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Toward tunable amphiphilic copolymers via CuAAC click chemistry of oligocaprolactones onto starch backbone

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ABSTRACT

Starch-based tunable amphiphilic copolymers are easily obtained by grafting polycaprolactone chains *via* 1,3 dipolar Copper-Catalyzed Azide-Alkyne Cycloaddition (click chemistry CuAAC), starting from propargylated starch and azido oligocaprolactones with different chain lengths as the precursors. The copolymers are characterized by ^{1}H and ^{13}C NMR, from which a degree of substitution of starch can tentatively be deduced. Besides these bulk characterizations, the surface of the functionalized starch is also characterized by XPS which confirms the triazole formation, particularly through the deconvolution of the N 1s peak, and by ToF-SIMS which, not only confirms the surface modification, but also highlights the disappearance of the Cu^{+} cations.

The solubility and swelling behaviours of these copolymers have been investigated, which clearly show the dependence both on the solvent and the PCL chain length. These investigations highlight the swelling dependence on the δ_d component of the Hansen solubility parameter of solvents. Finally, at low concentration, they present the capacity to organize themselves in aggregates in aqueous solutions, as seen from TEM and DLS investigations.

1. Introduction

The grafting of hydrophobic groups, such as biodegradable polyesters, to the polysaccharide chain enables to get new materials, able to overcome some drawbacks often seen in the case of polysaccharides, such as poor long-term stability and mechanical properties due to their hydrophilic nature (Cunha & Gandini, 2010a,b). These materials, based on renewable resources, can also be implemented in order to replace "standard" thermoplastic materials, for instance in packaging as environmentally friendly alternatives (Agarwal & Speyerer, 2010; Woodruff & Hutmacher, 2010) and are sometimes referred as thermoplastic-like starch (TPS) (Curvelo, de Carvalho, & Agnelli, 2001). Such grafted copolymers can also be employed as new versatile environmentally friendly polymer surfactants (Halila et al., 2008; Ydens et al., 2000).

Besides the motivations based on sustainable development, these macromolecules display some unusual properties in solution, based on intra and/or intermolecular interactions. Thus, associative systems with well defined unusual rheological properties or amphiphilic matrices in aqueous medium can be obtained, the behaviour of which is closely connected with the polymer concentration, the intrinsic characteristics of the polysaccharide and the hydrophobe moieties, as well as the degree of substitution onto the backbone (Colinet, Dulong, Hamaide, Le Cerf, & Picton, 2009). The grafting of hydrophobic groups onto polysaccharide chains has also gained increasing interest in the development of new controlled release systems particularly designed for biomedical or pharmaceutical applications (Bejenariu, Popa, Le Cerf, & Picton, 2008; Hamcerencu, Popa, Desbrieres, & Riess, 2010; Mano et al., 2007; Uliniuc, Hamaide, Popa, & Băcăiță, 2013).

Due to their natural abundance and low cost, various processes for starch modifications have been studied, either by blending or chemical modifications. In the first case, melts processable starch compositions are patented for a long time. Among all blending strategies, one consists in blending starch with polyesters, in order to obtain fully biodegradable materials with improved mechanical properties, neither expensive nor toxic (Averous, Moro, Dole, & Fringant, 2000; Chin-San, 2003; Myllymäki et al., 1998; Preechawong, Peesan, Supaphol, & Rujiravanit, 2004; Spěváček, Brus, Divers, & Grohens, 2007).

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The family of aliphatic polyesters is the ideal candidate for a range of temporary biomedical applications, especially for degradable drug delivery systems since its aliphatic ester bond is susceptible to hydrolysis (Meseguer-Dueñas, Más-Estellés, Castilla-Cortázar, & Escobar Ivirico, 2011). The advantages of polycaprolactone (PCL) are the high permeability to small drug molecules, a degradation without generation of any acidic environment (McDonald et al., 2010), low immunogenicity and toxicity (Mohamed & van der Walle, 2008). Materials obtained from blends of starch and polycaprolactone are now commercially available and certified as completely biodegradable and non-toxic during the composting process.

Besides blending, starch and cellulose derivatives can be submitted to chemical modifications (Tomasik & Schilling, 2004), particularly to give grafted copolymers. As reported a long time ago, these materials are successfully used as compatibilizer for starch/polycaprolactone blends (Mani, Tang, & Bhattacharya, 1998). The anchoring of polyester chains onto starch can be obtained by implementing a "grafting from" approach, which is the *in situ* ring opening polymerization (ROP) of CL or LA, as described by several groups (Chen et al., 2005; Choi, Kim, & Park 1999; Dubois, Krishnan, & Narayan 1999; Dubois & Narayan, 2003; Gadda et al., 2006; Lönnberg et al., 2006; Sugih, Picchioni, Janssen, & Heeres, 2009). A microwave-assisted ring-opening polymerization has also recently been reported (Chang et al., 2011). The driving idea is to take advantage of the hydroxyl functions of polysaccharides, in order to promote the metal alkoxyde needed for the initiation of the ROP, by using $Sn(Oct)_2$ or $AlEt_3$.

Starch-graft-polyesters can also be obtained by anchoring the polyester chains onto the starch backbone *via* a chemical derivation of the starch, such as reported by Gandini and collaborators (Abdelmouleh et al., 2004; Carvalho, Curvelo, & Gandini, 2005; Botaro & Gandini, 1998; Trejo-O'Reilly, Cavaille, & Gandini, 1997). Recently, cellulose acetate has also been directly used in a reactive process with an internal mixer at 180 °C through transesterification with oligocaprolactone (Klebert, Nagy, Domjan, & Pukanszky, 2009).

Besides usual chemical processes such as etherification or esterification, 1,3 dipolar cycloaddition (click chemistry CuAAC) constitutes another versatile tool, now widely used to chemically modify polysaccharides by organic moieties, as well as to obtain graft copolymers based on various polysaccharides. A first CuAAC on polysaccharides was reported starting from azido cellulose and alkynyl thiophene (Liebert, Hänsch, & Heinze, 2006). More recently, amino functionalized nanofibrillated cellulose was obtained from the corresponding azido cellulose without any change of the nanofibrillated structure (Pahimanolis et al., 2011). Other substrates, such as azido (1→3)-β-D-glucans were also used to anchor various low molecular weight organic moieties (Hasegawa et al., 2006). In a similar manner, alkynyl polysaccharides can also be used. For instance, potato starch was propargylated and subsequently submitted to various derivations (Tankam, Müller, Mischnick, & Hopf, 2007). CuAAC between propargylated cellulose esters and azido PCL has been reported (Krouit, Bras, & Belgacem, 2008).

We prepared amphiphilic copolymers by such approaches with ease and used them for the colloidal stabilization of polycaprolactone nanoparticles (Otman, Boullanger, Drockenmuller, & Hamaide, 2010). More recently, we investigated the synthesis of thermosensitive guar-based copolymers and hydrogels with tunable physico-chemical properties by CuAAC (Tizzoti, Creuzet, et al., 2010; Tizzoti, Labeau, et al., 2010). Finally, its fidelity in the presence of various surrounding functionalities allowed the synthesis of well-defined glyco-polyorganosiloxanes from cellobiose and xyloglucooligosaccharide without protecting groups (Halila et al., 2008) as well as one-pot approaches (Damiron et al., 2009; Tissandier et al., 2012).

