Brönsted acids catalyzed polymerization of ε-caprolactone in water, a mild and straightforward route to poly(ε-caprolactone)-*graft*-water-soluble polysaccharides

N. Stanley,[1] G. Bucataru,[1] Y. Miao,[1] A. Favrelle,[1] M. Bria,[2] F. Stoffelbach,[3] P. Woisel,[4] P. Zinck[1*]

[1] Unity of Catalysis and Solid State Chemistry, UCCS, UMR CNRS 8181, University Lille 1, Science and Technology, Bât C7, Cité Scientifique, 59655 Villeneuve d'Ascq Cédex, France. Fax : + 33 3 20 43 65 85; Tel: + 33 3 20 43 65 86; E-mail: philippe.zinck@univ-lille1.fr

[2] Centre Commun de mesure RMN, Université Lille 1, Science and Technology, Bât C4, Cité Scientifique, 59655 Villeneuve d'Ascq Cédex, France.

[3] Sorbonne Universités, UPMC Univ Paris 06, UMR CNRS 8232, IPCM, Chimie des Polymères, F-75005, Paris, France

[4] Unite des Materiaux Et Transformations, UMET, UMR CNRS 8207, Equipe Ingenierie des Systemes polymeres (ISP), Université Lille 1, Science and Technology, 59655 Villeneuve d'Ascq Cédex, France

Abstract

The polymerization of ε-caprolactone has been assessed in water using various Brönsted acids as catalysts. The reaction was found to be quantitative at 100°C, leading to number-average molecular weights up to 5000 g/mol. The Brönsted acid catalyzed polymerization of ε-caprolactone in water was further conducted in the presence of water-soluble polysaccharides thereby affording graft copolymers. The approach enables an easy, mild access to dextran hydroxyesters. For low degree of substitution, the latter self-assembles in water to form nanoparticles. Poly(ε-caprolactone)-*graft*-methylcellulose copolymers can also be obtained *via* a similar approach. It is noteworthy that the methodology reported herein is a one-step route to poly(ε-caprolactone)-*graft*-water-soluble polysaccharides, operating in mild conditions, *i.e* at low temperatures, using readily available metal-free catalysts and water as a solvent.

Introduction

Polyester-*graft*-polysaccharides copolymers are widely used in the biomedical field as drug carriers, due to their biocompatibility and biodegradability combined with the ability to form supramolecular assemblies in solution.[1-32] They are also known for applications as biocompatible coatings and compatibilizers for polymer blends and composite materials. For example, amphiphilic dextran esters and polyester-*graft*-dextran have been intensively investigated.[1-17] Dextran is a synthetic water-soluble polysaccharide whose structure consists of α(1-6) linked D-glucose as the main chain. Dextran dissolves easily in DMF (dimethylformamide) / LiCl mixtures upon heating to 90–100 °C. This solvent has been widely used for the esterification of dextran.[1-2;8;12;14] Recent studies also report the formation of dextran esters based nanoparticles in dimethylsulfoxide (DMSO).[6;8] Two consecutive or simultaneous esterification reactions involving the use of a coupling agent were required. The synthesis of amphiphilic poly(ε-caprolactone)-*graft*-dextran and polylactide-*graft*-dextran copolymers was also reported in the literature. Multistep strategies involving the activation of carboxylic acid end-capped polyesters *via* the use of coupling agents[5;18] have been investigated for this purpose, as well as protection-deprotection chemistries combined with metal-catalyzed ring-opening polymerization of cyclic esters, involving reactants purification and work-up under inert atmosphere.[10-11;13;17] The resulting polyester-*graft*-dextran copolymers were found to be watersoluble for low polyester contents and were capable to form supramolecular assemblies with hydrophobic domains. The formation of dextran esters, eventually leading to nanoparticles, is thus usually realized through multi-step strategies requiring reactants purification and work-up under inert atmosphere, or via approaches involving coupling agents or activated acids, and using toxic solvents. The formation of dextran ethers was also investigated in basic aqueous medium using phenylglycidylether as a substrate, via a hydroxyl initiated opening of the epoxide ring.[19-20]

Cellulose is the most abundant polysaccharide on earth. Its combinations with biocompatible polyesters have also been thoroughly investigated.[21] Several studies described the "grafting from" approach starting from cellulose whiskers or nanocrystals, *i.e* a heterogeneous process, with application of the resulting grafted compound in materials science.[21] Homogeneous procedures[22-27] were also reported in bulk or in solvent starting from cellulose derivatives such as hydroxyalkyls for example, but not in water as far as we know. The ring-opening polymerization of ε-caprolactone in the presence of cellulose was also studied in ionic liquids.[28-30]

The use of water as a solvent for these reactions is interesting for evident environmental considerations. The formation of poly(ε-caprolactone)-*graft*-chitosan was for example reported at high temperatures using water as a swelling agent.[31] The amino group of chitosan initiated an organic base catalyzed ring-opening polymerization of the lactone, while hydroxyl groups did not initiate the polymerization. The organocatalyzed functionalization of chitosan *via* ring-opening polymerization of L-lactide was also reported in the literature.[32] An aqueous solution of acetic acid was used as the solvent in order to dissolve chitosan, whilst triethylamine was used as a catalyst for the ring-opening polymerization. Starch[33] and amylopectin[34] were functionalized at high temperature in aqueous lactic acid in the presence of stannous 2-ethyl hexanoate, providing access to micellar aggregates under certain conditions.

