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# Amphiphilic Photo-Induced TriblockPolyoxazoline Through Coumarin Dimerization: Efficient Synthetic Tool for Nanoparticles

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## Abstract

Amphiphilic photo-induced triblock copolymers were successfully prepared by photo-dimerization of a photo-active initiator bearing coumarin moieties (CmTs<sub>2</sub>) before synthesizing, by cationic ring-opening polymerization (CROP), various lengths of polyoxazoline block. The DLS and TEM studies of the triblockcopolymers self-assembly in water revealed that over 99% of the nanoparticles have a D<sub>H</sub>-value of 10 nm. The total photo-activity of the coumarin units permitted  $\pi$ -stacking interactions in the nanoparticle core and further its crystallization as demonstrated by DSC and X-ray diffractometry. An original non-spherical morphology of the nanoparticles resulted with an elongated shape.

## Introduction

Amphiphilic copolymers are particularly interesting for their ability to self-assemble in selective solvents.<sup>[1-6]</sup> The stability of polymeric micellar systems is a crucial condition for some applications such as the encapsulation of active compounds.<sup>[7, 8]</sup> Various approaches have been proposed to stabilize polymeric micelles. Among them, the core-crosslinked micelle and the shell-crosslinked micelle are attractive ways to maintain the structural integrity of micellar object whatever the external conditions such as the dilution or thermal changes.<sup>[9-17]</sup> To prepare core-crosslinked polymeric micelles, numerous approaches have already been described including free-radical reaction, condensation,<sup>[10, 18]</sup> sol-gel or click chemistry.<sup>[19, 20]</sup> Nevertheless, these routes require some additives or initiators and produce by-products.<sup>[21-23]</sup> An attractive alternative is the photo-crosslinking: rapid, efficient, non-toxic and cost-effective process.<sup>[24-29]</sup> Among the current photo-crosslinkers employed (cinnamate,<sup>[30]</sup> thymine,<sup>[31]</sup> benzophenone<sup>[32]</sup> or anthracene<sup>[33]</sup>), we focus on the coumarin analogues *inter alia* used in medicine, biology, and material science.<sup>[22, 34]</sup> Coumarin photo-dimerizes into cyclobutane ring *via* a  $[2\pi + 2\pi]$  cycloaddition under UV-irradiation at  $\lambda > 310$  nm, and the resulting dimer can be reversibly dissociated into the two precursor unimers at  $\lambda < 260$  nm.<sup>[8, 34-38]</sup> Recently, the reversible photo-dimerization of coumarin has been explored for designing photo-controllable micelles especially used in pharmaceutical applications.<sup>[8, 28, 39, 40]</sup> For example, Luo *and al.* prepared photo-crosslinked dendrimeric micelles containing stable coumarin units under physiological media.<sup>[41]</sup> Otherwise, Jiet *al.* described a dual photo- and pH-responsive polymers bearing coumarin units avoiding unfavorable premature release of loaded drugs.<sup>[42]</sup>

Furthermore, polyoxazolines (POx)s represent valuable bioinspired polymers considered as an alternative to PEG. The pseudo-peptidic structure leads to biocompatibility, biodistribution,

blood clearance and protein adsorption properties.<sup>[43, 44]</sup> Well-defined POx are easily prepared by cationic ring-opening polymerization (CROP) of the corresponding 2-R-2-oxazolines. The properties of the POx depend on the nature of the R pendant chain (Me, Et, Pr, etc.). Many macromolecular architectures have already been described using hydrophilic and/or hydrophobic 2-oxazoline monomers or coupled to other polymer blocks.<sup>[45]</sup> The POx could be also combined to other polymerization processes.<sup>[46]</sup> All these strategies explained the keen interest of the manifold investigations on the decoration of POx using functional terminating agents<sup>[47]</sup> or initiators.<sup>[48-58]</sup> Recently, we described the synthesis of amphiphilic diblock polyoxazolines (Cm-POx<sub>n</sub>) bearing an UV-sensitive coumarin end-group (Figure 1, top route) as well as their self-assembly in water into spherical nanoparticles and finally their photo-dimerization.<sup>[59]</sup>

In this contribution, we report on an alternative pathway where the dimerization of the coumarin moieties is performed prior to the polymerization of 2-methyl-2-oxazoline and finally the self-assembly in water of the resulting symmetrical triblock copolymers (Figure 1, down route).<sup>[59]</sup> Herein, the advantages of the triblock copolymers route onto the size and the shape of the resulting nano-objects are detailed.