This paper deals first with the synthesis and characterizations of biodegradable, amphiphilic starch-graft-polycaprolactone copolymers, by using the 1,3 dipolar cycloaddition of oligocaprolactone onto a starch backbone. Herein, we focused on the reaction between propargylated starch and azido-PCL with various controlled oligocaprolactone chain lengths. These oligocaprolactone chains were previously synthesized by functional ring opening polymerization of ε-CL in the presence of 11-bromo-1-undecanol as a transfer agent and the subsequent substitution by sodium azide.

Besides NMR characterizations, the modification of the starch surface was studied by XPS and ToF-SIMS, in order to investigate the chemical grafting specifically at the surface of the samples. This was also undertaken to implement another characterization technique in order to ascertain the triazole ring formation. This study provided also interesting information on the residual Cu amount.

This approach enables to get samples with tunable amphiphilic properties, depending on the PCL chain length, as evidenced by swelling measurements. A second part of this work will address a comparative study of different samples in terms of solubility and swelling measurements in order to highlight the change in hydrophobicity provided by the PCL chain lengths. Finally, the feasibility of aggregates in aqueous medium will demonstrate the amphiphilic behaviour of these copolymers.

2. Materials and methods

2.1. Materials

2.1.1. Reagents

ε-Caprolactone (CL, 99%, Fluka) was dried over 3 Å molecular sieves for 3 days before use. The initiator of the ring-opening polymerization, triethylaluminium (TEA 1M, Aldrich) was used as received. 11-Bromo-1-undecanol (Aldrich) was dissolved in toluene and kept in a Schlenck tube under argon. Soluble starch (ACS reagent), sodium L-ascorbate, copper(II) sulfate pentahydrate, propargyl bromide, sodium azide were purchased from Sigma–Aldrich and used as received.

2.1.2. Propargylated starch

Starch (3 g, 37 mmol) was placed in a glass reactor, in 50 mL of isopropanol and stirred for 10 min at room temperature. Then, an aqueous solution of sodium hydroxide (5 wt%, 15.5 mL, 13 mmol) was added and after 1 h, propargyl bromide (8.5 g, 37 mmol) dropwise. The reaction was allowed to stir for 3 h at 60 °C. The resulting propargyl starch was precipitated in water, washed twice with isopropanol in order to remove the residual propargyl bromide and finally dried under vacuum at room temperature overnight (Tizzoti, Creuzet, et al., 2010; Tizzoti, Labeau, et al., 2010). The product was characterized by FTIR ($\nu_{sC\equiv C}$ at 2117 cm^{-1}) and HR-MAS NMR (DMSO-d_6) δ (ppm): ^{1}H NMR: 3–6.0 (m, anhydroglucose units), 2.18 (s, C≡C**H**). ^{13}C NMR (DMSO-d_6) δ (ppm): 58.0, 58.5 (—O—**C**H_2—C≡CH), 69.2 (—**C**H2— O—CH_2—C≡CH), 80.9 (O—CH_2—**C**≡CH).

2.1.3. Synthesis of azido-polycaprolactone PCL-N_3

As an example for obtaining a degree of polymerization $\overline{X_n} = 4$, a catalytic amount of $AlEt_3$ (1 mL from a 1.1 mol/L solution) was added to a determined amount of bromo-undecanol solution in toluene (38 mL, 0.020 mol, 0.52 mol L^{-1}). When the oil bath reached 50 °C, ε-caprolactone (4.5 g, 38.6 mmol) was added and after 5 h of stirring, the polymer was precipitated in cold heptane. The resulting polycaprolactone with bromine chain end PCL-Br was separated as a solid phase and dried in vacuum at room temperature.

The bromine atom was subsequently substituted with sodium azide. PCL-Br ($\overline{X_n} = 4$, 4.8 g, 0.063 mmol) and NaN_3 (1.08 g, 0.16 mmol) were dissolved in 100 mL DMF and the reaction was performed at 80 °C for 15 h, in the absence of light. The reaction by-products were removed by filtration and the solution was washed with deionized water and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and azido-polycaprolactone was obtained after removing the solvent.

^{1}H NMR ($CDCl_3$) δ (ppm): 1.24 (m, γ, γ′-PCL), 1.54–1.61 (m, β and β′-PCL), 2.23–2.29 (t, α and α′-PCL), 3.25 (t, α″-PCL and C**H**$_2$N$_3$), 3.58–3.63 (t, ε′-PCL), 4.02 (t, ε-PCL).

^{13}C NMR ($CDCl_3$) δ (ppm): 25.2 (s, β-PCL), 25.8 (s, γ-PCL), 28.7 (s, δ-PCL), 32.3 (s, α-PCL), 51.4 (s, **C**H$_2$N$_3$), 62.5 (s, ε-PCL), 173.5 (s, **C**=O).

2.1.4. Grafting of azido-polycaprolactone onto propargylated starch by click chemistry

The general procedure for the grafting of PCL onto starch by click chemistry is described below: propargylated starch (0.6 mmol) and azido-PCL (0.6 mmol) were dissolved in a 1:1 mixture of water and DMF (10 mL). Freshly prepared aqueous solution of sodium ascorbate (0.12 mmol, 120 μL, 1 M) was added followed by a 75% solution of copper(II) sulfate pentahydrate in water (8 μL, 0.024 mmol). The mixture was kept under stirring 24 h, in the absence of light, under inert atmosphere, at 60 °C. The graft copolymer was precipitated in water and dialyzed during 5 days using a cellulose dialysis bag (Orange Scientific, MWCO: 3500 Da) against a 0.1 mol L^{-1} aqueous ethylenediamine tetraacetic acid (EDTA) solution to remove catalyst. Water was refreshed two times a day. The product was freeze-dried to yield a white solid and characterized by HR-MAS NMR.

^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.31 (m, γ-PCL), 1.54 (m, β and δ-PCL), 2.25 (t, α-PCL), 3.37 (t, ε′-PCL), 3.98 (t, ε-PCL), 3.5–5.4 (m, broad peaks, starch), 8.09 (s, C=C**H**), triazole ring).

^{13}C NMR (DMSO-d$_6$) δ (ppm): 49.92 (CH$_2$—**C**H$_2$—N), 123.84 (C=**C**H, triazole ring), 144.75 (**C**=CH, triazole ring). Three grafted copolymers with different PCL chain length were synthesized and their codes further mentioned in this paper are the following ones: CC4 refers to the graft copolymer with PCL of $\overline{X_n} = 4$, CC14 with PCL of $\overline{X_n} = 14$ and CC20 with PCL of $\overline{X_n} = 20$.

2.2. General methods and analysis

2.2.1. FTIR and NMR measurements

FTIR spectra were recorded using KBr pellets with a Magna-IR Nicolet 550 collecting 32 scans from 400 to 4000 cm^{-1}. KBr pellets were prepared by grinding the samples with solid potassium bromide (KBr) and applying pressure (10 ton).

NMR spectra were recorded at 90 °C with a Bruker Avance III Spectrometer operating at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C. DMSO-d$_6$ was used as solvent. The inverse gate proton decoupling conditions for the acquisition are as follows: pulse angle of 70°, recycling time of 11.4 s.