Recently, some of us reported the polymerization of ε-caprolactone in water using triflate salts,[35] while others used lipase as a catalyst for this purpose.[36] From these approaches, we envisioned the functionalization of water soluble polymers with biocompatible poly(ε-caprolactone) hydrophobic grafts in mild conditions. Metal catalysts can however lead to residual traces of metal in the polymer, which can hamper its use for specific applications. Enzymes are, on the other hand, rather expensive catalysts. The recent success of

organocatalysis for the ring-opening polymerization of cyclic esters[37-38] notably applied to the functionalization of carbohydrates[39-50] prompted us to assess readily available Brönsted acids as catalysts in aqueous medium for the polymerization of ε-caprolactone and the one-step access to poly(ε-caprolactone)-*graft*-water-soluble polysaccharides using dextran and methylcellulose as precursors.

Experimental

Materials

ε-caprolactone (CL) and 6-hydroxyhexanoic acid were purchased from Acros and Alfa Aesar, respectively. Butanoic acid was purchased from Janssen Chimica. Methylcellulose (average M_n 40,000 g/mol, 1.6-1.9 mol methoxy per mol cellulose, 27.5-31.5 wt. % methoxy) and dextran (M_n 6000 g/mol) were purchased from Aldrich. Methanesulfonic acid was purchased from Acros, hydrochloric acid (34%) from Verbièse, phosphoric acid from Scharlau, sulfuric acid from Carlo Erba Reagenti, p-toluenesulfonic acid and (1R)-(−)-10-camphorsulfonic acid from Aldrich. All reagents were used as received.

ε-caprolactone polymerization in water

In a typical experiment, the catalyst (0.044 mmol), water (3.3 mmol) and ε-caprolactone (4.4 mmol) were added to a reaction flask in this order. After a given reaction time, the reaction product was filtered and dried under vacuum for 48h.

Dextran ε-caprolactone graft copolymerization in water

In a typical experiment, dextran (0.4 g) was added to a reaction flask. After this, water (0.5 mL) was added with stirring (350 RPM). Once dextran was fully dissolved, ε-caprolactone (0.85 g corresponding to a ε-caprolactone/dextran ratio of 3, or 0.66 g butanoic acid) and then the catalyst (*e.g* 13 mg p-toluenesulfonic acid corresponding to 1 mol% *vs.* ε-caprolactone) were added. The reaction conducted at room temperature was stopped after a given amount of time, and the reactive medium was precipitated in acetone, filtered, washed twice with acetone and dried under vacuum. All reactions were repeated 3 times.

Methylcellulose ε-caprolactone graft copolymerization in water

The procedure leading to a homogeneous solution of methylcellulose in water is described in the Fluka information sheet.[51] In a typical experiment, methylcellulose (0.2 g) was added to a reaction flask. 1 mL of water was then added, the mixture heated to 80ºC under stirring. The mixture was cooled down at room temperature and 1 additional ml of water was added. The reaction was further cooled down to around 4 ºC where the compound becomes soluble in water. ε-caprolactone (0.85 g corresponding to a ratio ε-caprolactone /methylcellulose of 4, or 0.66 g butanoic acid) was then added to the flask with stirring and p-toluenesulfonic acid (13 mg corresponding to 1 mol% *vs.* ε-caprolactone) was added at last. The flask was heated at 50°C for 24h and the reactive medium was precipitated in dichloromethane, filtered, washed twice with dichloromethane and dried under vacuum. All reactions were repeated 2 to 3 times. Acetone can also be used as precipitation solvent.

Measurements

Size exclusion chromatography of poly(ε-caprolactone) was performed in THF as eluent at 40°C using a Waters SIS HPLC-pump, a Waters 410 refractometer and Waters styragel column (HR2, HR3, HR4, HR5E) calibrated with polystyrene standards. The number-average molecular weight of PCL measured with polystyrene standards was corrected by a factor of 0.56.[52] NMR spectra of poly(ε-caprolactone) were recorded on Bruker Avance 300 MHz (7.0 T) instrument at room temperature in CDCl$_3$, while graft copolymers were analyzed in DMSO-d_6 using a Bruker Avance 400 MHz (9.4 T) instrument, at room temperature for poly(ε-caprolactone)-*graft*-dextran and at 50°C for poly(ε-caprolactone)-*graft*-methylcellulose. The chemical shifts were calibrated using the residual resonances of the solvent. Aqueous solutions of dextran hydroxyesters (1 wt%) for Dynamic Light Scattering (DLS) were prepared in ultra-pure deionized water (18 mΩcm^{-1}) (1 mL) using ultrasounds for 10 min. The solutions were analyzed after filtration (0.2 μm). The aggregation

behavior of the copolymer in water was characterized using a DLS apparatus (DynaPro NanoStar, Wyatt) at a temperature of 23°C. For cryogenic transmission electronic microscopy, the samples were dispersed in water to a concentration of 1 wt % in presence of phosphotungstic acid (0.66 wt %) and were treated with ultrasound for 10 min. The morphological analysis was performed on Quantifoil grids fast frozen in liquid ethane. Cryo-TEM images were recorded using a JEOL JEM2100 LaB6 working at 200 kV and equipped with a 2000 × 2000 pixels CDD GATAN Ultrascan 1000 camera. Image acquisition was performed at -180°C in low-dose conditions with an electron beam intensity less than 10 electron $A^{-2} s^{-1}$.

