied and discussed.



$R=H \text{ or } CH_3O(CH_2CH_2O)_nCH_2\overset{O}{\overset{\|}{C}}-$

Figure 1. Chemical structures of the comb-shaped cellulose ester derivatives bearing olig(oxyethylene)s

Experimental

Materials

Whatman CF-11 fibrous cellulose powder and methoxypolyethylene glycols ($CH_3O(CH_2CH_2O)_nCH_2COOH$) were used as starting materials. The chemicals of n=1 and 2 were purchased from Aldrich Chemicals. The reagents of n=3 and 8 were prepared from the corresponding methoxy-polyethylene glycol according to the ref. 10. Pyridine, tetrahydrofuran (THF), dimethyl acetoamide (DMAc), lithium chloride (LiCl) and dimethyl formamide (DMF) were dried and purified according to the standard procedures. Thionyl chloride and acetic anhydride were reagent grade and used without further purification. The methoxypolyethylene glycols ($CH_3O(CH_2CH_2O)_nCH_2COOH$) (0.4mol), DMF (0.04mol) and thionyl chloride (0.44mol) were mixed and heated at 80 °C for 2.5 h. Then the mixture solution was evaporated under vacuum to remove DMF and unreacted thionyl chloride. The residual liquid was monofunctional acid chloride, and was used for the next reaction without further purification.

Synthesis of the cellulose esters

The solution of 2% cellulose powder in LiCl-DMAc was prepared according to McCormick's method [11]. The cellulose ester derivatives were prepared by homogeneous esterification of cellulose with corresponding monofunctional acid chloride in a 10% LiCl-DMAc solution combined with pyridine as acid acceptor [12]. A known amount of acid chloride was added to the solution containing a small amount of co-solvent THF, which was a better solvent for the product [13], and the reaction was carried out at 60 °C for 4 h. The reaction mixture was poured into ethanol, and the precipitate was separated by filtration. For the water-soluble products, the precipitates were redissolved in deionized water, then dialysed, and finally freeze-dried. For the water-insoluble products, the precipitates were throughout washed with methanol and vacuum-dried at 60 °C. The samples were coded as EO-n-DS. Here, n represents the length of oxyethylene chains, and DS means the degree of substitution of the cellulose ester derivatives.

Characterization

^{13}C NMR spectra of the samples were recorded on a JEOL GX-400 spectrometer operating at 100.8 MHz in the proton noise-decoupling mode by using a standard 5 mm probe and deuterated DMSO (DMSO-d_6) as solvent at 80 °C. The quantitative-mode ^{13}C NMR measurement conditions followed closely those in the structural analysis of the cellulose derivatives [14,15]. The relative DS value at an individual hydroxyl group was estimated from the ratio between peak areas. The peak areas were determined by the weight cut from photocopies. Precipitation temperature (T_p) was evaluated on 1wt% aqueous solutions of the samples. A UV-2200 spectrophotometer (Shimadzu, Japan) was used for the evaluation of T_p. The light transmittance of the aqueous solutions at a 600nm wavelength was measured as a function of temperature. Since precipitation is time-dependent kinetic phenomena, the heating rates were fixed to 0.1 °C/min for all measurements. T_p in this study is expressed in terms of the temperature at which 50% of the original transmittance value [16]. T_p and the lower critical solution temperature (LCST) are of the same meaning. In order to confirm the stability of the derivatives with low DS values in aqueous solution at 60 °C, their inherent viscosity $1n\eta_r/c$ of the polymer solution (c=0.004 g/mL) was measured by viscometry.

Results and discussion

Structure characterization

Figure 2 shows the ^{13}C NMR spectrum of the sample EO-2-1.7, the assignment of the peaks is according to ref. 17. From the ring carbon region (50~100 ppm) and the carboxyl group region (165~175 ppm), the total DS value and the distribution of substituents within the anhydroglucose (AHG) units were determined according the method of ref. 14,15. The results of the DS value and distribution of the substituent of the cellulose ester derivatives are summarized in Table 1. The cellulose esters bearing olig(oxyethylene)s with different DS value from 0.4 to 3.0 (n=1), from 0.5 to 3.0 (n=2), from 0.3 to 2.85 (n=3) and from 0.1 to 1.9 (n=8) were successfully synthesized. To be noted here is that the acid chlorides of oligo(oxyethylene)s preferentially react with the primary hydroxyl group at C-6, that is, the reactivity order is C-6 >> C-2 > C-3. Such a regioselectivity is quite different from the case of the cellulose acylates prepared by the acid-anhydride method [18].