2.2.2. XPS spectroscopy

The surface chemical composition of the samples was analyzed by X-ray photoelectron spectroscopy (XPS) using a PHI-5000 VersaProbe photoelectron spectrometer (ULVAC-PHI, Inc.) with a hemispherical energy analyzer (0.85 eV energy resolution, for organic materials). A monochromatic Al Kα X-ray radiation ($h\nu$ = 1486.7 eV) was used as the excitation source. Sample powders were pressed into a pellet for analysis. The standard take-off angle used for analysis was 45°, producing a maximum analysis depth in the range of 3–5 nm. Low-resolution survey spectra were recorded in 0.5 eV steps with 117.4 eV analyzer pass energy. In addition, high-resolution spectra were recorded in 0.1 eV steps with 58.7 eV analyzer pass energy. The surface quantification has been carried out via the standard procedure by using the core level XPS narrow spectra of O 1s, N 1s and C 1s (the C—C/C—H C 1s peak at 284.6 eV served for binding energy scale calibration). The elemental concentration was calculated from peak surface areas, taking into account the sensitivity factors provided by the spectrometer manufacturer. Peak fitting was done using the PHI MultiPak software to identify the chemical environments. The C 1s and N 1s peaks were decomposed by using a least square fitting procedure with gaussian curves and taking care that full widths at half maximum (FWHM) display around the same value for all the components of the same peak.

2.2.3. ToF-SIMS measurements

ToF-SIMS measurements were carried out using a Physical Electronics TRIFT III ToF-SIMS instrument (ULVAC-PHI, Inc.) operated with a pulsed 22 keV Au^+ ion gun (ion current of 2 nA) rastered over a 300 μm × 300 μm area. Sample powders were hand pressed onto indium foil. An electron gun was operated in pulsed mode at low electron energy for charge compensation. Ion dose was kept below the static conditions limits. Data were analyzed using the WinCadence™ software. Mass calibration was performed on hydrocarbon secondary ions. Data were normalized to the total intensity minus $H^{+/-}$ intensity because of its low reproducibility. The mean and standard deviations were calculated from measurements acquired on three different areas of each sample.

2.2.4. Dynamic light scattering measurements

DLS measurements were performed using a Malvern Nanosizer S equipped with a 10-mW He/Ne laser beam operating at 633 nm at 90° scattering angle. All values were triplicates of 10 measurements each, obtained at 25 °C. For a monodisperse colloid, the polydispersity index should be below 0.1, but values up to 0.1 can be used for comparison purposes.

2.2.5. Electron microscopy

Electron microscopy was performed using a TEM Philips CM120 microscope operated at 80 kV. To prepare aqueous dispersions, double distilled water (1 mL) was added dropwise to a THF solution (20 mL) of copolymers (5 mg) under a mild stirring. The micellar solution was obtained after gently stripping THF by rotary evaporation under vacuum (30 °C, 3 h) up to a final concentration of 0.5 mg/mL. A small drop of the aqueous solution of the copolymers was placed onto a copper grid coated with carbon and dried at room temperature.

3. Results and discussion

3.1. Synthesis and NMR characterizations of PCL-g-starch

As stated in the introductory part, PCL-g-starch copolymers are obtained by reaction between azido oligocaprolactone and propargylated starch backbone according to a 1,3 dipolar cycloaddition. The oligocaprolactone chains are previously synthesized by functional ring opening polymerization of ε-CL in the presence of 11-bromo-1-undecanol as a transfer agent and the subsequent substitution by sodium azide.

Azido polymer derivatives are usually issued from alcohols by a two-steps procedure, taking advantage of good leaving groups such as methanesulfonyl or *p*-toluenesulfonyl groups. For instance, this approach was successfully used to prepare azido-PEG (Ostaci et al., 2008; Tissandier et al., 2012). Krouit et al. converted commercial dihydroxy telechelic PCL according to the same approach (Krouit et al., 2008). To get rid of the commercial constraints and taking advantage of our expertise in the field of the ring opening

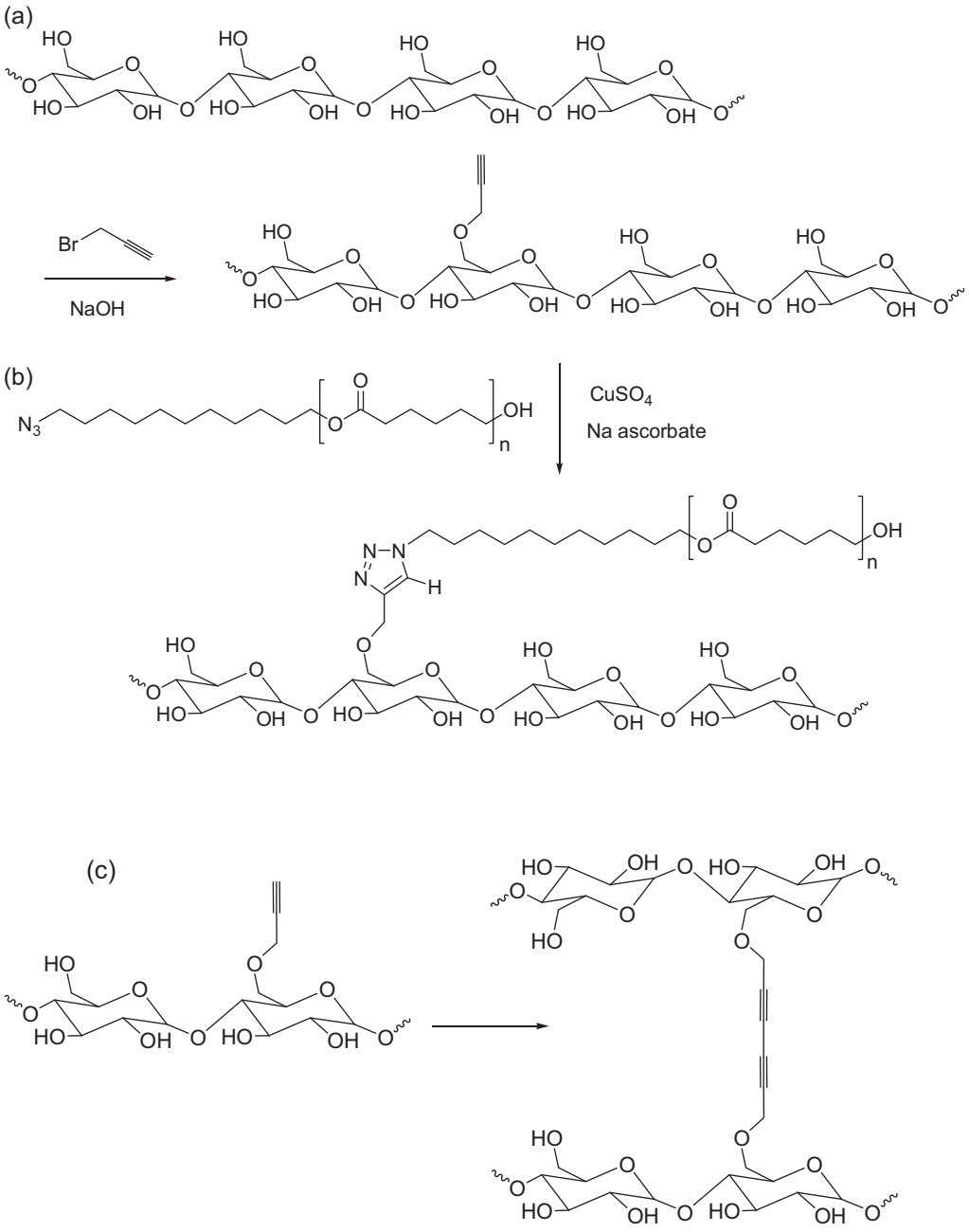

Fig. 1. Functionalization of starch by propargyl bromide on O-6 (a) and subsequent copper (I)-catalyzed cycloaddition (CuAAC) with azido-polycaprolactone (b). The same reaction can also take place on both O-2 and O-3. Glaser oxidative coupling of alkyne moieties can also take place (c).

polymerization, we first synthesized a brominated PCL by anionic coordinated ring-opening polymerization of ε-caprolactone with an aluminum alkoxide, issued from reaction of triethyl aluminum on 11-bromo-1-undecanol as the initiator. We also used this alcohol in excess in order to promote a fast transfer reaction. This functional oligomerisation reaction enables to produce easily well-defined functionalized oligocaprolactones with a controlled average molecular weight (Miola-Delaite, Hamaide, & Spitz, 1999; Tortosa, Miola, & Hamaide, 1997). The subsequent substitution with NaN_3 yields the desired azido-PCL. Three azido-oligocaprolactones ($\overline{X_n} = 4, 14, 20$) were synthesized and their degrees of polymerization were determined by ^{1}H NMR. More details on syntheses and ^{1}H NMR characterisations are reported in supporting information.