Results and discussion

Polymerization of ε-caprolactone in water using Brönsted acids as catalysts

Entries representative of the polymerization of ε-caprolactone in water catalyzed by various Brönsted acids presented in Scheme 1 are given in Table 1. As ε-caprolactone is soluble in water, the reactive medium is homogeneous at the beginning of the reaction. A translucent phase appears as the reaction proceeds, and settles down when stirring is stopped. The reaction is quantitative for all catalysts. A blank experiment conducted without catalyst did not yield polymer. All acids except HCl led to number-average molecular weights between 4000 and 5000 g/mol. These values are of the same order of magnitude as the molecular weight of the poly(ε-caprolactone) obtained using yttrium triflate as catalyst in similar conditions. [35]
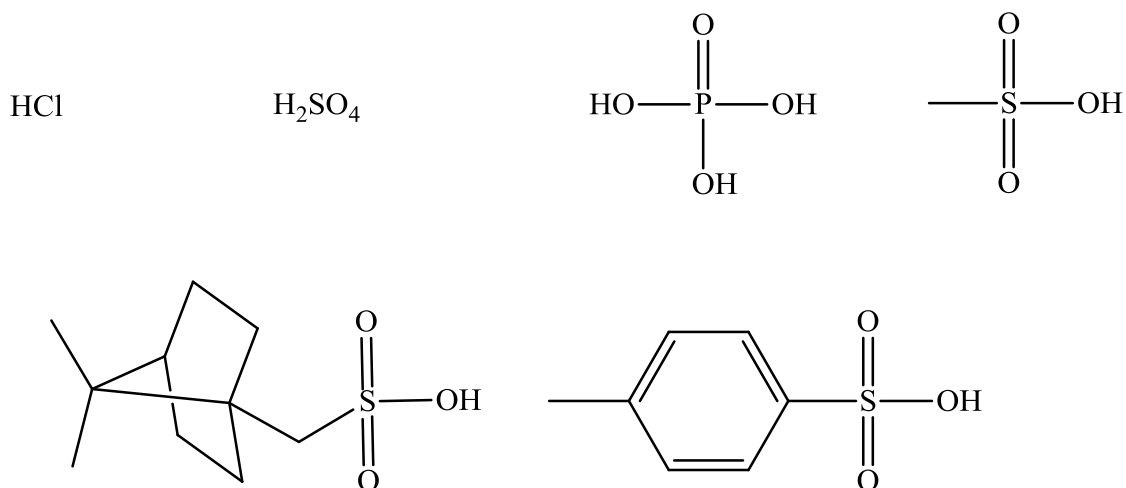
Scheme 1. Brönsted acids used as catalysts in this study. From left to right, top : hydrochloric, sulfuric, phosphoric and methanesulfonic acids. Bottom: (1R)-(-)-10-camphorsulfonic (CSA) and *p*-toluenesulfonic (TSA) acids.

Table 1. Brönsted acids catalyzed polymerization of ε-caprolactone in water. Reactions conditions: ε-caprolactone/H_2O = 1.3, 24h, 100°C, 1 mol% catalyst *vs.* ε-caprolactone

Reaction	Catalyst	Yield (%)	M_n^a (g/mol)	$Đ_M^a$
1	-	0	-	-
2	HCl	100	< 800	-
3	H_3PO_4	97	5000	1.7
4	H_2SO_4	99	5100	1.8
5	CH_3SO_3H	99	4600	1.7
6	CSA[c]	99	4300	1.7
7	TSA[d]	98	4200	1.7
8[b]	TSA[d]	96	5700	1.9

[a] Number average molecular weight measured by size exclusion chromatography and corrected by a factor 0.56 and dispersity
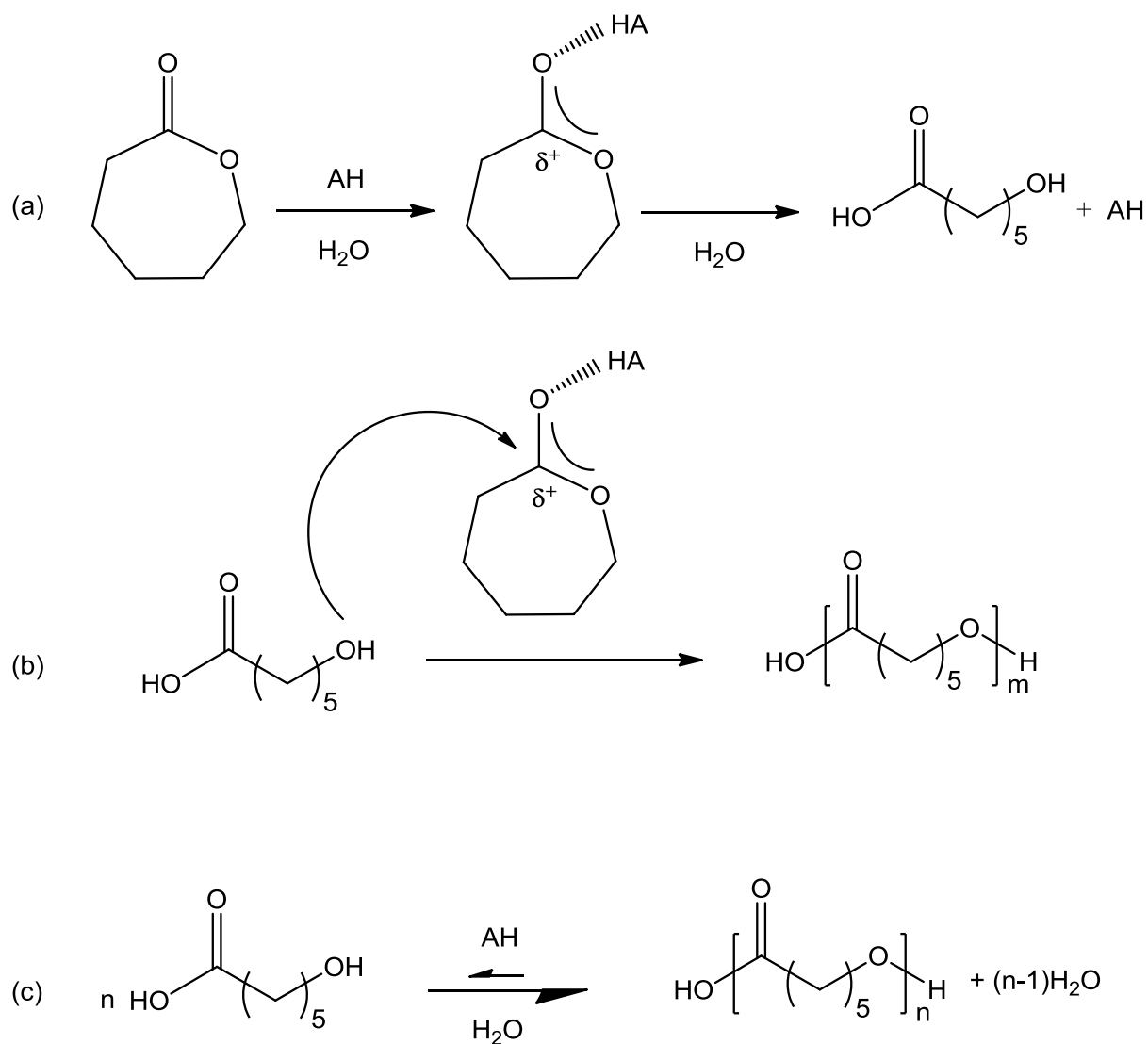
[b] 6-hydroxyhexanoic acid as monomer

