Carbohydrate Polymers 114 (2014) 530–536

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Novel pH- and temperature-responsive polymer: Tertiary amine starch ether

Xu Yuan, Benzhi Ju*, Shufen Zhang

State Key Laboratory of Fine Chemicals, Dalian University of Technology, 2 Linggong Rd., Hi-tech Zone, Dalian 116024, Liaoning, PR China

ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form 8 August 2014
Accepted 8 August 2014
Available online 26 August 2014

Keywords:
Starch
Tertiary amine polymer
Phase separation
Stimuli-responsive polymers

ABSTRACT

A novel double pH- and temperature-responsive tertiary amine starch ether (TAS) has been developed. Synthesis was performed by grafting dipropyl or dibutyl epoxypropylamine onto hydroxyethyl starch. The cloud point temperatures (T_C) of TAS could be tuned to a wide range from 26 to 72.8 °C by changing the alkyl chain length, their average molar substitution (MS), and pH value of the solution. The T_C of TAS increases with decreasing the alkyl chain length, MS, and pH value of the solution. A linear relationship occurs between the T_C and the pH, indicating well-tunable T_C. These TAS also showed single pH-sensitive property due to the existence of tertiary amino and hydrophobic alkyl groups. The synthetic strategy presented here could be employed in the preparation of other novel biomaterials with dual pH- and temperature-responsive properties from a variety of polysaccharides.

1. Introduction

Polymers responding to more than one stimulus, in particular to temperature and pH, have received much attention. These dual functional systems have great importance in biological applications and can mimic the responsive macromolecules found in nature (Chen & Hoffman, 1995; Klaikherd, Nagamani, & Thayumanavan, 2009). In the past decade, various types of pH- and temperature-responsive polymers have been prepared. Among them, tertiary amine-containing polymers are some of the most frequently investigated pH- and temperature-responsive polymer (Deen, 2012; Han et al., 2013; Jung, Song, Lee, Jeong, & Lee, 2011; Xiao et al., 2014). The most widely studied example of this type of polymer is poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMA) and its related copolymers (Han et al., 2013; Plamper et al., 2007). PDMA has antibacterial, hemostatic, and anticancer activity (Rawlinson et al., 2010). It has been employed in the preparation of new drug or gene delivery systems because of excellent biocompatibility (Newland et al., 2013; Peng et al., 2011). The cloud points of PDMA can be easily turned by adjusting the pH of the aqueous solution. This is possible since the protonation degree of the tertiary amine group in PDMA varies depending on pH of the aqueous solution, and the hydrophobic–hydrophilic balance of PDMA change significantly at different pH. The analogous poly(*N*,*N*-diethylaminoethyl methacrylate) (PDEA) (Schmalz, Hanisch, Schmalz, & Muller, 2010) and poly(*N*-ethylpyrrolidine methacrylate) (PEPyM) (Gonzalez, Elvira, & Roman, 2005) homopolymers also exhibit pH- and temperature-responsive properties due to the presence of ionizable amine groups and hydrophobic *N*-alkyl groups. Contrarily, the cloud points of PDEA and PEPyM are low compared to that of PDMA. For example, at pH 7 the cloud point of PDMA is 80 °C, whereas the value for PDEA is 40 °C. Furthermore, PDEA exhibits pH-dependent solubility and is soluble in acidic solution as a weak cationic polyelectrolyte. At 25 °C, PDEA phase-separates out at a neutral pH, whereas PDMA is soluble over the whole pH range. These differences can be attributed to the more hydrophobic alkyl substituents at the amino group of PDEA.

In recent years, pH- and temperature-responsive polysaccharides have raised interest due to their degradable potential and biocompatibility. A popular preparation strategy is the grafting of stimuli-responsive polymers onto a polysaccharide backbone. Various dual sensitive grafted polysaccharide derivatives have been researched, such as cellulose-graft-poly(*N*,*N*-dimethylamino-2-ethyl methacrylate) (cellulose-g-PDMA) (Sui et al., 2008), hydroxypropyl cellulose-graft-poly(*N*,*N*-dimethyl aminoethyl methacrylate) (HPC-g-PDMA) (Ma et al., 2010b, hydroxypropylcellulose-graft-poly(4-vinyl pyridine) (HPC-g-P4VP) (Ma, Kang, Liu, & Huang, 2010a), chitosan-graft-poly[2-(*N*,*N*-dimethylamino)ethyl methacrylate] (CS-g-PDMA) (Yuan et al., 2011). However, the main drawback of most techniques reported is an unwanted homopolymer produced with the graft copolymer (Sui et al., 2008). On the other hand, the polysaccharides render stimuli-responsiveness due to the LCST transition of the stimuli-responsive polymers

* Corresponding author. Tel.: +86 411 84986269; fax: +86 411 84986264.
E-mail address: jubenzhi@dlut.edu.cn (B. Ju).

http://dx.doi.org/10.1016/j.carbpol.2014.08.043
0144-8617/

grafted onto polysaccharide backbone. Thus, the LCST of stimuli-responsive polysaccharides is usually similar to that of grafted stimuli-responsive polymers and difficult to adjust.