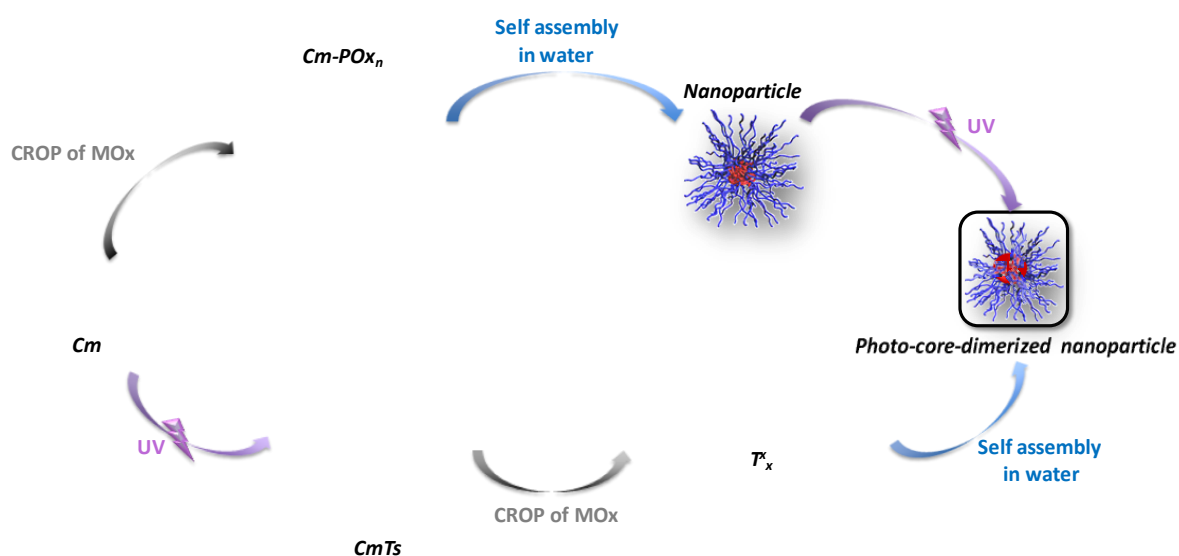


Figure 1: Triblock copolymer synthesis and the self-assembly in water relative to that of the diblock copolymer.

## Results and discussion

### *Synthesis of the triblock copolymers $T_x^x$*

The photo-dimerization of the lipophilic UV-sensitive initiator, CmTs, into the corresponding bis-functional initiator, CmTs<sub>2</sub>, prior to the polymerization of 2-methyl-2-oxazoline was investigated (Figure 1, down route). The starting compound, CmTs, reacted both as a tosylated initiator and a photo-dimerizable system by the coumarin unit. To reach an optimal photo-conversion rate, CmTs was first dimerized into CmTs<sub>2</sub> under UV-illumination at  $\lambda = 350$  nm giving a hydrophobic bis-initiator for the cationic ring-opening polymerization (CROP) of 2-methyl-2-oxazoline (Figure 2). The  $[2\pi+2\pi]$  photo-reaction was monitored by UV spectroscopy using the UV-absorbance band of the coumarin unit at  $\lambda = 320$  nm (Figure SI-1). The photo-dimerization rate was confirmed by <sup>1</sup>H NMR spectroscopy regarding the shift of the characteristic signals of the unimer (H<sub>2</sub>, H<sub>6</sub>, H<sub>7</sub> and H<sub>9</sub>) into the cyclobutane dimer (H<sub>2</sub>\*, H<sub>6</sub>\*, H<sub>7</sub>\* and H<sub>9</sub>\*) (Figure 3). A maximum of dimerization rate of 88% was achieved after one hour whereas a duration of 1 or 2 days was required in the literature for another polymeric structures bearing the similar photo-active unit.<sup>[60, 61]</sup> The residual unimer CmTs was removed by recrystallization giving only CmTs<sub>2</sub> as illustrated by comparison between CmTs and CmTs<sub>2</sub> SEC traces (Figure SI-2).