Starch was functionalized *via* nucleophilic substitution of propargyl bromide by sodium alkoxydes issued from starch (Fig. 1a). The reaction was performed in heterogeneous medium on swollen starch under basic conditions according to a procedure previously described by Tizzotti et al. (Tizzoti, Creuzet, et al., 2010; Tizzoti, Labeau, et al., 2010) for alkyne functionalized guars. NaOH was used to decrease inter- and intramolecular hydrogen bonds and to promote optimal swelling of starch, as well as the activation of the hydroxyl groups. After reaction, the propargyl starch was precipitated in water and washed twice with isopropanol in order to remove the residual propargyl bromide.

The functionalization can be ascertained by IR ($\nu_{sC\equiv C}$ at 2117 cm^{-1}) and ^{1}H NMR (δ = 2.18 ppm (C≡C**H**)) (spectra not shown). It's noteworthy that the resolution of ^{1}H NMR spectra is low, therefore precise peak integration and consequently the calculation of the degree of substitution (DS) are not really possible. The DS can nevertheless be further determined from the ^{1}H spectra of the clicked copolymer, assuming that DS is the same before and after click coupling. This procedure was already successfully applied for

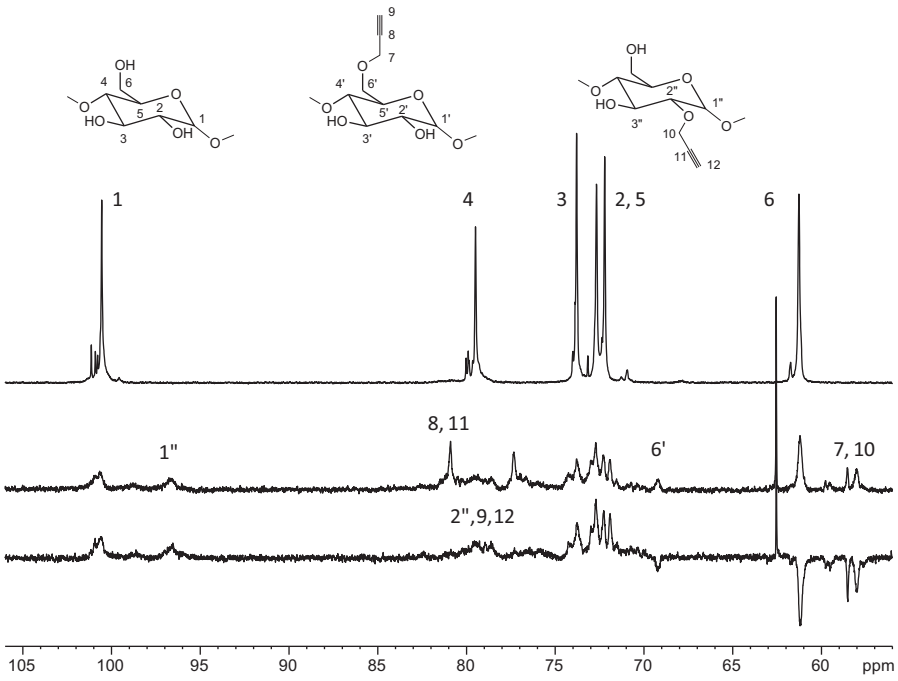

Fig. 2. ^{13}C NMR spectra of starting starch (a), propargylated starch (b) and the corresponding DEPT 135 spectrum (c). DMSO-d_6 was used as solvent. For the sake of clarity, the only functionalizations on O-2 and O-6 have been drawn. Functionalization can also occur on O-3, leading to additional peaks 3‴, in the same δ range as 2″. The peak at 62.7 ppm is assigned to residual iPrOH.

the characterization of PEGylated guar (Tizzoti, Creuzet, et al., 2010; Tizzoti, Labeau, et al., 2010).

A ^{13}C NMR spectrum of propargylated starch is depicted on Fig. 2, as well as the corresponding DEPT 135 spectrum. For comparison is also shown the spectrum of starting starch. The propargylation reactions can occur at O-2, O-3 and O-6 leading to more or less strong variations $\Delta\delta$ of chemical shifts of adjacent carbons. For instance, the O-6 propargylation leads to a chemical shift for C-6 from 61.2 up to 69.2 ppm ($\Delta\delta$ = +8 ppm). The same $\Delta\delta$ for C-2 and C-3 after propargylation lead to resonance peaks around 78–80 ppm. As a consequence, the signals assigned to the C-2, C-3 and C-4 carbons became broader because of the many possibilities for substitutions.

In addition, the O-2 propargylation is noticed by the chemical shift for C-1 from 100.5 down to 96.7 ppm. Resonance peaks assigned to **C**H_2—C≡CH were noticed in the range between 56 and 60 ppm. The C≡**C**H carbon is expected around 78 ppm and is not quite visible. In addition, two peaks attributed to quaternary carbons (Cq) (80.9 ppm and 77.3 ppm) appeared. One of these two peaks is assigned to Cq of propargyl moiety. The second one cannot be assigned to Cq of residual propargyl bromide because we should observe another peak at 13.5 ppm assigned to **C**H_2—Br displaying the same intensity, which is not the case with purified products. Therefore, this results suggests the presence of diacetylenic structures, which may be due to a Glaser aerobic oxidative coupling, leading to —C≡C—C≡C— bonds, as mentioned before for reactions involving acetylenes (Chu & Qing, 2010; Liu & Burton, 1997; Tedeschi, Saccavini, Maurette, Soleilhavoup, & Chauvin, 2003) (Fig. 1c). It has been known that the oxidation is best performed by the use of cuprous acetylides, but the best yields of diynes are obtained by oxidizing the acetylide by free oxygen, rather than by cupric salts (Cliford & Waters, 1963). On the other hand, Tankam et al. (2007) reported unexpected modifications in the case of propargylated starches, more precisely the loss of propargyl residues initiated by the intramolecular addition of free OH to the triple bond and subsequent hydrolysis of these enolic structures.

In that latter case, performing quantitative ^{13}C NMR on those samples would enable to determine a DS directly on the propargylated starch from the peaks of **C**-1 and (**C**-6 + **C**H_2C≡CH), but care must be taken because all alkyne functions are taken into consideration here, whilst only free alkyne groups will lead to the click reaction.