In this work, a new strategy has been proposed for preparing pH- and temperature-responsive polysaccharides. Additionally, a new kind of pH- and temperature-responsive tertiary amine containing polymer, namely tertiary amine starch ethers (TAS), has been developed. Starch is the second most abundant polysaccharide produced by plants. Starch and its derivatives have emerged as one of the most promising biomaterials for drug carriers due to their biodegradability and biocompatibility. It has been demonstrated that thermo-responsive starch can be synthesized by controlling the hydrophobic–hydrophilic balance of starch derivatives (Ju, Cao, & Zhang, 2013; Ju, Yan, & Zhang, 2012). Epoxypropyl tertiary amines contain ionizable amino groups, two hydrophobic alkyl chains, and highly reactive epoxy groups. It is expected that starch modified by epoxypropyl tertiary amine would be sensitive to temperature and pH changes due to the existence of ionizable amine groups, a hydrophilic starch backbone, and hydrophobic *N*-alkyl groups. Based on this, a novel class of pH- and temperature-responsive TAS has been successfully prepared by a simple etherification reaction between epoxypropyl tertiary amine and hydroxylethyl starch (HES). The hydrophobic–hydrophilic balance of TAS can be tailored by controlling the alkyl chain lengths, their average molar substitution (MS), and the pH of the aqueous solutions, resulting in tunable LCST within a wide range. Scheme 1 illustrates the outline of the TAS synthesis by an etherification reaction. In this paper, the effects of the alkyl chain lengths, MS, and the pH of the aqueous solutions on tuning the cloud point temperatures (T_C) of TAS by spectrophotometry are discussed in detail.

2. Experimental

2.1. Materials

Hydroxyethyl starch (MSOH = 0.5, 200 kDa) was purchased from Hustlife Scitech (Wuhan PR China). All other reagents were used as received, without further purification.

2.2. Synthesis of dialkyl epoxypropylamine (DAEPA)

The synthesis of DAEPA was prepared based on existing reports (Gilman et al., 1946). In a 2 L three-necked flask placed in an ice-water bath, 465 g epichlorohydrin (5.03 mol) and 15 mL water were mixed by vigorous stirring, while the temperature was maintained below 15 °C. 3.96 mol di-*n*-propylamine/di-*n*-butylamine was added in drop-wise and reacted for 48 h with continuous stirring, during which the temperature was maintained at 15–20 °C. At the end of the reaction, the mixture was cooled with an ice-water bath. Cooled 500 g sodium hydroxide solution (40 wt%) was added slowly, maintaining the temperature below 20 °C. The mixture was stirred vigorously for 40 min and poured into 200 mL water. The upper organic layer was separated; the lower aqueous layer was extracted with 50 mL ether 3 times. The ether extracts were combined to the upper layer then dried with anhydrous sodium sulfate. The final product was received after distillation under reduced pressure.

Dipropyl epoxypropylamine: 48.7%, b.p. 92.0 ~ 93.6 °C, 25 mmHg. Massspectrum ACPI: *m*/*z* (relative intensity) 158 (100%) [$(M+H)^+$, $C_9H_{19}NO$]; ^{1}H NMR (400 MHz, (CD3)2SO): δ 0.90 (t, 6*H*), δ 1.46 (m, 4*H*), δ 2.57–2.29 (m, 6*H*),δ 2.73–2.63 (m, 2*H*), δ2.95–2.91 (m, 1*H*).

Dibutyl epoxypropylamine: 58.0%, b.p. 90 ~ 93 °C, 4 mmHg. Massspectrum ACPI: *m*/*z* (relative intensity) 186 (100%) [$(M+H)^+$, $C_{11}H_{23}NO$]; ^{1}H NMR (400 MHz, (CD3)2CO): δ 0.92 (t, 6*H*), δ1.47–1.30 (m, 8*H*), δ2.57–2.29 (m, 6*H*), δ2.73–2.63 (m, 2*H*), δ2.95–2.91 (d, 1*H*).

2.3. Synthesis of TAS

An amount of 4.0 g HES (MSOH 0.5, 200 kDa, 21.7 mmol anhydroglucose units AGU), a volume of 16 mL DMSO, and an amount of 0.5 g (40 wt%) NaOH (10 mmol) were added to a 100 mL three-necked flask. After the HES suspended completely under stirring, a predetermined amount of DAEPA was added to the flask in drop wise. The reaction was carried out for 10 h, and the temperature was maintained at 90 °C. At the end of the reaction, the mixture was cooled to room temperature and neutralized to pH 3.0 with 6 M HCl. After the products were precipitated by the addition of acetone, they were purified by dialysis in deionized water for two days followed by freeze-drying.

2.4. Characterization

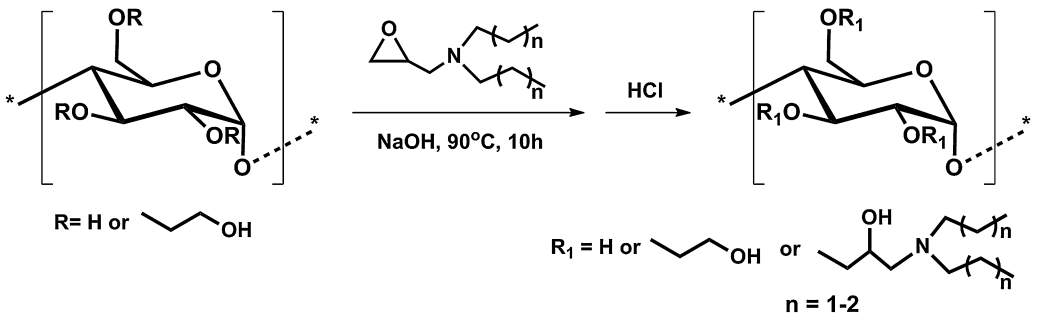
^{1}H-NMR spectra were executed on a Varian INOVA 400 spectrometer. The temperature was kept at 25 °C, and D_2O used as solvent. All of the titration measurements were carried out with a Mettler Toledo T90 titrator. The transmittance was measured at 590 nm. The concentration of the TAS was 1.0 g/L. The solutions were adjusted to pH ≈ 3.8 with 0.1 M HCl, and then titrated to pH ≈ 10.5 with 0.1 M NaOH at 20 °C while transmittance was measured at the same time. The temperature was controlled by a LAUDA E200 water bath, and the heating gradient was fixed to 1.0 °C/min when it was needed. The cloud point temperatures (T_C) are defined as the temperature at which the transmittance of the solution becomes 50%. Several solutions were prepared in Briton–Robinson buffer solution for the measurement of UV–vis spectra in different pH. The molecular weights and molecular weight distribution of TAS and HES were measured on an Agilent Technologies 1200 series gel permeation chromatograph equipped with ultrahydrogel 1000 column. Sample was dissolved in 1 mL of eluent (concentration 0.5%, w/w). The H_2O was used as the elu-ent at a flow rate of 1 mL/min at 30 °C. Polysaccharide (Polymer Laboratories Inc.) was used for calibration.