The CROP of 2-methyl-2-oxazoline was performed under microwave conditions as regard to the low thermal stability of CmTs<sub>2</sub>. Indeed, 50 % of de-dimerization was observed after several hours at 80 °C. Even though higher temperature was used (140 °C), this technique drastically reduced the reaction time (30 min *versus* 15 h) avoiding the scission by de-dimerization of the polymer chains into amphiphilic diblock copolymers (Cm-PO<sub>x</sub><sub>n</sub>). After the termination step in the presence of potash, three photo-induced amphiphilic and symmetric

triblock copolymers ( $T_X^X$ ) were prepared knowing that the degree of polymerization of each POx block (X) ranged from 6 to 24, as reported in Table 1.

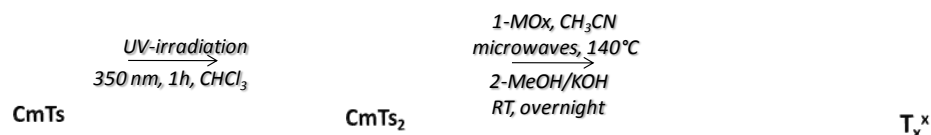


Figure 2: Synthesis of the amphiphilic triblock copolymers (e. g.  $T_6^6$ ).

The characteristic signals of  $T_X^X$  were detected by  $^1\text{H}$  NMR spectroscopy as illustrated in Figure 3 with the occurrence of POx protons  $H_a$ ,  $H_b$  and  $H_d$  at 2.2-1.8 and 3.7-3.2 ppm as well as the peculiar alkyl chain signals  $H_{11-21}$  at 4.0, 3.5, 2.25 and 1.7-1.2 ppm. The dimerization of the coumarin units were illustrated with the shift of coumarin aromatic protons  $H_7^*$ ,  $H_9^*$  and  $H_6^*$  at 6.6 and 5.9 ppm as well as  $H_2^*$  at 7.0 ppm. The very small amount of coumarin unimer showed the negligible de-dimerization during the CROP process and attest to the compatibility of this chromophore with the CROP.

Besides, by size exclusion chromatography (SEC), the monomodal traces indicated that only ABA amphiphilic copolymers were obtained without unintended de-dimerization and formation of diblock copolymers (Figure SI-3). The relatively high dispersity of the triblock copolymers ( $\mathcal{D}$  around 1.4-1.5) can be easily explained by: i) the dual functionality of the twin-initiation  $\text{CmTs}_2$ , ii) the unfavourable hydrophobic character of the initiator to polymerize hydrophilic oxazoline monomer and iii) the electron-rich character of the coumarin units which could interfere during the attack of the first monomers into the coumarinated propagating chains. The low molecular weight of the resulting copolymers  $T_6^6$ ,  $T_{12}^{12}$  and  $T_{24}^{24}$  ranged from 2100 to 5200  $\text{g}\cdot\text{mol}^{-1}$  with a high hydrophilic ratio of 67, 83 and

87%, respectively corresponding to  $M_{\text{hydrophilic}}/M_{\text{hydrophobic}}$  ratio of 2, 4.9 and 6.7, respectively. Thus, POx-based triblock copolymers bearing dimerized coumarin units have been successfully synthesized in a one-pot route, without traces of residual undimerized chains.