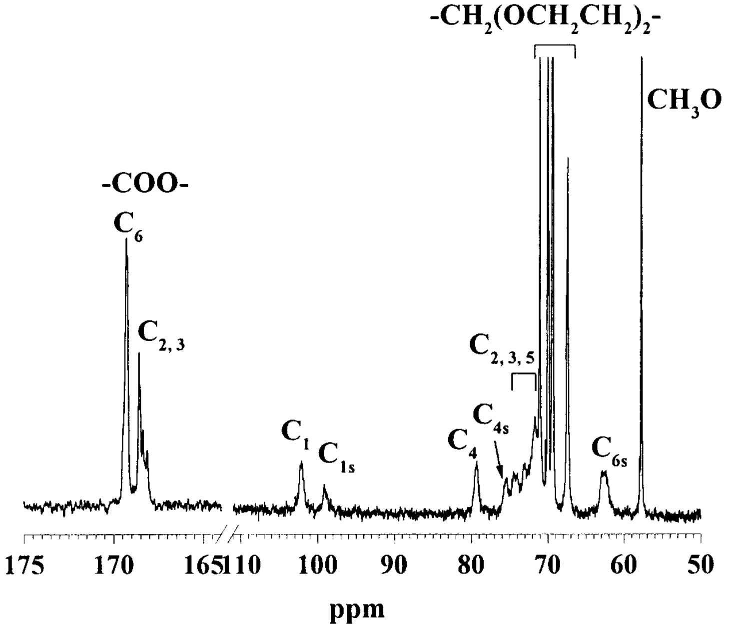


Figure 2. ^{13}C NMR spectra of samples EO-2-1.7 (DS=1.7) in DMSO-d_6 at 80 °C

Solubility of the cellulose esters

The cellulose esters synthesized from a homogeneous reaction have a uniform distribution of substituents along the main chain, which result in a uniform solubility [13]. The solubility of the derivatives is also summarized in Table 1. Clearly, the solubility depends on the total DS value and the length of the substituents. In the case of n=2, the derivatives having a DS value higher than about 0.5 were completely soluble in water, and those having a DS higher than 1.7 became amphiphilic derivatives, which are soluble in both water and common organic solvents.

Table 1. Solubility, DS value and distribution of the substituents of the cellulose esters having pendant oligo(oxyethlene)s

Sample code	Solubility [a]				DS at position			Total
	H_2O	DMSO	THF	$CHCl_3$	C_6	C_2	C_3	DS
EO-1-0.4	O	O	×	×	0.4	0	0	0.4
EO-1-1.1	O	O	×	×	0.8	0.2	0.1	1.1
EO-1-1.3	O	O	×	×	0.9	0.2	0.2	1.3
EO-1-2.5	O	O	O	O	1.0	0.8	0.7	2.5
EO-1-3.0	O	O	O	O	1.0	1.0	1.0	3.0
EO-2-0.5	O	O	×	×	0.5	0	0	0.5
EO-2-0.7	O	O	×	×	0.7	0	0	0.7
EO-2-1.3	O	O	×	×	1.0	0.2	0.1	1.3
EO-2-1.7	O	O	O	O	1.0	0.4	0.3	1.7
EO-2-2.0	O	O	O	O	1.0	0.5	0.5	2.0
EO-2-2.6	O	O	O	O	1.0	0.8_5	0.7_5	2.6
EO-2-3.0	O	O	O	O	1.0	1.0	1.0	3.0
EO-3-0.3	O	O	×	×	0.3	0	0	0.3
EO-3-1.5	O	O	O	O	0.8	0.4	0.3	1.5
EO-3-2.4	O	O	O	O	0.9	0.8	0.7	2.4
EO-3-2.8	O	O	O	O	1.0	0.9_5	0.9	2.8_5
EO-8-0.1	×	O	×	×	0.1	0	0	0.1
EO-8-0.2	O	O	×	×	0.2	0	0	0.2
EO-8-0.7	O	O	×	×	0.6	0.0_5	0.0_5	0.7
EO-8-1.2	O	O	O	O	0.7	0.3	0.2	1.2
EO-8-1.9	O	O	O	O	0.9	0.6	0.4	1.9