The cycloaddition between azido-PCL and propargylated starch was performed in a 1:1 mixture of water and DMF (Fig. 1b). The success of the coupling was first confirmed by FT-IR (spectra not shown). The alkyne and azide characteristic peaks at 2117 cm^{-1} and 2100 cm^{-1} respectively, disappeared after the triazole formation. In the same way, the peak assigned to the —C**H$_2$**N_3 proton at 3.24 ppm on ^{1}H NMR spectrum disappeared entirely and a new triazole peak appeared in the 7.8–8.1 ppm range (figure not shown). ^{13}C NMR confirms the formation of the triazole ring at 123.8 (C═**C**H) and 144.7 (**C**═CH) ppm (Fig. 3). In addition, NMR spectra display the resonance peaks assigned to the oligocaprolactone chains.As stated in the previous paragraph, DS of the starch backbone was determined from the ^{1}H spectra of the clicked copolymer, assuming that DS is the same before and after click coupling. In that case, the DS calculated from the ^{1}H spectrum takes into account only the free alkyne functions. As an example, the DS value of sample CC20 was 0.25 based on ^{1}H spectrum and 0.43 from quantitative ^{13}C corresponding to the percentage of acetylenic coupling during the synthesis. It can also be noticed that both carbon signals at 80 and 77 ppm are still present after the click reaction, but with a different ratio. The signal at 77 ppm kept almost the same integration, while the intensity of the signal at 80 ppm decreased because of the triazole formation. The same conclusions have been drawn from the NMR spectra related to the other samples.

3.2. XPS and ToF-SIMS surface characterization

XPS was used to investigate the changes in atomic composition resulting from the surface modification of starch, *via* the carbon signal and the oxygen signal around 285 and 532 eV respectively. For instance, Fig. 4a and b reflect the change of the O/C ratio after

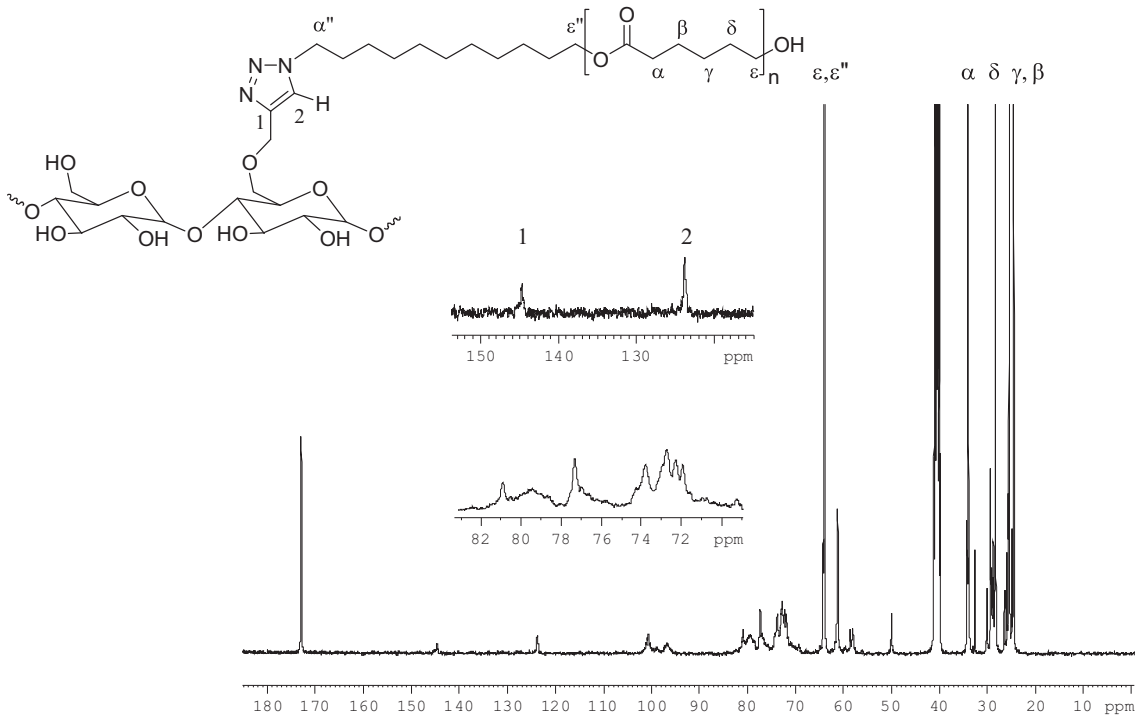

Fig. 3. ^{13}C NMR spectra of PCL-g-starch CC14. DMSO-d_6 was used as solvent.

grafting of the PCL chains onto the starch surface. In addition, the chemical grafting can be highlighted *via* the N signal at around 400 eV, as discussed below. It must be noticed that very small nitrogen content was detected on the surface of the starting starch. This nitrogen is often detected and believed to originate from proteins present in the native starch (Bengtsson, Koch, & Gatenholm, 2003; Rindlav-Westling & Gatenholm, 2003; Saad, Gaiani, Mullet, Scher, & Cuq, 2011). In order to have the most significant N signal, the starch grafted with the shortest PCL chain, namely CC4, was the only one to be studied using surface analysis techniques.

XPS investigations on starch, and particularly the C 1s peak, have been reported in numerous papers (Bengtsson et al., 2003; Rindlav-Westling & Gatenholm, 2003; Rouxhet et al., 2008; Saad et al., 2011). This peak is usually deconvoluted into four components, namely the two expected peaks C—O (alcohol) at 286.1 eV and O—C—O (acetal) at 287.5 eV as well as two other peaks O—C=O (carboxyl and ester functions) at 288.7 eV and C—C/C—H at 284.6 eV. The intensity of the O—C=O peak is always very low and is sometimes neglected. These last two peaks are usually related to impurities, because of the presence of non starch components (additives and/or surface contamination), resulting in a more or less important decrease O/C ratio with respect to the theoretical one of 0.83 $[(C_6H_{10}O_5)_n]$. Our experimental O/C ratio (0.65) is somewhat different from other reported values, for instance 1.14 (Krouit et al., 2008), or 0.73 (Saad et al., 2011) but all results report significant surface contamination (by definition somewhat variable from one sample to the other).

In addition, it must be stressed that results depends strongly on the deconvolution methods. All the examples picked in the literature indicate that both the resolution of the instrument and the deconvolution parameters play a significant role in the deconvolution between the components C—O and O—C—O on one hand and O—C—O and C—C/C—H on the other hand. Unfortunately, these parameters are usually not often reported.

In our case, the deconvolution of the C 1s XPS spectrum (FWHM in the range of 1.4–1.7 eV) clearly shows an important contribution of the peak related to C—C and C—H, corresponding to 32% of the C 1s peak (Fig. 4c). The intensity of the O—C=O peak represents less than 5% of the total intensity. The value of the C—O/O—C—O ratio is 2.5, to be compared with the previously reported values (4.3 – Saad et al., 2011; 3.8 – Krouit et al., 2008; 2.4 – Rindlav-Westling & Gatenholm, 2003), which are always lower than the theoretical value of 5. All these impurities interfere thus with the analysis of starting starch, affect the O/C ratio, and therefore could influence similarly the surface analysis results obtained from all the other modified products.

The O/C ratio of the propargylated starch decreases significantly from 0.65 to 0.45. The C 1s XPS spectrum (Fig. 4d) clearly shows a significant increase of the C—C/C—H peak to around 42.6% (Table 1) and the value of the C—O/O—C—O ratio increases slightly to 2.7 because of the grafting of the O—CH_2—C≡CH moiety. Due to the significant differences compared to the theoretical values, while a qualitative description can easily be provided from the modification of XPS spectra, a quantitative approach leading to the calculation of the surface DS is somewhat uncertain and was not attempted.