[c] (1R)-(-)-10-camphorsulfonic acid

[d] *p*-toluenesulfonic acid

Protic species such as water are known to open cyclic esters in the presence of an acid leading to the corresponding α-ω-hydroxy-acid. The latter can (i) initiate a ring-opening polymerization of the lactone, and/or (ii) get involved in a polycondensation yielding poly(ε-caprolactone). As discussed in the next section where the reaction is conducted in the presence of a polysaccharide, mechanism (i) cannot be disregarded. An experiment was conducted with 6-hydroxyhexanoic acid in order to assess the possibility of the condensation mechanism occurring. The results are given in Table 1, entry 8. It can be seen that the polycondensation of 6-hydroxyhexanoic acid efficiently occurs in these conditions. The following mechanism can thus be proposed. In the first step, ε-caprolactone is activated by the Brönsted acid *via* its carbonyl group, leading to a cationic complex (Scheme 2a). The

electrophilic attack onto H_2O leads to the formation of 6-hydroxyhexanoic acid, which either initiates the ring-opening polymerization of the lactone (Scheme 2b), or is involved in a polycondensation to yield poly(ε-caprolactone) (Scheme 2c). Up to a certain molecular weight, poly(ε-caprolactone) becomes insoluble in water and aggregates into domains, resulting in the expelling of the water. This expelling may (i) facilitate ring-opening polymerization *vs.* cyclic ester hydrolysis and (ii) displace the esterification equilibrium toward the formation of the ester. This results in the formation of poly(ε-caprolactone) with number average molecular weights of several thousand observed here.

Scheme 2. Proposed polymerization mechanisms. (a) hydrolysis of the lactone to 6-hydroxyhexanoic acid; (b) polycondensation pathway and (c) ring-opening polymerization pathway. The ring-opening polymerization of the lactone starting from the polycondensate obtained via pathway (b) can also occur, but has not been represented for simplicity

Graft copolymerization of ε-caprolactone with water-soluble polysaccharides

Attempts to perform ε-caprolactone – dextran graft copolymerizations in water at high temperature were not conclusive, and successful results were obtained at room temperature. Representative entries are given in Table 1. As ε-caprolactone is soluble in water, the reactive medium is homogeneous at the beginning of the reaction. A translucent phase appears rapidly as the reaction proceeds, turning to a white precipitate after several hours. A typical ^{1}H NMR spectrum of the resulting material is presented in Figure 1. Assignments of the signals corresponding to the protons of dextran were made considering that, due to the low degree of substitution, the chemical shifts are similar to that of pure dextran. The assignment of the NMR signals of dextran in DMSO-d_6 can be found in the literature.[1] The amount of hydrophobic grafts was determined by the integration of the protons H*(B,C,D)* signals between 1.1 and 1.7 ppm and the proton H*1* signal of dextran at 4.7 ppm. The number average-degree of polymerization (DP) and the degree of substitution (DS) were calculated using DP=[H*(B,C,D)*/3]/[H*(B,C,D)*/3-H*E*] and DS=[H*(B,C,D)*/3-H*E*]/(2H*1*).