[a] O, soluble; ×, insoluble. For 1% (w/w) solution at 25 °C

The lower limits for the DS values of water-soluble derivatives and amphiphilic derivatives with different length of oxyethylene chains are summarized in Table 2. Amphiphilic derivatives mean that they are soluble in both water and common organic solvents. With increasing length of oxyethylene chains, the lower limit DS value for amphiphilic derivatives decreases, while that for water-soluble derivatives also slightly decreases. Interestingly, in the case of n=8, the lower limit DS value for water soluble derivatives is about 0.2, which is much lower than those of water-soluble methylcellulose (MC, DS=0.7) [19] and water-soluble O-(2-hydroxy-3-butoxypropyl)cellulose (HBPC, DS=0.4) [20], and the lower limit DS value for amphiphilic derivatives is also very low (DS=1.2). It is obvious that such solubility is owing to the introduction of hydrophilic and bulky olig(oxyethylene)s substiuents and also the hydrophilicity of the cellulose ester derivatives increases with increasing length of oxyethylene chains.

Table 2. Solubility behavior of cellulose esters having pendant oligo(oxyethylene)s

n [a]	Lower limit DS	
	Water-soluble	Amphiphilic [b]
1	0.4	~2.5
2	0.5	~1.7
3	0.3	~1.5
8	0.2	~1.2

[a] $CH_3O(CH_2CH_2O)_nCH_2COO–$
[b] soluble in chloroform

Phase transition in aqueous solution

The phase transition of thermosensitive polymers in aqueous solution is attributed to a change in the hydrophilic-hydrophobic balance of the polymers with respect to their interaction through hydrogen bonding between the polymer and water molecules. Below the LCST, the hydrogen-bonding interactions predominate over the hydrophobic interaction of the polymers, which results in water-soluble solutions. On the other hand, when the hydrogen-bonding interactions are weakened and the hydrophobic interaction of the polymer increases, the polymer precipitates from the solution [5]. The cellulose ester derivatives with low DS values were soluble in hot water, i.e., no precipitation or gelation was observed even when the temperature was raised to 100°C. The storage time (t) dependences of $\ln\eta_r/c$ values of the samples EO-8-0.2 and EO-8-0.7 in aqueous solution at 60°C is shown in Figure 3. The $\ln\eta_r/c$ values did hardly change even after 6 hours, suggesting the cellulose ester derivatives with low DS values are stable in the presence of water.

On the other hand, it was found that the amphiphilic derivatives, which are soluble in both water and chloroform, precipitate out from aqueous solution on heating without gel forming. The T_p value of derivatives is range from 54°C to 96°C with different DS value and length of oxyethylene chain. Figure 4 shows the DS dependence of precipitation temperature (T_p) of the cellulose ester derivatives bearing olig(oxyethylene)s in 1 wt% aqueous solution. The T_p decreases with increasing the total DS value, and increases with an increase in the length of oxyethylene chains. The hydrophilicity of the derivatives increases with an increase in the length of oxyethylene chain, and causes an increase in the T_p of the derivative solution. This result is consistent with the polyphosphazenes substituted with various alkyl ethers by Allcock [21]. It was noted that with increasing the alkyl ether chain length the opportunities for hydration of alkyl ether groups increased, resulting in an increase of LCST. On the other hand, the hydrophobicity of the derivatives increases with an increase in the total DS value, resulting in a decrease in the T_p temperature, similar to the methyl cellulose [8].