After grafting of the azido-PCL ($\overline{X_n} = 4$), the O/C ratio decreases to 0.31 (Fig. 4e) and the carbon atomic percentage becomes even higher, clearly indicating that further grafting with hydrocarbon based material did take place, which is consistent with the expected chemical modification. Such a decrease in the O/C ratio can indeed be related to the long hydrocarbon chain of PCL, as evidenced by the increase of the C—C/C—H peak to around 73.5% (Table 1).

In addition to the C 1s peak, the N 1s peak at 400 eV indicates that the triazole group was detected (Table 1). Indeed, the deconvolution of the N 1s peak of the starting PCL-N_3 displayed three identical peaks at 399.5 (—CH_2—N=N^+=N^-), 401.4 (—CH_2—N=N^+=N^-) and 403.0 (—CH_2—N=N^+=N^-) eV, respectively, their ratio close to 1:1:1 (Fig. 4f) while the N 1s peak of CC4 has a more complex shape. A first fitting reveals two main peaks at 400.1 eV and 401.7 eV, with a ratio close to 2:1, which can be

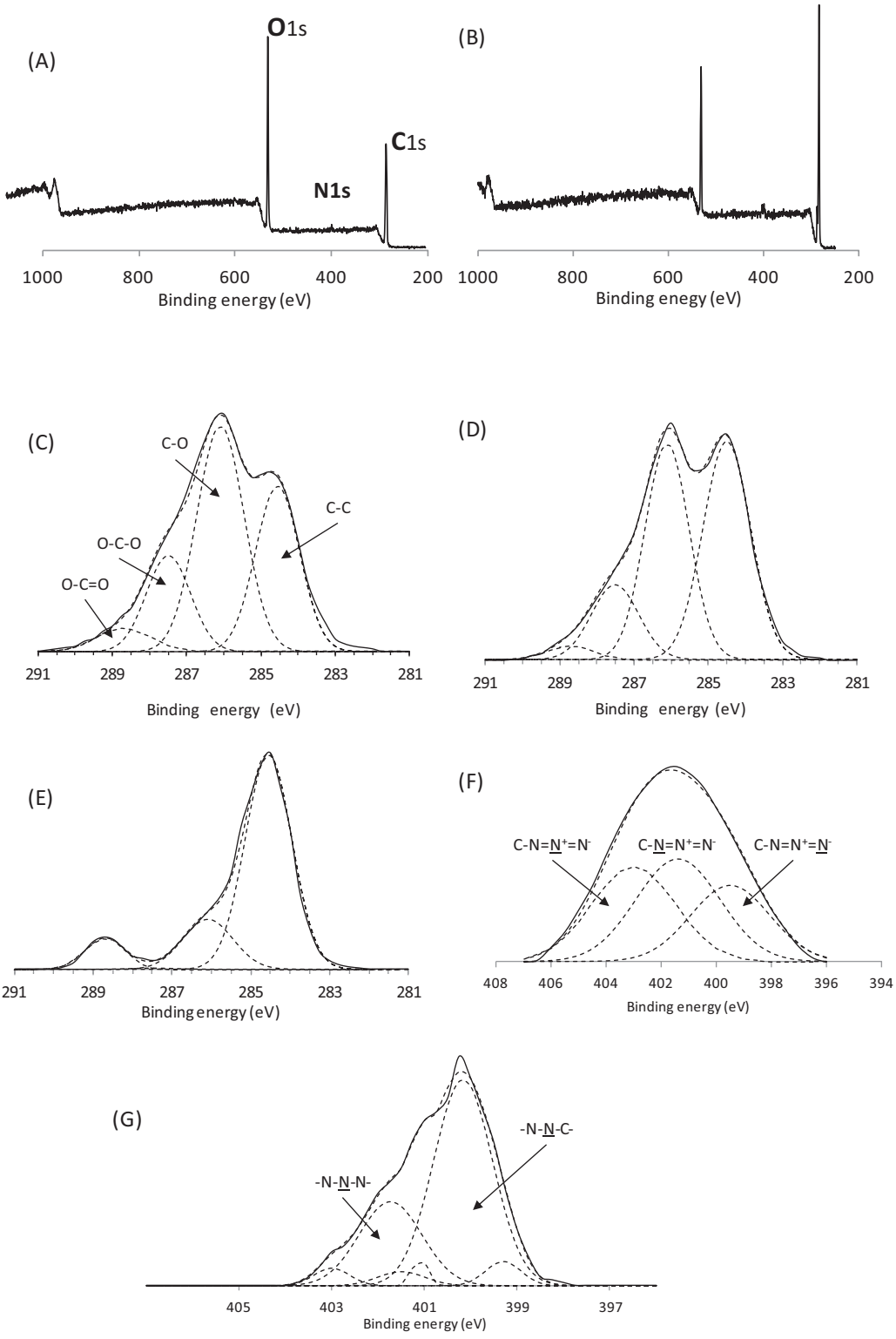

Fig. 4. Wide scan XPS spectra of starch (a) and CC4 (b). The O/C ratio of the PCL-grafted starch decreases significantly from 0.65 to 0.31. C 1s XPS spectra of starch (c), propargylated starch (d), "clicked" starch (e) and N 1s XPS spectra of azido-oligocaprolactone (f) and CC4 (g) showing the experimental (full line) and deconvoluted (dotted line) spectra. For the sake of clarity, the ordinate (in counts s^{-1}) is not represented.

assigned to N—N—C and N—N—N, respectively (Fukuda, Onogi, & Miura, 2009; Liu, Zheng, Ma, Yan, & Xiao, 2011) (Fig. 4g). Nevertheless, this simple deconvolution leaves residual peaks which can be assigned to some unreacted azido-oligocaprolactone. Finally, the best fitting is obtained by taking into account the nitrogen peak observed on the starting starch.

Fig. 5 displays the ToF-SIMS spectra in the negative mode in the m/z = 40–140 mass range. The starch spectrum exhibits peaks characteristic of oxygen containing hydrocarbon peaks (CHO_2^-, $C_2H_3O_2^-$ and $C_3H_3O_2^-$) together with hydrocarbon characteristic peaks. CN^- is also slightly detected (data not illustrated). For the propargylated starch, Br^- ions were detected at m/z = 79–81,

Table 1
XPS C 1s and N 1s peak fitting (%) at the surface of the starch, propargylated starch and polycaprolactone-grafted starch (CC4).

Binding energy (eV)	Functions	Starch	Propargylated starch	Azido-PCL	CC4
284.6	C—C, C—H, C≡C	32.1	42.9		73.5
286.1	C—O, C—N	44.9	39.7		15.9
287.5	O—C—O, C=O	17.8	14.8		1.2
288.7	O—C=O	5.2	2.6		9.4
399.8	—N=N⁺=N—			34.0	–
401.8	—N=N⁺=N—			33.0	–
403.0	—N=N⁺=N—			33.0	–
400.1	—N—N—C—		–		64.5
401.6	—N—N—N—		–		35.5

issued from some residual NaBr. Characteristic peaks derived from PCL are detected in the spectrum of azido-PCL. Some fragments are identical to those detected for starch, but at least some peaks such as $C_6H_{11}O_3^-$ at $m/z = 131$ appear to be detected only for PCL. All the main characteristic signatures detected in the previous spectra are also visible in the spectrum of the CC4 copolymer (except for Br^-, which indicates that it is not detected at the surface of the copolymer), confirming therefore that the copolymer was obtained. This proves the successful surface modifications and is consistent with main conclusions taken from XPS results.