3. Results and discussion

3.1. Synthesis and characterization of TAS

Convenient etherification of starch was used to prepare TAS (Scheme 1). HES was used in this work due to its fine solubility, biodegradability, and biocompatibility. TAS were synthesized in homogeneous system, which employed DMSO as solvent and NaOH as catalyst to achieve a homogeneous distribution of substituent. TAS with different MS and alkyl were prepared: TAS with dipropyl (DP-TAS) and dibutyl (DB-TAS) show the tunable dual pH- and temperature responsive properties.

The characteristics and solution properties of four DP-TAS and four DB-TAS samples are summarized in Table 1. A typical ^{1}H NMR spectrum of TAS and the spectrum of HES are shown together in Fig. 1. The MS was calculated using the ratio of the integral of $-CH_3$ in the dialkylamino groups to the six times of the integral of H1 in the AGU by ^{1}H NMR (in Fig. 1). In GPC analysis, the most observed molecular weights for TAS was less than that of hydroxyethyl starch ($M_W = 2.69 \times 10^5$ g/mol) except DP-TAS 1.12. These measurements showed a decrease with increasing MS, which can be attributed to the degradation of HES under alkaline conditions and the formation of an entity of reduced hydrodynamic dimension. The latter occurs due to hydrophobic interaction in the inner domain comparing to the parent HES.



Scheme 1. Synthesis of TAS.

3.2. pH-induced phase transition

TAS solutions' transmittances versus pH were measured in a range of pH 4.0–10.5. The initial polymer solution was prepared at pH 3.8 with 0.1 N HCl, and the solution pH values were adjusted by adding 0.1 N NaOH solution. The results indicated that DP-TAS 0.84 and 1.12 with higher MS exhibited sharp pH transitions (Fig. 2A). For the case of more hydrophobic DB-TAS, the transmittance of all tested sample solution drastically turned down when the pH got to a certain value for each sample (Fig. 2B). It is known that HES itself was one of the hydrophilic backbones and is soluble in water. The introduced di-alkyl amino segment of TAS displayed hydrophilic or hydrophobic in protonated or deprotonated form, respectively (Weaver et al., 2008). It is obvious that the phase transition can be attributed to the hydrophobicity of the amino groups by deprotonation. On the other hand, TAS with diethyl (DE-TAS), DP-TAS 0.25 and 0.43 (Fig. 2A) were well dissolved in water, showing no phase transition as the solution pH increased from 4 to 10.5. The reason is that the hydrophilic HES backbone plays the main role in determining the polymer solubility due to the lack of hydrophobic amino groups with shorter carbon chains and lower MS' TAS even if the amino groups were totally deprotonated (He et al., 2008; Schwikal & Heinze, 2007). These results suggest that the hydrophobicity and MS of amino groups play a vital role in the pH-responsiveness of TAS.

The pH_t (defined as the pH at which the transmittance reached to 50% of its initial value) of the TAS is between 8.5 and 10 according to the MS and alkyl (Table 1). It can also be seen that the increase of TAS's MS resulted in the decrease of pH_t. It has been demonstrated that for the weak polybases, the pH_t shifted