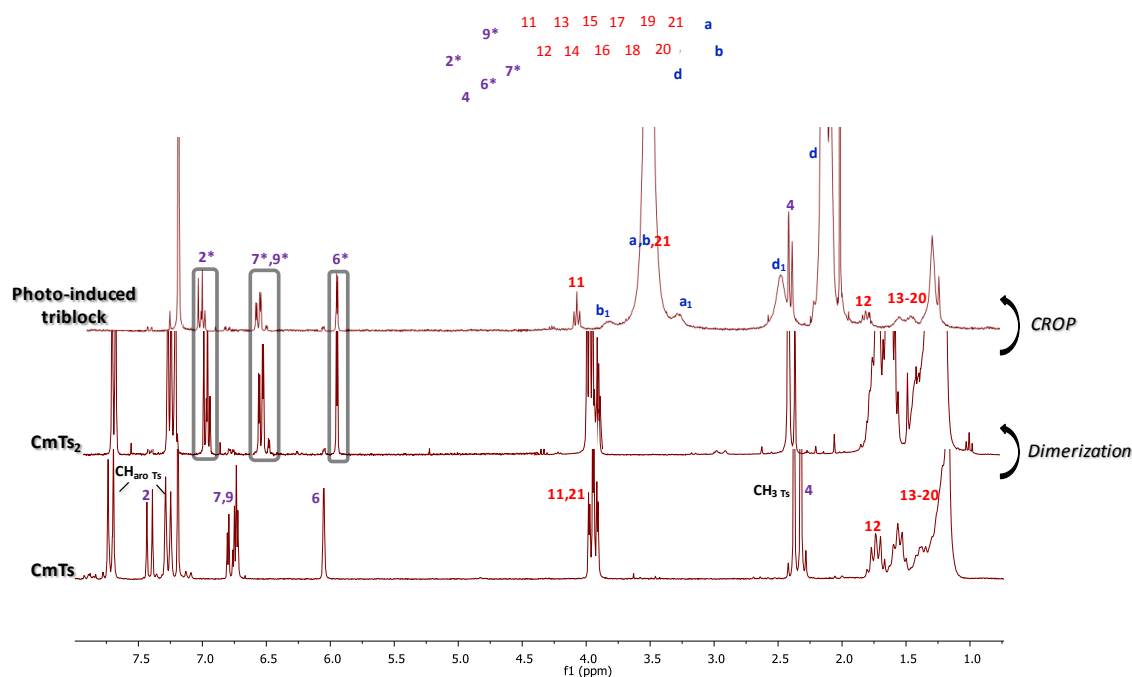


Figure 3:  $^1\text{H}$  NMR spectra (300 MHz,  $\text{CDCl}_3$ ) of  $\text{CmTs}$ ,  $\text{CmTs}_2$  and  $\text{T}_6^6$ .

### Self-assembly of the photo-induced amphiphilic triblock copolymers

The ability of the photo-induced amphiphilic triblock copolymers  $\text{T}_X^X$  to self-assemble in water into ordered nanostructures was investigated by dynamic light scattering (DLS) and transmission electron microscopy (TEM). In all cases, the nano-objects were spontaneously shaped by direct dissolution of the copolymers in aqueous media ( $4 \text{ mg}\cdot\text{mL}^{-1}$ ) without any filtration. For  $\text{T}_6^6$ ,  $\text{T}_{12}^{12}$  and  $\text{T}_{24}^{24}$ , two distributions co-existed with a hydrodynamic diameter ( $D_H$ ) of around 11 and 300 nm as shown in Figure 4 and summarized in Table 1. They can reasonably be attributed to micellar nanoparticles and larger aggregates. We noted that the  $D_H$ -values of the smaller nanoparticles determined by DLS were consistent with those of

TEM, except for  $T_{12}^{12}$  (nanoparticles twice larger by TEM). By DLS measurements, the length of the POx block seemed to have a little impact on the nanoparticle size and similar  $D_H$ -values than the corresponding photo-active diblock copolymer, Cm-POx<sub>n</sub>, and un-photoactive diblockcopolymer, C<sub>18</sub>-POx<sub>n</sub> as previously reported.<sup>[59]</sup> Moreover, as CoumC<sub>11</sub>-POx<sub>n</sub>, an inexplicable maximum in size was observed for the intermediate length of POx,  $T_{12}^{12}$ .<sup>[59]</sup> The DLS measurements being much more sensitive to the bigger objects than smaller ones,<sup>[62]</sup> the percentage of small nanoparticles was calculated related to the big ones according to the calculation described in the previous work on diblock copolymers. Assuming that the present nanoparticles behave like hard spheres in water and that all the nanoparticles have the same density, the percentage of small nanoparticles can be calculated using eq (1):

$$\frac{N_{Small}}{N_{Big}} = \left(\frac{\tau_{Big}}{\tau_{Small}}\right)^3 \left(\frac{S_{Small}}{S_{Big}}\right) \quad (1)$$

where  $N_{Small}$  refers to the number of small nanoparticles (fast relaxation mode),  $\tau_{Small}$  is the relaxation time corresponding to the small nanoparticles and  $S_{Small}$  represents the surface area under the peak related to the small nanoparticles. For instance, for  $T_6^6$  at  $90^\circ$ , we have  $N_{small} = 1009 N_{big}$  meaning that the small nanoparticles represent 99.90% of the nanoparticles in number. The same calculation gave 99.94 and 99.76% for  $T_{12}^{12}$  and  $T_{24}^{24}$ , respectively. The small amount of aggregates was confirmed on TEM images.