Reactions conducted without catalyst did not lead to the esterification of dextran (entry 9). Using *p*-toluenesulfonic acid as catalyst under our "standard" conditions (entries 10-11) leads to a functionalized dextran characterized by an oligo(ε-caprolactone) content of *ca.* 15 mol%, and a degree of substitution around 0.30. The compounds are neither soluble in water, nor in DMF, but dissolve in DMSO. For 10h reaction (entry 12), both the global hydrophobic content and degree of substitution decrease substantially, leading to a water-soluble graft copolymer. Interestingly, the latter dextran hydroxyester self-assembles after a simple dissolution in water into particles ($<D_h> \approx 80$ nm by dynamic light scattering). Interestingly, these were found to be stable over several days.[1] Cryogenic transmission electronic microscopy (Cryo-TEM) was further used for the direct visualization of the size and

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[1] Unmodified dextran led to a size of 2 nm in similar conditions, while ε-caprolactone and *p*-toluene sulfonic acid led to sizes of 0.4 and 1.8 nm respectively

morphology of the particles. As depicted in Figure 2, cryo-TEM shows quasi-spherical individual particles, with a hydrophobic core size of around 50 nm with a dispersity value of around 20%.[2]
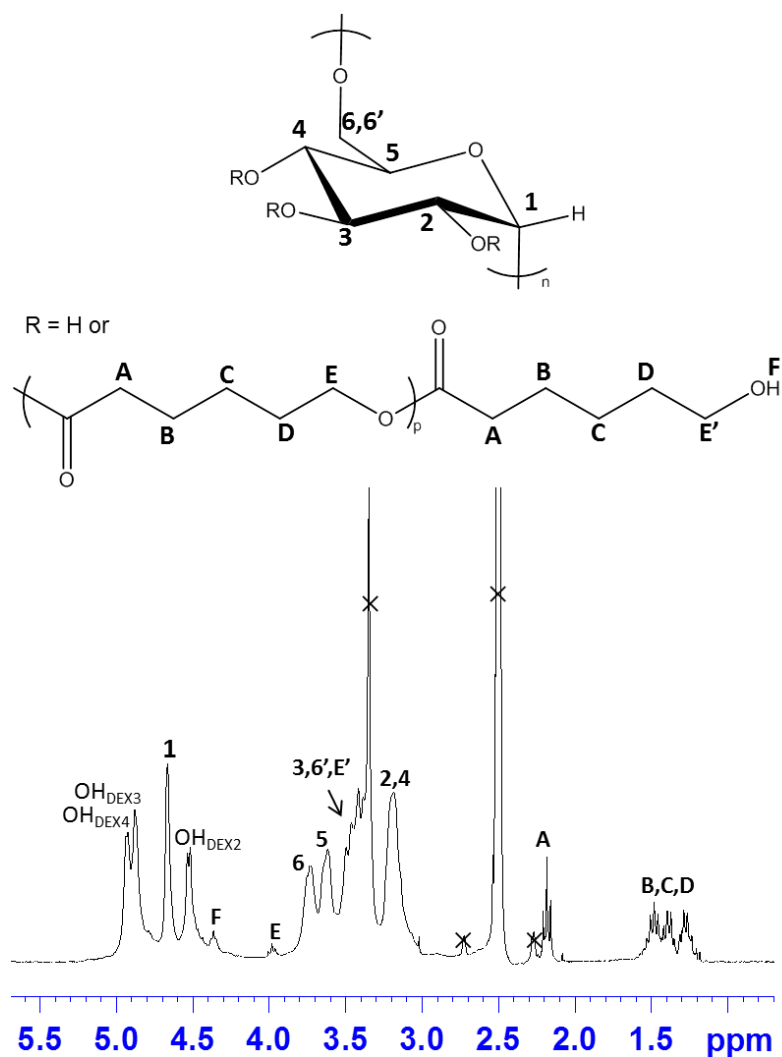

Figure 1. ^{1}H NMR spectra of a typical functionalized dextran in DMSO-d_6 at room temperature

[2] The overestimation of the size determined by dynamic light scattering (calculated from the signal intensity) *vs.* that determined by cryogenic transmission electronic microscopy can be explained on the basis of dynamic light scattering data treatment, see for example S.K. Filippov, A.V. Lezov, O.Y. Sergeeva, A.S. Olifirenko, S.B. Lesnichin, N.S. Domnina, E.A. Komarova, M. Almgren, G. Karlsson, P. Štepanek, Eur. Polym. J. 2008, 44, 3361 and P.J. Patty, B.J. Frisken, Appl. Opt. 2006, 45, 2209.

Table 2. Reaction between water-soluble polysaccharides and ε-caprolactone in water in the presence of 1% acid catalyst. Reaction conditions: Dextran : room temperature, 1 equiv. ε-caprolactone *vs.* OH$_{dextran}$, ε-caprolactone/catalyst=100. Methylcellulose : 50°C, 2 equiv. ε-caprolactone *vs.* OH$_{methylcellulose}$, ε-caprolactone/H$_2$O=0.07, ε-caprolactone/catalyst=100

Entry	Polysaccharide[a]	CL/H$_2$O[b]	Cata.[c]	Time (h)	Temp. (°C)	Hydrophobic content (mol%)[d]	DP[e]	DS[f]	Mn[g] (g/mol)
9	D	0.27	-	24	25	-	-	-	-
10	D	0.27	TSA	1	25	15	1.8	0.30	8300
11	D	0.27	TSA	5	25	14	1.5	0.33	8100
12	D	0.27	TSA	10	25	3	1	0.09	6400
13	D	0.12	TSA	1	25	18	2.3	0.28	8700
14	D	0.44	TSA	1	25	15	1.3	0.42	8300
15	D	0.27	CSA	1	25	12	1.8	0.23	7700
16	D	0.27	H$_3$PO$_4$	1	25	19	1.3	0.55	9000
17[h]	D	0.27	TSA	1	25	3	-	0.08	6200
18	MC	0.07	TSA	24	50	87	7.8	2.6-2.9	229700
19	MC	0.07	-	24	50	4	n.d	n.d	n.d
20[h]	MC	0.07	TSA	24	50	22	-	1.8-2.1	43700