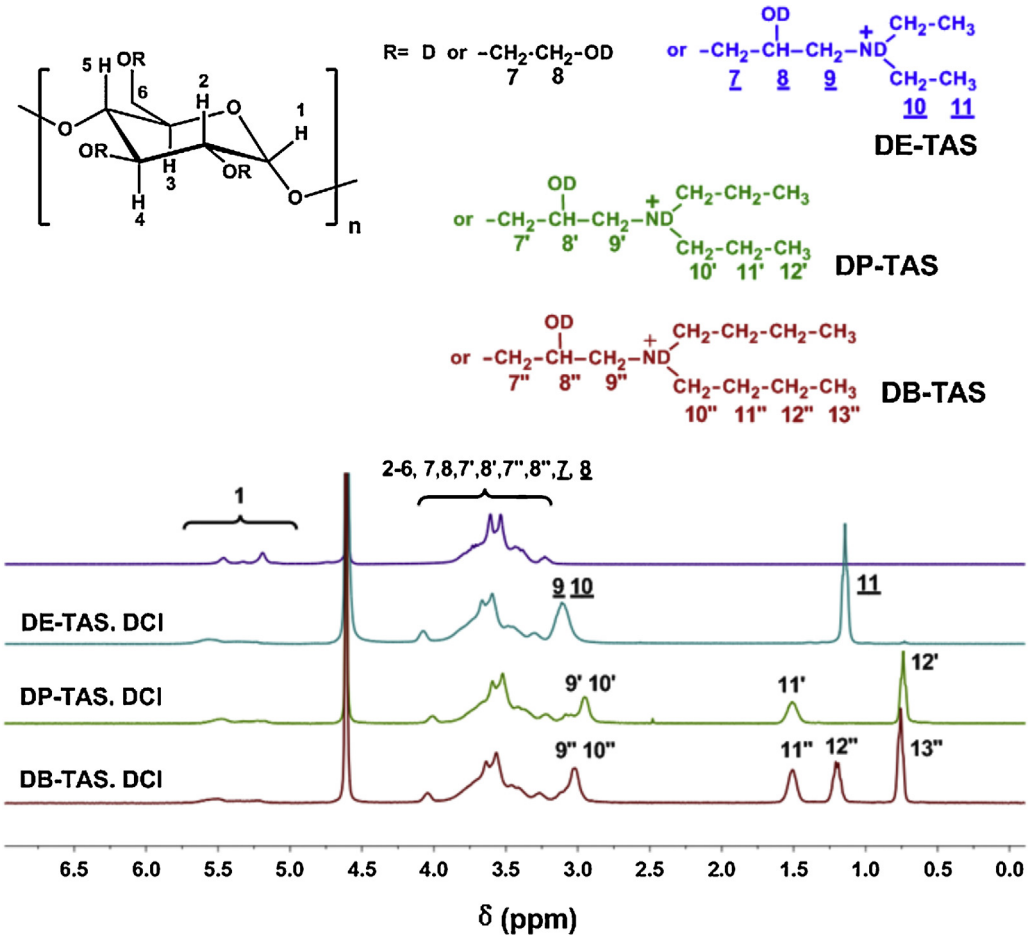


Fig. 1. ^1H NMR spectra for HES and TAS in D_2O. (The including three TAS was DE-TAS 0.80, DP-TAS 0.43 and DB-TAS 0.45, respectively.).

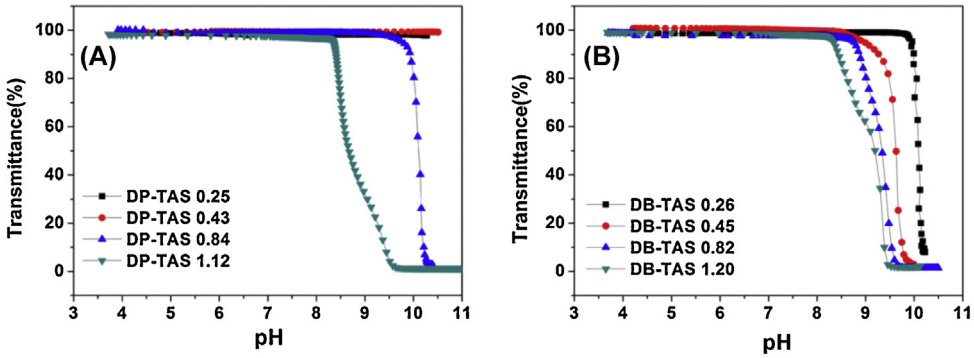


Fig. 2. Transmittance of 1.0 g/L DP-TAS (A) and DB-TAS (B) aqueous solution at different pH values at 20 °C.

Table 1
Preparation and characterization of DP-TAS and DB-TAS.

Sample	MS[a]	Efficiency (%)[b]	pH_t[c]	M_W ($\times 10^5$)[d]	PDI[d]
HES	–	–	–	2.69	5.15
DP-TAS0.25	0.25	85.3	–	2.64	4.03
DP-TAS 0.43	0.43	81.5	10.16	2.13	3.44
DP-TAS0.84	0.84	81.8	8.65	1.82	6.04
DP-TAS 1.12	1.12	76.4		2.95	1.27
DB-TAS 0.26	0.26	86.2	10.09	2.06	3.48
DB-TAS 0.45	0.45	89.5	9.63	1.86	3.11
DB-TAS0.82	0.82	82.1	9.32	1.51	2.93
DB-TAS 1.20	1.20	79.5	9.16	1.48	3.08

[a] Characterized by ^{1}H NMR.
[b] Calculated by the ratio of MS to DAEPA:AGU.
[c] pH_t measured by potentiometric/UV-vistitrations, and iconicity in that situation. 25 °C.
[d] Determined by GPC.

to lower pH when hydrophobic groups were introduced, and the higher the hydrophobicity of the polymer the larger the shift of transition pH they showed. For the TAS, the more hydrophobicity provided by TAS with higher MS, the pH_t turned lower when DAAPS's MS turned higher (Schwikal and Heinze, 2007). Fig. 2 also shows that the pH transition processes of the TAS with lower MS were longer than those of the TAS with higher MS. This may be because the more hydrophobic TAS with higher MS, resulting in phase transition, occurred from relatively lower pH and partially precipitation from solution at pH exceeding pH_t.

3.3. Temperature-induced phase transition

As expected, TAS exhibit the LCST behaviour. The heating-cooling cycled transmittance of DP-TAS 0.84 is shown in Fig. 3A, as the representation of the TAS. Rather broad transitions and the clear hysteresis between the heating and cooling scans were observed. Similar to the hysteresis of poly(*N*-isopropylacrylamide), the obvious hysteresis is likely due to the formation of inter- and intra-chain hydrogen bonds of residual —OH groups of TAS in the aggregate (Bohrisch & Zimmermann, 2007; Gao, Jia, Li, Liang, & Wei, 2010; Zhang et al., 2005). The concentration dependence of the phase transition behaviour was investigated in the range of 0.1–5 g/L of DP-TAS 0.84 aqueous solutions, and the results were plotted in Fig. 3B. It can be seen that the T_C, defined as the temperature at which the transmittance of a polymer solution reaches 50% of the initial value, showed slight difference in these measured concentrations as the concentration decreased from 5.0 to 0.1 g/L, while the T_C was maintained between 40 and 42 °C. However, the lowest transmittance was increased to 23% and 46% when the concentration was 0.2 and 0.1 g/L, respectively. These results suggest intramolecular collapse and insufficient polymer aggregate formation in the diluted solutions of the TAS, leading to incomplete transition. This is in accordance with thermo-responsive polymers in other literatures (Gao et al., 2009; Jia, Zhu, Liu, & Li, 2012). The solutions with 1.0 g/L were prepared for the following experiments to discuss the thermo-responsive properties. Fig. 4A displays the effect of molar substitution (MS) on phase transition behaviour of DP-TAS and DB-TAS with different MS in pH 8.25 solutions. From the plots of T_C values against MS (Fig. 4B), it indicates that the T_C of DP-TAS decreases linearly with increasing MS, and an increase