*Table 1: Characteristics of triblock copolymers ( $T_X^X$ ).*

Sample	$DP_n^{POx}$ <sup>b</sup>	$M_{n,SEC}$ <sup>c</sup> (g.mol <sup>-1</sup> )	$D^c$	$D_H^d$ (nm)		$N_{Small}/N_{big}^d$	$D_{TEM}^e$ (nm)
				Small	Big		
$T_6^6$ <sup>a</sup>	6+6	2100	1.47	10.6	353	1009	12
$T_{12}^{12}$ <sup>a</sup>	12+12	4000	1.51	12.8	272	1711	24
$T_{24}^{24}$ <sup>a</sup>	24+24	5200	1.44	9.6	308	416	10

<sup>a</sup>: CROP initiated by CmTs<sub>2</sub> performed in a microwave reactor at 140 °C in CH<sub>3</sub>CN during 30 min. <sup>b</sup>: Determined by <sup>1</sup>H NMR in CDCl<sub>3</sub>. <sup>c</sup>: Determined by SEC in DMAc (PMMA standards). <sup>d</sup>: Determined by dynamic light scattering using CONTIN method. <sup>e</sup>: TEM image and the corresponding statistical treatment carried out on more than 300 objects.

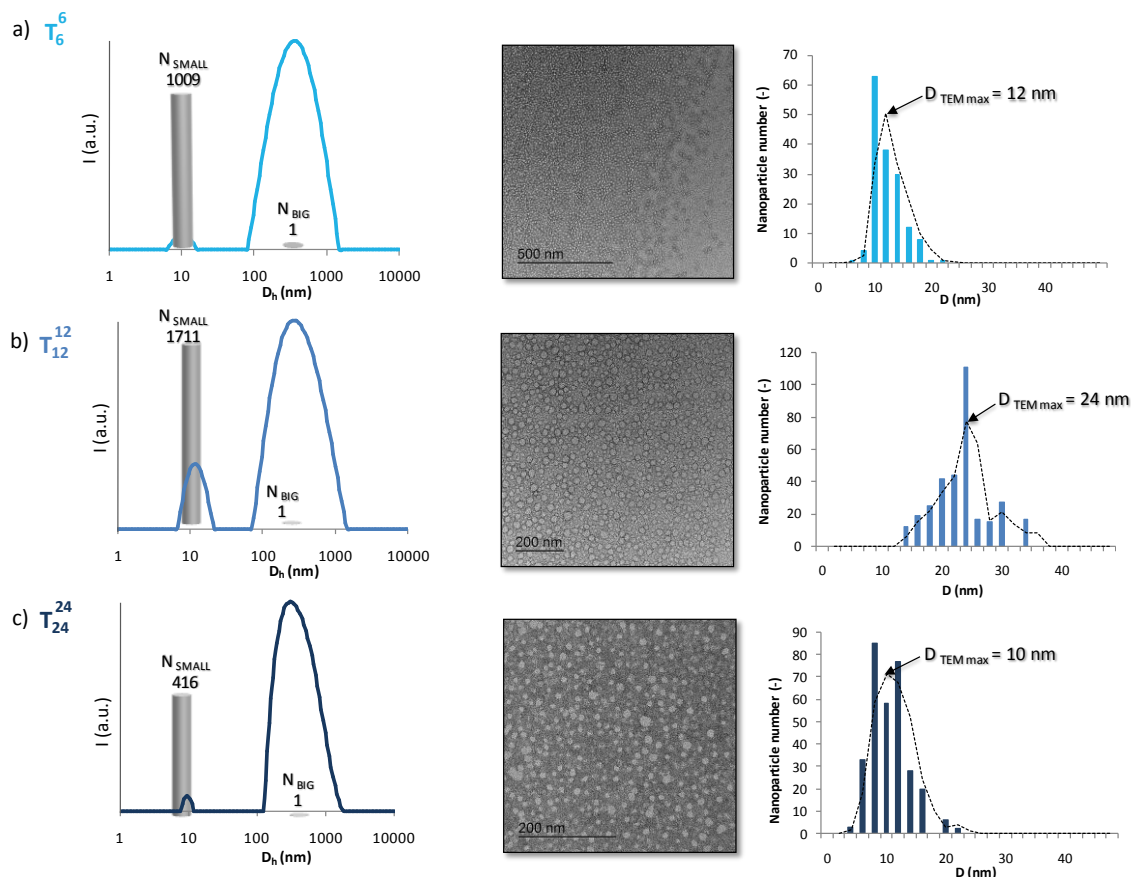


Figure 4: DLS traces and  $N_{small}/N_{big}$  (bar) calculated from CONTIN analysis as well as TEM images and the corresponding statistical treatment carried out on more than 300 objects for a)  $T_6^6$ , b)  $T_{12}^{12}$  and c)  $T_{24}^{24}$ .

The efficiency of UV-illumination for the crosslinking of the nanoparticles has been proved by Zhao.