[a]D=dextran, MC=methylcellulose; [b]CL=ε-caprolactone; [c]TSA=*p*-toluenesulfonic acid, CSA=(1R)-(-)-10-camphorsulfonic acid; [d]determined by NMR in DMSO-d_6. D copolymer : ^{1}H NMR, integral of H*1* around 4.7 ppm *vs.* H*(B,C,D)* at 1.2-1.6 ppm. MC copolymer : quantitative ^{13}C NMR, integral of C*1* around 102.5 ppm *vs.* C*C* at 28.4 ppm; [e]Number-average degree of polymerization determined by ^{1}H NMR in DMSO-d_6. D copolymer : [H*(B,C,D)*/3]/[H*(B,C,D)*/3-H*E*]; MC copolymer : (H*E'*+H*E*)/H*E'* after deconvolution of the H*E'* zone using a cubic spline method; [f]Degree of substitution defined as the number of grafts per glucose unit (DS$_{MAX}$ = 3) determined by NMR. D copolymer : [H*(B,C,D)*/3-H*E*]/2/H*1*; MC copolymer : DS=(1.6-1.9)+C*C*/(C*1**DP); [g] Number-average molecular weight calculated using the DP and DS values determined by NMR and the number-average molecular weight of the polysaccharide precursors, *i.e* 6000 and 40000 g/mol for dextran and methylcellulose, respectively; [h]Butanoic acid was used instead of ε-caprolactone
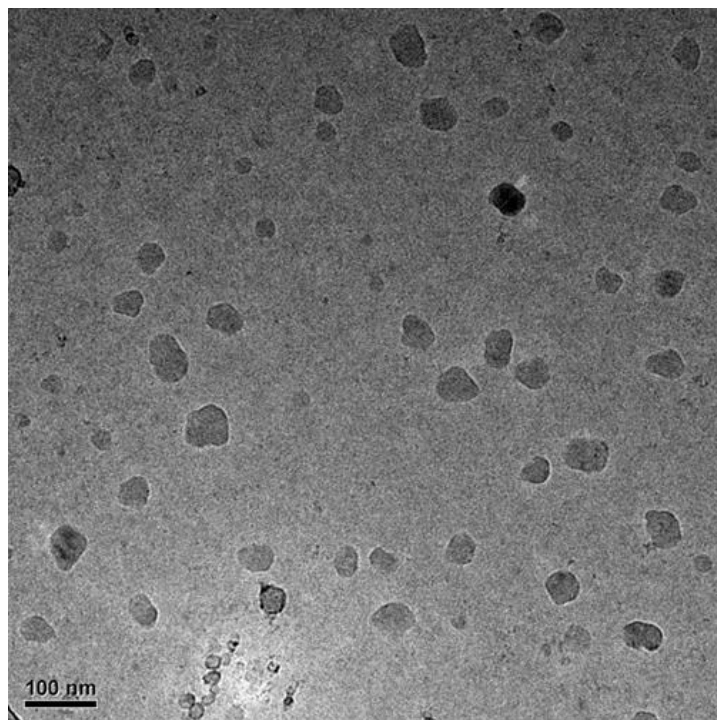
Figure 2. Cryogenic transmission electronic microscopy image of entry 12

The influence of the amount of water in the reactive medium and the nature of the catalyst was further studied. The increase in the former leads to an increase of the degree of polymerization (entry 13 *vs.* 10), while a decrease in the amount of water enables an increase of the degree of substitution (entry 14 *vs.* 10), with a lower number-average degree of polymerization. Using camphorsulfonic acid as a catalyst instead of *p*-toluenesulfonic acid induces a decrease in the degree of substitution (entry 15 *vs.* 10), while phosphoric acid leads to a substantial increase (entry 16 *vs.* 10). Both the nature of the catalyst and the amount of water grant thus the ability to tune the microstructure of the graft copolymer in a certain range. All the materials except entry 12 were found to be insoluble in both water and DMF, whilst soluble in DMSO.

The reaction was then conducted using butanoic acid instead of ε-caprolactone to grant insight into the reaction mechanism (entry 17, *p*-toluenesulfonic acid as the catalyst). The resulting degree of substitution of 0.08 shows that esterification can occur in these conditions. A higher degree of substitution was obtained using ε-caprolactone under similar conditions (0.30, entry 10). This tends to show that ring-opening polymerization can also occur in a substantial way. The amount of hydrophobic grafts observed after 1 and 5h can thus tentatively be attributed to both (i) dextran hydroxyl initiated ring opening-polymerization of ε-caprolactone and (ii) esterification of *in situ* formed 6-hydroxyhexanoic acid or higher oligomers with dextran. The resulting poly(ε-caprolactone)-*graft*-dextran copolymer then undergoes hydrolysis in this acidic medium, leading to a decrease of both the degree of substitution and the hydrophobic content (entry 12).