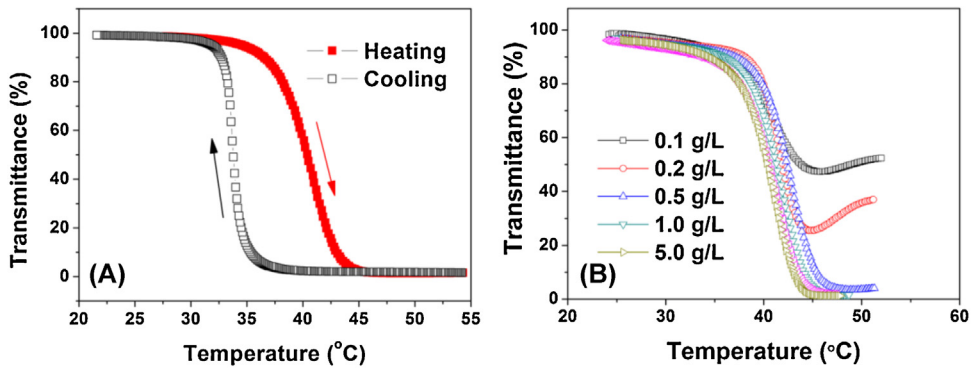


Fig. 3. (A) Plot of transmittance as a function of temperature for aqueous solution of DP-TAS 0.84 (1.0 g/L) at a heating/cooling rate of 0.5 °C/min, pH 9.00; (B) influence of temperature on the transmittances of different concentrations of DP-TAS 0.84 in buffer.

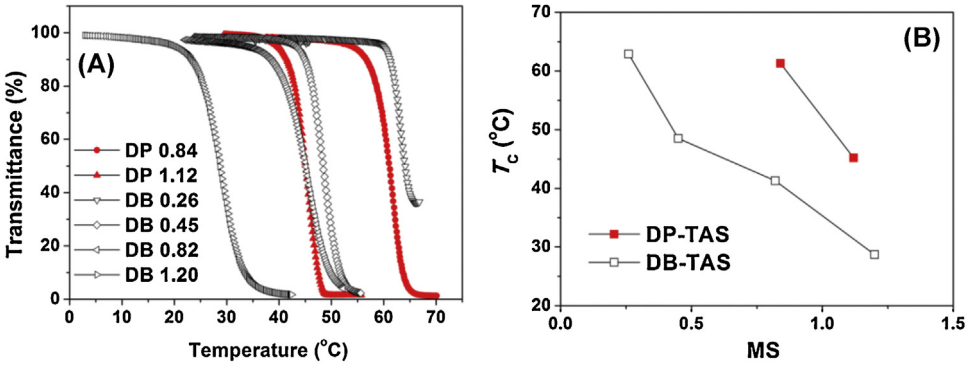


Fig. 4. (A) Transmittance of DP-TAS and DB-TAS aqueous solutions as a function of temperature at pH 8.25; (B) The T_C as a function of the MS.

of the MS from 0.26 to 1.20 resulted in a decrease in the T_C from 62.9 to 28.7 °C. For the DP-TAS, the T_C change trend with the MS is similar to DB-TAS, even though the DB-TAS performed at a lower T_C than the DP-TAS. This is due to the fact that the TAS, which has the longer carbon chains or higher MS, is more hydrophobic. It revealed that varying the MS value and length of carbon chains could control the T_C of TAS.

Like PDMA, the TAS also exhibit dual pH- and temperature-responsive properties due to the existence of ionizable amine groups and hydrophobic *N*-alkyl groups. The transmittance of