<sup>[8]</sup> This methodology is suitable for the both core-<sup>[63]</sup> and shell-<sup>[11]</sup> crosslinked of the nanoparticles using amphiphilic grafted copolymers bearing pendent chains with UV-active species. By contrast, the photo-dimerization of the nanoparticle core employing amphiphilic diblock copolymers has been little studied. For  $T_x^x$ , the UV-dimerization of

coumarin units occurring before self-assembling, the light-induced destabilization of the nanoparticles has been avoided.

A deeper observation of the TEM images of  $T_X^X$  revealed a non-spherical shape of the nanoparticles (Figure 5). Whatever the size, an elongated shape was observed with a diameter around 0.8-0.9 times smaller than that of the corresponding spherical nanoparticles. The original shape was illustrated with  $T_{12}^{12}$  giving the larger nanoparticles. Such morphology has already been described for amphiphilic copolymers containing very hydrophobic<sup>[64]</sup> or fluorinated<sup>[65]</sup> blocks. Jordan *et al.*<sup>[66]</sup> have also recently reported the same trend for hydrophilic/fluorophilic poly(2-oxazoline) diblock copolymers in water.

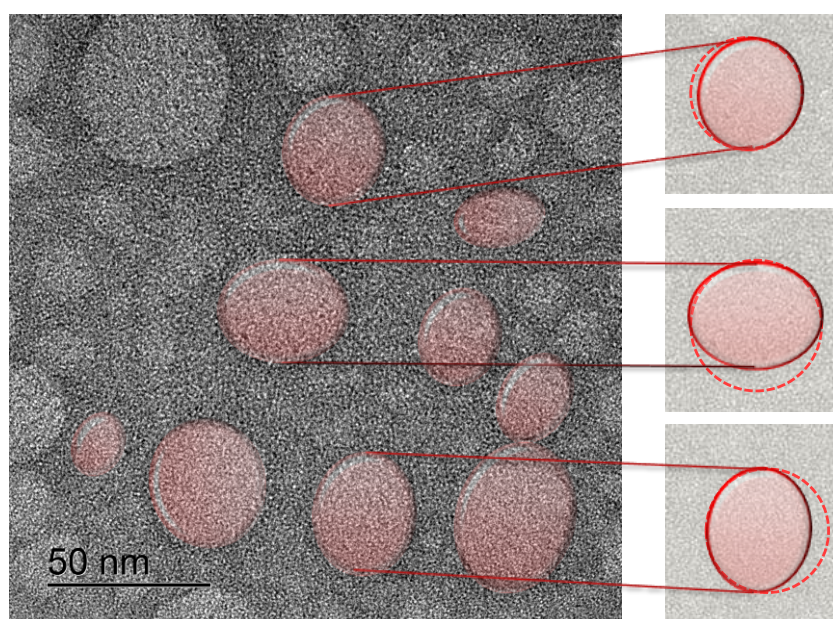


Figure 5: TEM image of non-spherical nanoparticles of  $T_{12}^{12}$  after direct dissolution in water (full line: contour of elongated nanoparticle and dotted line: corresponding spherical nanoparticle).