A quantitative treatment of ToF-SIMS data was attempted, using the normalized intensity for $m/z = 131$, a characteristic peak for PCL in the negative mode ($C_6H_{11}O_3^-$). The PCL part in CC4 is then estimated to be of ~20%, a result somewhat similar to that obtained from NMR data. It should be noted here that ToF-SIMS is a surface analysis based on the detection of secondary ions and is thus able to trace a specific compound (here PCL) without any significant disturbance from ubiquitous hydrocarbon impurities.

Finally, $^{63}Cu^+$ and $^{65}Cu^+$ ions can be detected on the copolymer at $m/z = 62.9$ (within the detection limits for Cu ions, namely 0.1 atomic %). These investigations allowed determining the necessary time for purifying the copolymers by dialysis. This is an imperious determination for these products, which are aimed to be used in biomedical applications.

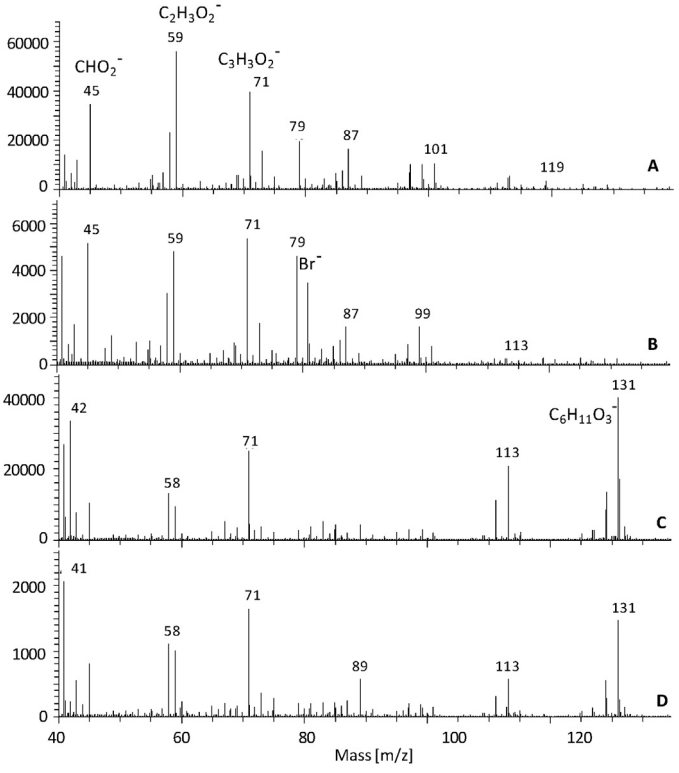

Fig. 5. TOF-SIMS negative mode spectra of starch (a), propargylated starch (b), $PCLN_3$ (c), CC4 (d). The ordinate is in total counts.

Therefore, as a first conclusion, click chemistry allows to obtain easily PCL-*g*-starch. It is clear that this reaction could be extended to starch backbone displaying other degrees of substitution. On the other hand, the PCL chain length can also be controlled by ε-caprolactone ROP. In addition to usual NMR characterizations, the XPS is another powerful tool to highlight the successful formation of a triazole ring through the N 1s peak deconvolution. On the other hand, TOF-SIMS investigations provide substantial information relevant to contamination issues by Cu^+. The second part of this work will address a comparative study of the three samples in terms of thermal properties and highlight the change in hydrophobicity provided by the PCL chain through swelling measurements.

3.3. Swelling properties

In order to evaluate the potential properties of these grafted copolymers as possible tunable amphiphilic gels, the swelling behaviour of copolymers in different solvents was qualitatively investigated in terms of a swelling degree Q arbitrary quantified on a scale of 0 (insoluble) to 5 (soluble) (see details in supporting information). These observations were tentatively interpreted in terms of the Hansen solubility parameters (HSP) of the solvents (Eq. (1))

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

where δ_d, δ_p and δ_h are respectively the dispersion, polar and hydrogen-bonding components of δ (Handbook of Polymers, 1983).

Fig. 6a depicts the usual Q-δ representation for the copolymer CC14. The other results are in supporting information. The maxima of the curves indicate a δ value ~~of~~ for the copolymers of about 25 $MPa^{1/2}$. Whatever the PCL chain length, DMSO appears to be the best solvent, closely followed by THF and chloroform exhibits the same high capacity of swelling for all copolymers. The ability of acetone to swell the copolymers decreases when increasing the PCL chain length. This could be surprising if considering the δ values, but it must be recalled that PCL is actually not totally soluble in acetone, and may even be insoluble when dealing with high molecular weights. An interesting effect is displayed by toluene, which shows an increase in swelling with the increase of PCL length chain. Finally, only CC4 showed a slight affinity towards water, because of its shorter hydrophobic chain.

The effect of the PCL chain length on the copolymers solubility in toluene can be analyzed in terms of individual HSP parameters. The δ_p and δ_h value components for toluene are very low, thence the dispersion component δ_d could be the main parameter governing the swelling. This is more visible when plotting the swelling vs. the only δ_d component (Fig. 6b and supporting information) which depicts a linear trend, even if THF deviates slightly from this general

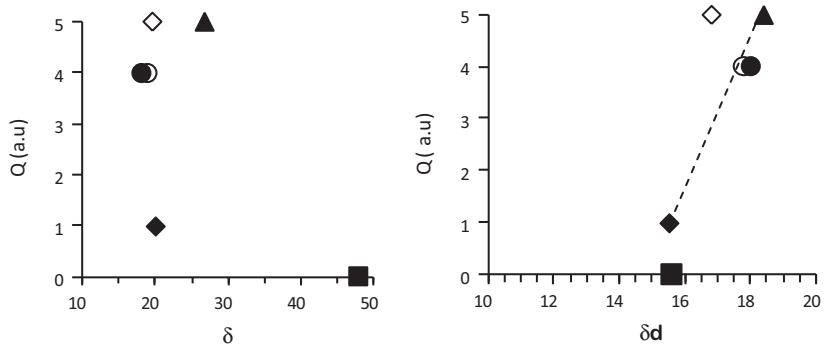

Fig. 6. Dependence of the swelling behavior of grafted copolymer, CC14 on δ of solvents: (●) toluene; (○) chloroform; (♦) acetone; (◊) THF; (▲) DMSO; (■) water.

trend. This behaviour might be interpreted in terms of preferential solvation of PCL chains by toluene.

On the other hand, the HSP of the copolymers can tentatively be determined by assuming an additivity rule (Eq. (2)), as often applied for solvent mixtures for which the HSP values are in most cases proportional to the volume fractions of their components and sometimes applied for random copolymers (Caykara, 2004). Other studies reported that block SBR copolymers displayed solubility parameters in the same range as random SBR with the same styrene content, that supports this approach (Ovejero, Pérez, Romero, Guzman, & Dıez, 2007)

$$\delta = \varphi_1\delta_1 + \varphi_2\delta_2 \quad (2)$$

where φ_1 and φ_2 stand for the volume fractions PCL and starch respectively, assuming that the DS = 0.25 (i.e., a OCL chain per four anhydroglucose unit).