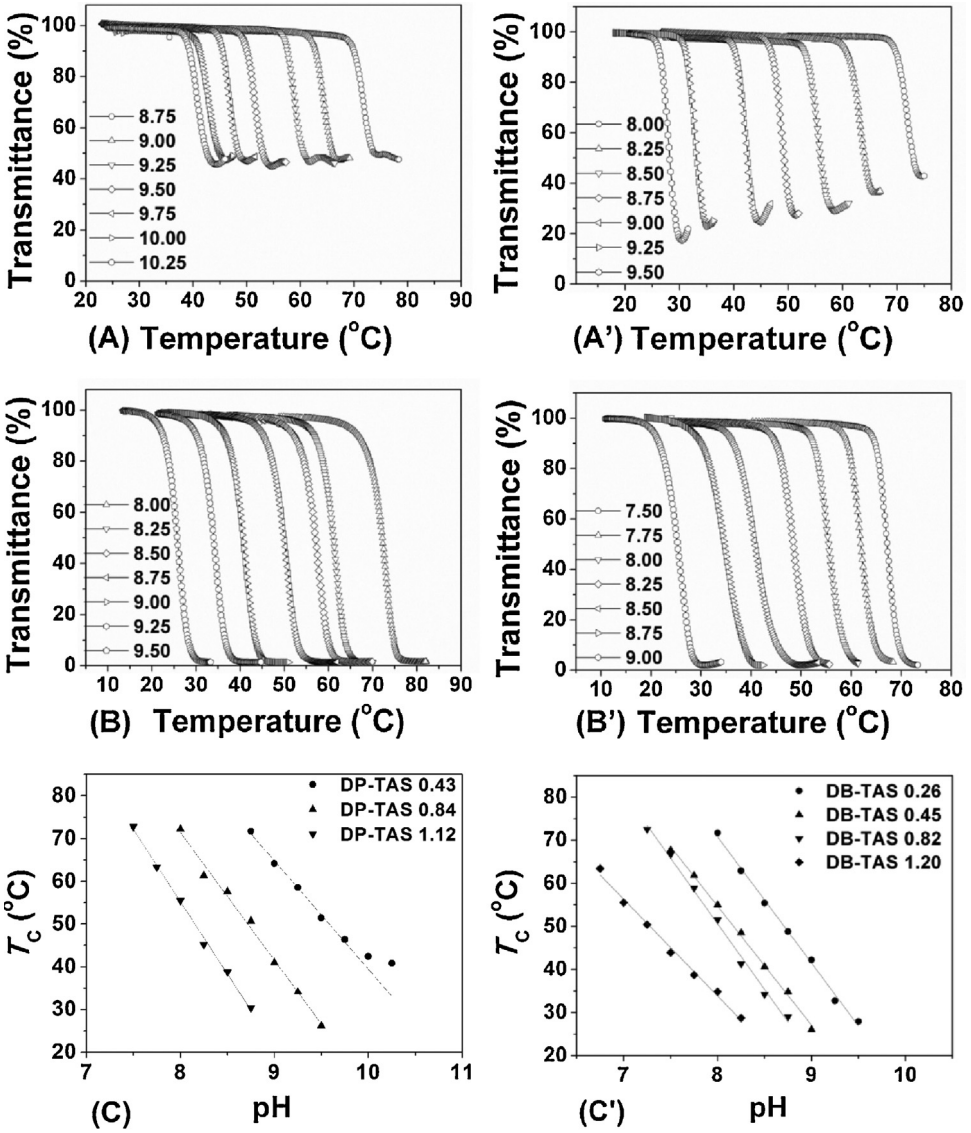


Fig. 5. Transmittance of (A) DP-TAS 0.43, (B) DP-DAS 0.84, (A′) DB-TAS 0.26 and (B′) DB-TAS 0.45 aqueous solution at different pH values as a function of temperature, concentration 1.0 g/L; The T_C of (C) DP-TAS and (C′) DB-TAS as a function of pH values.

the TAS solutions with different pH during heating (15–80 °C) was tested (Fig. 5). The tested samples were prepared in a Briton–Robinson buffer solution to tune the pH; the ones with the other MS were shown in Fig. S1-S3. In these figures, the transmittance of every solution decreased sharply as the solution temperature increased, and the higher the solution's pH resulted in a lower T_C. This occurs when the anhydration and hydrogen bond break from heating the solution and the polysaccharide precipitates out. In more basic solution, the higher hydrophobicity of the deprotonated TAS produced a lower T_C. This result is in good agreement with the result from other researches of dual responsive copolymers (Gil & Hudson, 2004; Mendrek, Mendrek, Adler, Dworak, & Kuckling, 2009). The one obvious difference between DP-TAS 0.43 (Fig. 5A) and DP-TAS 0.84 (Fig. 5B) is that the lowest transmittance value of DP-TAS 0.43 in each pH were nearly 50%, rather than 2% of DB-TAS 0.84. This may be explained by the less hydrophobic DP-DAAPS 0.43 with the lower MS, which did not have aggregations so big or compact where light could not totally scatter (Gao et al., 2009; Luo, Liu, & Li, 2012). Consequently, DP-TAS 0.25, with the much lower MS, and DE-TAS, with a diethylamino group, had almost no transmittance change even in pH 10.5 and 80 °C solution (not shown) due to much less hydrophobicity. Interestingly, in the test of TAS solution, DB-TAS 0.26 performed obvious transmittance decrease (Fig. 5A′). The dibutylamino group, unlike the di-propylamino group of DP-TAS 0.25, increases hydrophobicity of DB-TAS 0.26 even though these two samples have similar MS. This phenomenon has been previously described and discussed in the research of polysaccharide derivative (Schwikal & Heinze, 2007). Also, longer carbon chains force the lowest transmittance to decrease gradually (from 45% to 20%) with the increased pH (from 8.00 to 9.50) instead of those that are constantly 50% in DP-TAS 0.43. In addition, the gradually changing lowest transmittances gave evidence that the hydrophobicity contributed to the lowest transmittance at the same time. Once the MS came to a certain quantity, the lowest transmittance of the TAS was about 2% for DP-TAS 0.84 (Fig. 5B) and DB-TAS 0.45 (Fig. 5B′). In other words, the hydrophobic modification of the HES not only influenced the derivatives' T_C but also changed the degree of phase transition (performed at the lowest transmittance).

For simple comparison, the dependence of T_C on the pH value is shown in Fig. 5C and 5C′. The pH domains and T_C of each TAS are summarised in Table 2. The results reveal that the T_C were in almost linear variation on solution pH except for DP-TAS 0.43. For DP-TAS 0.43, when pH increased to 10.0, the T_C of DP-TAS 0.43 changed slowly and came to a parameter. At the same time, calculations from the titration test for the DP-TAS 0.43 (in Fig. S4) indicated that the deprotonation driven by increasing pH ceased when pH reached 10.5. It is implied that the variation of T_C was influenced by the hydrophobicity–hydrophobicity (Bignotti et al., 2000) change in the deprotonation–protonation of di-alkylamino groups. When pH came to 10.5, the T_C would come to one constant parameter that halted further deprotonation of the amino group. As presented in Table 2, the pH range for the thermal transition of TAS was about 1.5, but the lowest pH value for the thermal transition of TAS shifts down as MS increases. The temperature examined in this study for the thermal transitions ranged from 26 to 72.8 °C; as the pH increased by 0.25, the average range of decrease for each TAS's T_C was 5.78–8.48 °C. It should be noted that each TAS solution had a different and distinct range of pH values that induced thermal transitions within the given temperature ranges. The linear verification of T_C to pH signifies that it was possible to prepare one kind of TAS product that responded exactly to an expected temperature and pH by adjusting its MS and the length of di-alkylamino group's carbon chains.