Methylcellulose was further assessed as a substrate using this strategy. Reactions conducted at room temperature were not conclusive, whilst successful results were obtained at 50°C. A typical example is given in Table 2, entry 18. The molar percentage of ε-caprolactone grafted onto the polysaccharide can be determined from the ratio between the carbon CI of methylcellulose around 102.5 ppm and the carbon CC of poly(ε-caprolactone) at 28.4 ppm on the quantitative ^{13}C NMR spectra presented in Figure 3. Methylcellulose assignments were made based on the literature.[53] This leads to *ca.* 90% poly(ε-caprolactone) in the grafted copolymer. The number-average degree of polymerization around 8 can be determined by DP=(HE'+HE)/HE' on the ^{1}H NMR spectra after deconvolution of the zone of interest using a cubic spline method (see Figure 4). This leads to a degree of substitution of 2.6-2.9 using DS=(1.6-1.9)+CC/(CI*DP). Experiments conducted without catalyst led to a substantially lower amount of hydrophobic grafts (entry 19, 4% *vs.* 87% for entry 18), when in fact no grafting at all was observed using dextran without catalyst. This difference in behaviour when compared to dextran may be due to the presence of primary alcohols along

the backbone of methylcellulose, which are more reactive than secondary alcohols in such chemistries. The reaction temperature is furthermore higher (50°C for methylcellulose *vs.* room temperature for dextran). The influence of residues from the methylation of cellulose may also not be fully discarded. It should be noted that the ring-opening polymerization of ε-caprolactone initiated by hydroxypropylcellulose without catalyst was reported after 24h at 150°C under nitrogen atmosphere.