The δ value, as well as HSP components of PCL, have been well investigated (Bordes et al., 2010) and are reported in Table 2. Those of starch are quite less documented and using the δ values of cellulose could be questionable. δ values of cellulose are sometimes used to estimate the compatibility between starch and polymer in melt processable starch compositions, that is in experimental bulk conditions completely different from our systems in solution. Solubility problems are strongly related to the morphology of the materials (which depends on the drying conditions, the age of the samples, the source, etc.), the accessibility of hydroxyl groups forming hydrogen bonds. For instance, a δ value for commercially available samples of rice and wheat starch was found close to 0 due to their high crystalline content (Heng, Pearse, Thielmann, Lampked, & Bismarck, 2007). The δ value goes up to 14.4 $MPa^{1/2}$ and 22.6 $MPa^{1/2}$ below and close to the glass transition temperature respectively for extruded potato starch. Finally, a value of around 37 $MPa^{1/2}$ was measured for lower molecular weight materials with similar structure. This behavior was interpreted in terms of the more or less accessibility of the probe molecule (water) into the bulk structure of the polymer chains. Concerning our materials, the grafted copolymers are issued from previous chemical reactions in a mixture of water and DMF in which the associations that govern the formation of helices, if any, will take place in a very small proportion. In addition, the grafting of oligocaprolactone chains onto the backbone will largely interfere with the formation of these conformations. DSC analysis of copolymers reveals only a small crystallinity ratio due to the longest oligocaprolactone chains. Under these conditions, one can reasonably assume that the δ values of starch could be close to those of cellulose.

We used the HSP values of cellulose, experimentally determined from solutions of cellulose acetate at various degrees of substitution and extrapolation to zero DS (Elidrissi, El Barkany, Amhamdi, Maaroufi, & Hammouti, 2012). (Table 2) We preferred these values as they are more representative for our operating conditions (polymer in solution). The HSP values of copolymers can then be calculated from the volume fractions (Eq. (3)) in order to determine the δ value.

$$\delta_i = \varphi_1\delta_{i,1} + \varphi_2\delta_{i,2}, \quad i = d, p, h \quad (3)$$

The three δ_i and δ values for the copolymers are reported in Table 2 and are quite close from those calculated from Eq. (2).

Finally, another approach consists in determining the solubility parameter distance R_a between a solvent (S) and the polymer (P), as developed in the supporting information part. All these calculations confirm the experimental observations, except for acetone, which is a rather bad solvent for PCL, consequently, will not dissolve our copolymers.

3.4. Aggregation of copolymers in aqueous medium

Due to the amphiphilic character of the copolymers, their ability to organize in aggregated structures was investigated by TEM. This process requires first the dissolution of the copolymer in an organic compound that is miscible with water. We chose THF because it was easier to evaporate. The organic solution is then mixed with water at controlled rate and the further evaporation of the organic solvent yields copolymer molecules in aggregate forms in water.

The morphology of the formed structures was investigated by TEM (Fig. 7). The shape of self-aggregates in water is spherical and the particle size is uniform over the whole area. The influence of the

Table 2
Hansen solubility parameters of PCL and cellulose and estimation of the solubility parameters of grafted copolymers.

	w	φ	δ^a $(MPa)^{1/2}$	δ_d $(MPa)^{1/2}$	δ_p $(MPa)^{1/2}$	δ_h $(MPa)^{1/2}$	δ^b $(MPa)^{1/2}$
PCL				17.7	6.2	7.8	18.7
Cellulose				24.4	14.9	30.9	42.1
CC4	0.52	0.59	29.2	20.9	10.4	18.9	28.5
CC14	0.73	0.78	25.1	19.5	8.6	14.0	24.5
CC20	0.80	0.83	24.0	19.0	7.9	12.4	23.5

w: OCL weight fraction; φ: OCL volume fraction assuming DS = 0.25.
[a] δ calculated from volume fraction.
[b] δ calculated from the HSP components.

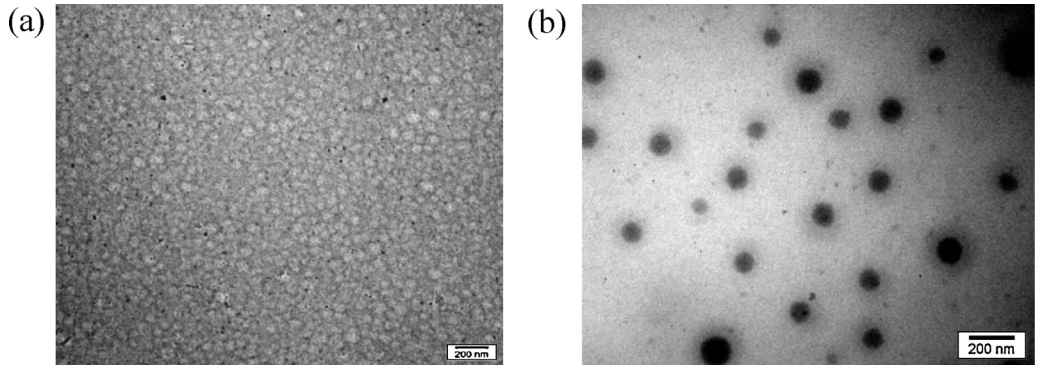

Fig. 7. TEM images of CC4 (a) and CC20 (b).

PCL length chain is obvious when comparing the three copolymers. Hence, due to their short hydrophobic chains, CC4 and CC14 showed different TEM images, with less individualized micelles than CC20. CC4 presented a uniform size distribution, whereas CC14 and CC20 had distinguished nodules with a broader size. Further investigation was carried out on the size of polymeric micelles and their size distribution was determined using dynamic light scattering measurements when aggregation appeared, which skewed the distribution of diameters, resulting in an increase in polydispersity, phenomena reported by other authors (Dal Bó et al., 2011) for such an analysis on amphiphilic copolymers. The average diameter of these structures was 594 nm for CC4, 772 nm for CC14 and 1016 nm for CC20, the diameter increases thus with the increase of the chain length of grafted PCL.

DLS measurements were carried out in solutions while TEM actually revealed the core dimensions of the micelles in the dry state. Polymer aggregates deposition onto the carbon grid implied sample drying which could lead to the shrinkage of the particles and thus smaller radii detected by TEM. Also, during the TEM sample preparation procedure, polymer self-assemblies can be flattened on the TEM grids, due to the adsorption forces. Moreover, since DLS reports the intensity-average dimensions of particles in solution, it contains considerable contribution from the hydrophilic starch corona, more prone to aggregation in aqueous environment.

4. Conclusion

Polycaprolactone-grafted starch copolymers with different PCL chain lengths can easily be obtained by click chemistry from a propargylated starch and tailor-made azido-polycaprolactones. In addition to usual NMR characterizations, the N 1s peak deconvolution of XPS spectra is also an indicative of the successful formation of the triazole ring. Particularly, XPS becomes a powerful investigation tool in the case of insoluble or less swollen samples. On the other hand, TOF-SIMS investigations provide substantial information relevant to contamination issues by Cu^{+} in relation with the biocompatibility requirements of the polymers. The solubility and swelling measurements clearly highlight how the hydrophobic character depends on the PCL chain length. Finally, due to their amphiphilic character, these copolymers are able to form micelles in an aqueous solution at low concentration.

This work can easily be extended to other starch-based graft-copolymers in order to get quite tunable amphiphilic gels through both the control of the grafts distribution onto the starch backbone and the PCL chain length.

Many applications can be envisioned with this product, e.g., for controlled drug delivery, as stabilizers for nanoparticles and emulsions, in cosmetics, fields where aqueous environments are preferred. The applications of these materials to encapsulate hydrophobic drugs are currently under investigations.

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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.2013.03.047.

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