Table 2
pH dependence of the T_C of aqueous solutions of TAS[a].

Samples/pH	6.75	7.00	7.25	7.50	8.00	8.25	8.75	9.00	9.50	10	10.25
DE-TAS											
DP-TAS0.25											
DP-TAS0.43	**Soluble**						71.7	64.2	51.4	42.4	40.8
DP-TAS0.84	**At 20 °C ~ 80 °C**				72.2	61.3	50.7	41.0	26.2		
DP-TAS1.12				72.8	55.5	45.2	30.4			**Insoluble**	
DB-TAS0.26					71.7	62.9	48.8	42.2	27.9		
DB-TAS0.45				67.7	55.0	48.5	34.8	26.0	**Below 20 °C**		
DB-TAS0.82			72.5	66.7	51.5	41.3	29.0				
DB-TAS1.20	63.4	55.5	50.4	43.9	34.8	28.7					

[a] The pH domains and T_C are highlighted in grey when phase separation occurs below 80 °C.

4. Conclusions

A series of TAS have been successfully synthesized by the efficient etherification of HES. Once suitable MS was present, the TAS displayed pH-sensitive properties due to the existence of tertiary amino and hydrophobic alkyl groups. The transition pH value (pH_t) was dependent on alkyl chain length and the MS. Furthermore, these polysaccharide derivatives exhibit excellent dual pH- and temperature-responsive properties with well-tunable LCST. The LCSTs also strongly depend on alkyl chain length, the MS, and solution pH. It was found that a shorter alkyl chain, smaller MS, and more acidic solution induce a higher LCST. Additionally, the T_C and pH for each TAS exhibit a linear relationship, meaning a tunable T_C that is required in various applications can be easily achieved. It should be mentioned that the same synthetic methodology could be employed for a wide range of other polysaccharides to yield new biomaterials with dual pH- and temperature-responsive properties. Further studies on such polysaccharides and their functionalization are under current research.

Acknowledgements

The authors gratefully acknowledge the financial support from the National Science Foundation of China (No. 21376041 and 21076033), the Program for Changjiang Scholars and Innovative Research Teams in Universities (IRT13R06) and the Program for Innovative Research Teams of Dalian University of Technology (DUT2013TB07).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2014.08.043.

References

Bignotti, F., Penco, M., Sartore, L., Peroni, I., Mendichi, R., Casolaro, M., et al. (2000). Synthesis, characterisation and solution behaviour of thermo- and pH-responsive polymers bearing L-leucine residues in the side chains. *Polymer*, *41*(23), 8247–8256.

Bohrisch, J., & Zimmermann, A. (2007). Amino starches as pH-sensitive coatings: Synthesis and application. *Starch-Starke*, *59*(5), 208–216.

Chen, G. H., & Hoffman, A. S. (1995). Graft-copolymers that exhibit temperature-induced phase-transitions over a wide-range of Ph. *Nature*, *373*(6509), 49–52.

Deen, G. R. (2012). Solution properties of water-soluble smart poly(*N*-acryloyl-*N*′-ethyl piperazine-*co*-methyl methacrylate). *Polymers*, *4*(1), 32–45.

Gao, M., Jia, X. R., Kuang, G. C., Li, Y., Liang, D. H., & Wei, Y. (2009). Thermo- and pH-responsive dendronized copolymers of styrene and maleic anhydride pendant with poly(amidoamine) dendrons as side groups. *Macromolecules*, *42*(12), 4273–4281.

Gao, M., Jia, X. R., Li, Y., Liang, D. H., & Wei, Y. (2010). Synthesis and thermo-/pH-dual responsive properties of poly(amidoamine) dendronized poly(2-hydroxyethyl) methacrylate. *Macromolecules*, *43*(9), 4314–4323.

Gil, E. S., & Hudson, S. M. (2004). Stimuli-reponsive polymers and their bioconjugates. *Progress in Polymer Science*, *29*(12), 1173–1222.

Gilman, H., Sherman, C. S., Price, C. C., Elderfield, R. C., Maynard, J. T., Reitsema, R. H., et al. (1946). Synthesis of 1-diethylamino-2,3-epoxypropane, 3-diethylamino-2-hydroxypropylamine, and 4-diethylamino-3-hydroxybutylamine. *Journal of the American Chemical Society*, *68*(7), 1291–1293.

Gonzalez, N., Elvira, C., & Roman, J. S. (2005). Novel dual-stimuli-responsive polymers derived from ethylpyrrolidine. *Macromolecules*, *38*(22), 9298–9303.

Han, X., Zhang, X. X., Yin, Q. Y., Hu, J., Liu, H. L., & Hu, Y. (2013). Thermoresponsive diblock copolymer with tunable soluble-insoluble and soluble-insoluble-soluble transitions. *Macromolecular Rapid Communications*, *34*(7), 574–580.

He, C. L., Zhao, C. W., Chen, X. S., Guo, Z. J., Zhuang, X. L., & Jing, X. B. (2008). Novel pH- and temperature-responsive block copolymers with tunable pH-responsive range. *Macromolecular Rapid Communications*, *29*(6), 490–497.

Jia, Y. G., Zhu, X. X., Liu, L. Y., & Li, J. (2012). Multi-responsive properties of a poly(ethylene glycol)-grafted alternating copolymers of distyrenic monomer with maleic anhydride. *Langmuir*, *28*(9), 4500–4506.