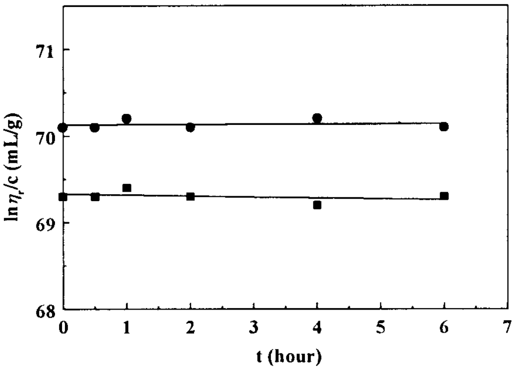


Figure 3. The storage time (t) dependences of $\ln\eta_r/c$ values of the samples EO-8-0.2 (■) and EO-8-0.7 (●) in aqueous solution at 60°C

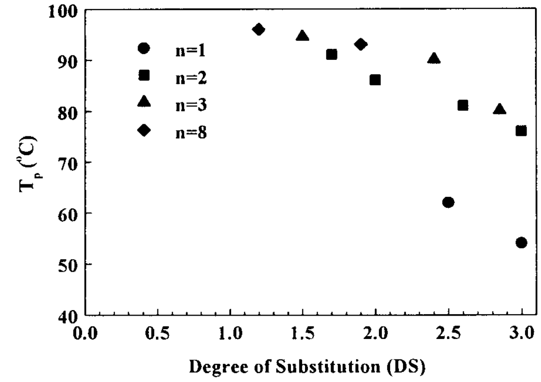


Figure 4. DS dependence of precipitation temperature (T_p) of the cellulose ester derivatives bearing olig(oxyethylene)s in 1wt% aqueous solution

Figure 5 shows the concentration dependence of precipitation temperature (T_p) for the cellulose ester derivatives EO-1-3.0, EO-2-3.0, EO-3-2.8, which was determined in concentration range of 0.1-15 wt% of the derivatives in aqueous solution. The derivatives precipitated at all concentrations, and no significant differences in the concentration dependence of T_p behavior were found among the derivatives. The T_p value of the derivatives was found to be almost independent in the concentration range of 1-15 wt %, however the T_p value increases sharply with decreasing polymer concentration when the concentration is lower than 1 wt%, similar to other thermosensitive polymers [5].

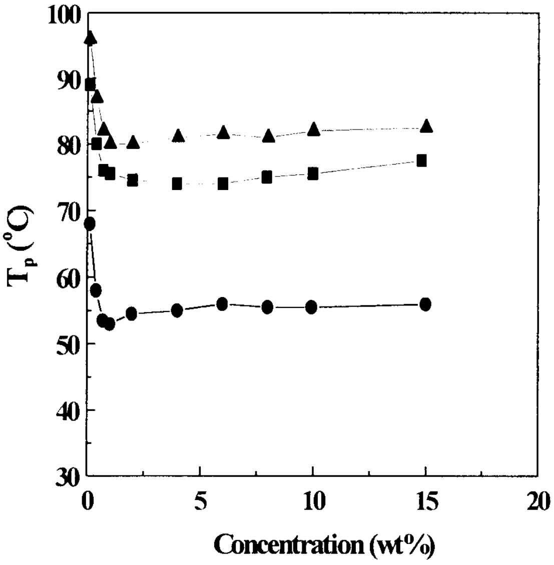


Figure 5. Concentration dependence of precipitation temperature (T_p) for the cellulose ester derivatives EO-1-3.0 (●), EO-2-3.0 (■), EO-3-2.8 (▲)

Conclusions

A series of cellulose esters bearing olig(oxyethylene)s with different DS values and different length of the oxyethylene chain were successfully synthesized by a homogeneous reaction of cellulose with corresponding monofunctional acid chloride in a 10% LiCl- DMAc solution. It was found, that the solubility and the phase transition behavior of such cellulose ester derivatives was rather depend on the total DS values and the length of the oxyethylene chain than the polymer concentration in the aqueous solution. Such results indicate that appropriate length of oxyethylene chain and the degree of substitution can control the Tp value of the cellulose ester derivatives. These thermosensitive cellulose ester derivatives are expected to be useful for application to various fields because of their useful properties, such as amphiphilicity, non-ionic character, biocompatibility and biodegradability.

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