[26] The reaction was then conducted using butanoic acid instead of ε-caprolactone (entry 20) to grant insight into the reaction mechanism, leading to a degree of substitution of 1.8-2.1. A higher degree of substitution was obtained using ε-caprolactone under similar conditions (DS=2.6-2.9, entry 18). This tends to show that ring-opening polymerization can also occur in a substantial way. This enables to advance for ε-caprolactone − methylcellulose graft copolymerization the same combination of mechanisms than that proposed using dextran as substrate, *i.e* a simultaneous (i) methylcellulose hydroxyl initiated ring-opening polymerization of ε-caprolactone and (ii) esterification of *in situ* formed 6-hydroxyhexanoic acid or higher oligomers with methylcellulose.
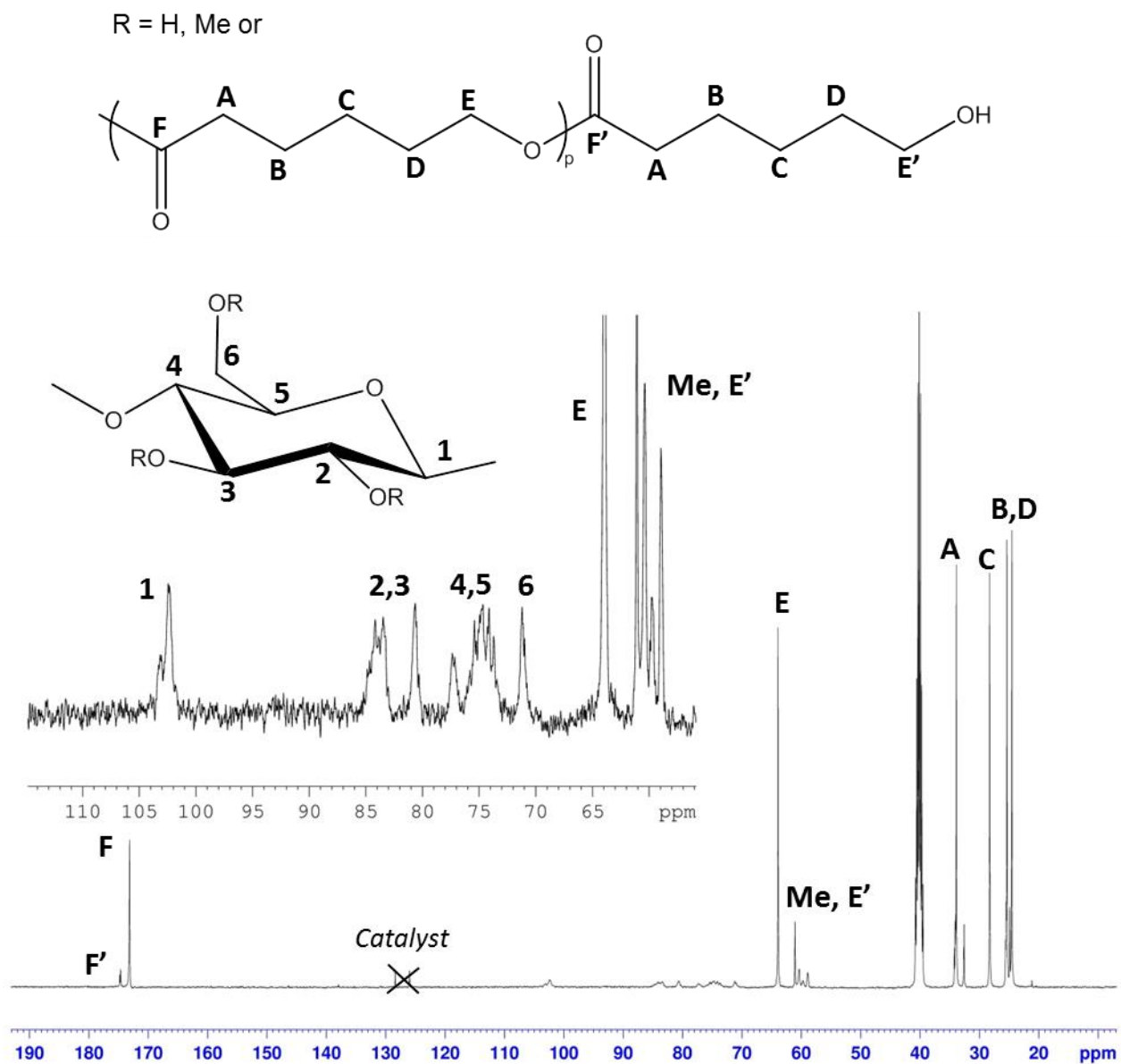
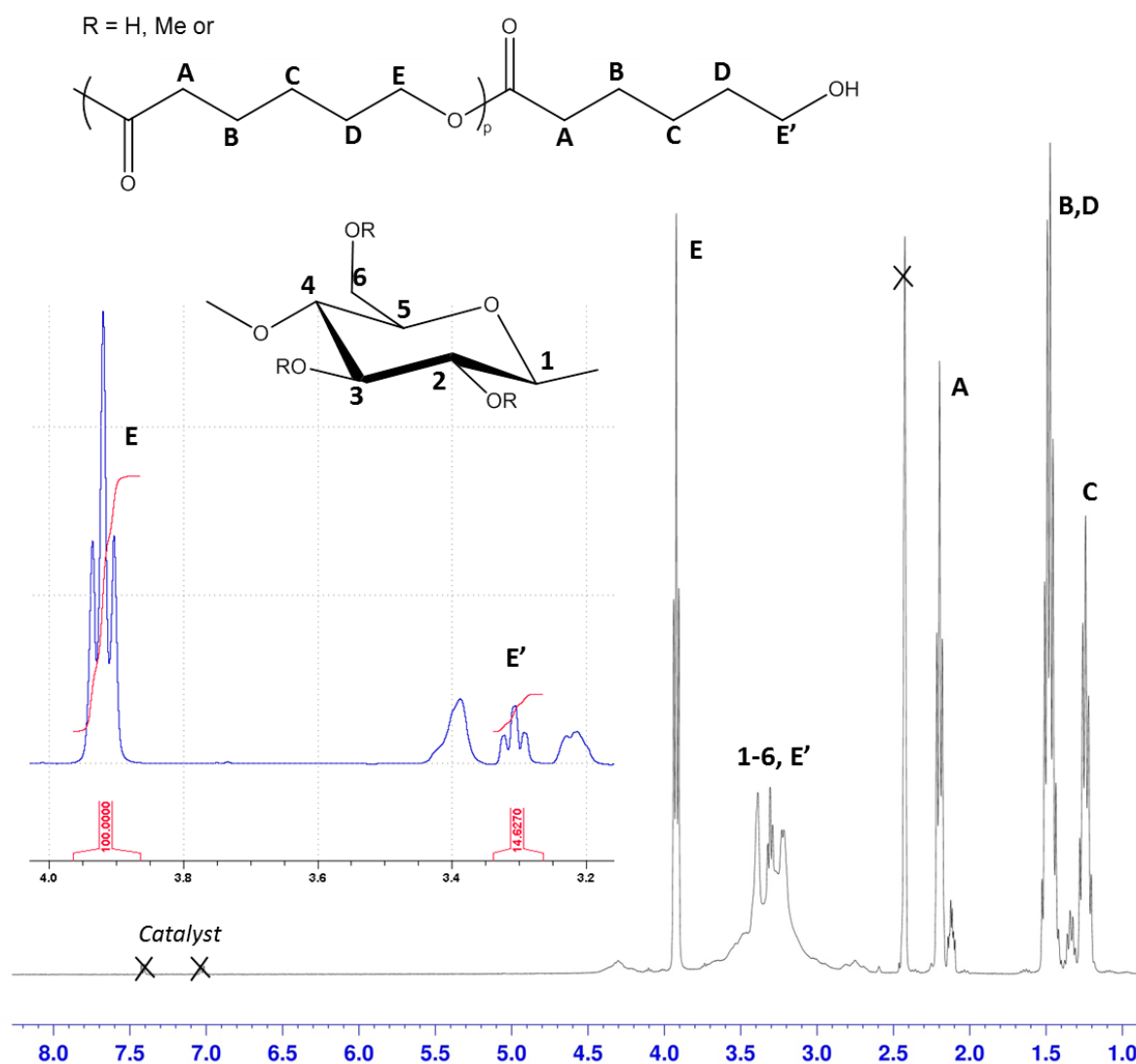Figure 3. ^{13}C NMR spectra of a typical functionalized methylcellulose in DMSO-d_6 (50°C)

Figure 4. ^{1}H NMR spectra of a typical functionalized methylcellulose in DMSO-d_6 (50°C)

Conclusion

Brönsted acids are efficient catalysts for the polymerization of ε-caprolactone in water. Poly(ε-caprolactone) with number-average molecular weights of around 5000 g/mol are obtained at 100°C in the presence of 1% catalyst. The same reaction conducted at lower temperatures in the presence of a water-soluble polysaccharide yields in a one-step procedure the corresponding poly(ε-caprolactone)-*graft*-polysaccharide. Degrees of substitution around 0.30-0.50 and 2.6-2.9 are obtained using dextran at room temperature and methylcellulose

(initial degree of substitution 1.6-1.9) at 50°C, respectively. The resulting number-average degrees of polymerization are 1.3-2.3 for dextran and 8 for methylcellulose. The degree of substitution of dextran hydroxyesters can be decreased to 0.1 by hydrolysis under prolonged reaction times, yielding a water-soluble dextran hydroxyester that self-assembles into particles of diameter 50-80 nm in water.

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