Ju, B. Z., Cao, S. Q., & Zhang, S. F. (2013). Effect of additives on the cloud point temperature of 2-hydroxy-3-isopropoxypropyl starch solutions. *Journal of Physical Chemistry B*, *117*(39), 11830–11835.

Ju, B. Z., Yan, D. M., & Zhang, S. F. (2012). Micelles self-assembled from thermoresponsive 2-hydroxy-3-butoxypropyl starches for drug delivery. *Carbohydrate Polymers*, *87*(2), 1404–1409.

Jung, S. H., Song, H. Y., Lee, Y., Jeong, H. M., & Lee, H. I. (2011). Novel thermoresponsive polymers tunable by pH. *Macromolecules*, *44*(6), 1628–1634.

Klaikherd, A., Nagamani, C., & Thayumanavan, S. (2009). Multi-stimuli sensitive amphiphilic block copolymer assemblies. *Journal of the American Chemical Society*, *131*(13), 4830–4838.

Luo, C., Liu, Y., & Li, Z. (2012). Pathway-dependent re-assembly of dual-responsive ABC terpolymer in water. *Soft Matter*, *8*(9), 2618–2626.

Ma, L., Kang, H. L., Liu, R. G., & Huang, Y. (2010). Smart assembly behaviors of hydroxypropylcellulose-graft-poly(4-vinyl pyridine) copolymers in aqueous solution by thermo and pH stimuli. *Langmuir*, *26*(23), 18519–18525.

Ma, L., Liu, R. G., Tan, J. J., Wang, D. Q., Jin, X., Kang, H. L., et al. (2010). Self-assembly and dual-stimuli sensitivities of hydroxypropylcellulose-graft-poly(*N*,*N*-dimethyl aminoethyl methacrylate) copolymers in aqueous solution. *Langmuir*, *26*(11), 8697–8703.

Mendrek, S., Mendrek, A., Adler, H. J., Dworak, A., & Kuckling, D. (2009). Synthesis and characterization of pH sensitive poly(glycidol)-*b*-poly(4-vinylpyridine) block copolymers. *Journal of Polymer Science A—Polymer Chemistry*, *47*(7), 1782–1794.

Newland, B., Abu-Rub, M., Naughton, M., Zheng, Y., Pinoncely, A. V., Collin, E., et al. (2013). GDNF gene delivery via a 2-(dimethylamino)ethyl methacrylate based cyclized knot polymer for neuronal cell applications. *ACS Chemical Neuroscience*, *4*(4), 540–546.

Peng, C. L., Tsai, H. M., Yang, S. J., Luo, T. Y., Lin, C. F., Lin, W. J., et al. (2011). Development of thermosensitive poly(*n*-isopropylacrylamide-*co*-((2-dimethylamino)ethyl methacrylate))-based nanoparticles for controlled drug release. *Nanotechnology*, *22*(26)

Plamper, F. A., Ruppel, M., Schmalz, A., Borisov, O., Ballauff, M., & Muller, A. H. E. (2007). Tuning the thermoresponsive properties of weak polyelectrolytes: Aqueous solutions of star-shaped and linear poly(*N*,*N*-dimethylaminoethyl methacrylate). *Macromolecules*, *40*(23), 8361–8366.

Rawlinson, L. A. B., Ryan, S. M., Mantovani, G., Syrett, J. A., Haddleton, D. M., & Brayden, D. J. (2010). Antibacterial effects of poly(2-(dimethylamino ethyl)methacrylate) against selected gram-positive and gram-negative bacteria. *Biomacromolecules*, *11*(2), 443–453.

Schmalz, A., Hanisch, M., Schmalz, H., & Muller, A. H. E. (2010). Double stimuli-responsive behavior of linear and star-shaped poly(*N*,*N*-diethylaminoethyl methacrylate) in aqueous solution. *Polymer*, *51*(6), 1213–1217.

Schwikal, K., & Heinze, T. (2007). Dialkylaminoethyl xylans: Polysaccharide ethers with pH-sensitive solubility. *Polymer Bulletin*, *59*(2), 161–167.

Sui, X. F., Yuan, J. Y., Zhou, M., Zhang, J., Yang, H. J., Yuan, W. Z., et al. (2008). Synthesis of cellulose-graft-poly(*N*,*N*-dimethylamino-2-ethyl methacrylate) copolymers via homogeneous ATRP and their aggregates in aqueous media. *Biomacromolecules*, *9*(10), 2615–2620.

Weaver, J. V. M., Williams, R. T., Royles, B. J. L., Findlay, P. H., Cooper, A. I., & Rannard, S. P. (2008). PH-responsive branched polymer nanoparticles. *Soft Matter*, *4*(5), 985–992.

Xiao, C. S., Cheng, Y. L., Zhang, Y., Ding, J. X., He, C. L., Zhuang, X. L., et al. (2014). Side chain impacts on pH- and thermo-responsiveness of tertiary amine functionalized polypeptides. *Journal of Polymer Science A—Polymer Chemistry*, *52*(5), 671–679.

Yuan, W. Z., Zhao, Z. D., Yuan, J. Y., Gu, S. Y., Zhang, F. B., Xie, X. M., et al. (2011). Synthesis of pH- and temperature-responsive chitosan-graft-poly[2-(*N*,*N*-dimethylamino) ethyl methacrylate] copolymer and gold nanoparticle stabilization by its micelles. *Polymer International*, *60*(2), 194–201.

Zhang, W. Q., Shi, L. Q., Ma, R. J., An, Y. L., Xu, Y. L., & Wu, K. (2005). Micellization of thermo- and pH-responsive triblock copolymer of poly(ethylene glycol)-*b*-poly(4-vinylpyridine)-*b*-poly(*N*-isopropylacrylamide). *Macromolecules*, *38*(21), 8850–8852.