To explain this nanoparticle elongation, we proposed the crystallization of the coumarin units inducing an internal stress and a preferential orientation of the triblock copolymers. Indeed,

the coumarin units are well-known to act as crystallization promoters by charge transfer complex and  $\pi$ - $\pi$  interactions caused by their photo-induced alignment. To check the crystallization of the nanoparticle core, a comparative DSC analysis was realized on the photo-induced triblock copolymers ( $T_6^6$ ,  $T_{12}^{12}$  and  $T_{24}^{24}$ ) and their precursor  $CmTs_2$  (Figure SI-4 and Table 2). Preliminarily to the study of the triblock copolymers,  $CmTs_2$  was investigated and shown a  $T_g$ -value of  $-20$  °C and a  $T_m$ -value of  $88$  °C. The copolymers  $T_x^x$  crystallized with an increase of the melting temperature ( $T_m$ ) with the length of polyoxazoline block ( $91$  °C for  $T_6^6$  to  $135$  °C for  $T_{24}^{24}$ ). The micro-phase segregation between the hydrophilic and the hydrophobic blocks was confirmed with two  $T_g$ -values corresponding approximatively to those of  $CmTs_2$  ( $T_{g1}$ ) and polyoxazoline ( $T_{g2}$ ). Lastly, note that the melting enthalpy of the triblock copolymers was higher than that of  $CmTs_2$  ( $-45$  J.g $^{-1}$ ) and exceeded  $-95$  J.g $^{-1}$  demonstrating the higher crystalline character of  $T_x^x$ .

Table 2: DSC values (10 °C/min under nitrogen atmosphere) and XRD data of  $CmTs_2$ ,  $T_6^6$ ,  $T_{12}^{12}$  and  $T_{24}^{24}$ .

Sample	$T_{g1}$ (°C)	$T_{g2}$ (°C)	$T_m$ (°C)	$\Delta H_m$ (J.g $^{-1}$ )	$\chi_c^c$ (%)
$CmTs_2$	-20	- <sup>a</sup>	88	-45	- <sup>d</sup>
$T_6^6$	5	53	91	-95	26
$T_{12}^{12}$	4	57	94	- <sup>b</sup>	13
$T_{24}^{24}$	-10	44	135	-84	14

<sup>a</sup>: Glass transition not visible. <sup>b</sup>: None value by overlapping between the glass transition and melting phenomena. <sup>c</sup>: Determined by XRD. <sup>d</sup>: Not calculated.

The crystalline character of  $T_6^6$ ,  $T_{12}^{12}$  and  $T_{24}^{24}$  was confirmed by X-ray diffraction (XRD) analysis (Figure 6). Thanks to Bragg's law:  $n\lambda = 2d\sin\theta$ , where  $n$  represented an integer number (here,  $n_{\text{air}} = 1$ ),  $\lambda$  the wavelength of the beam and  $\theta$  the incident angle, each diffraction peak allowed to deduce the distance between diffracting planes,  $d$  (Å). In addition, to a broad diffusion peak between 4 and 6 Å, a high sharp peak was detected at 3.2 Å for each  $T_x^x$ . Additional peaks at 5.7, 5.1, 4.5, 4.1 and 3.5 Å, characteristic to long distance interactions and spaced with the same gap (0.6 Å), were observed for the triblock with shorter POx chains ( $T_6^6$ ) that demonstrated its higher ability to crystallize. XRD and DSC analyses were in good agreement and gave the same evolution of the crystallinity with the length of POx block. Besides, the crystallization phenomenon was lower for  $T_{24}^{24}$  than for  $T_6^6$  since only the high sharp peak at 3.2 Å was observed. The crystallization was disturbed by the longer POx chains as evidenced by the measurement of the crystallinity ratio ( $\chi_c$ ) ranging from 13 to 26% (Table 2). The crystallinity ratio was calculated through the crystalline area ( $A_c$ ) and the amorphous area ( $A_a$ ) obtained by DRX<sup>[67-69]</sup> according to equation 2:

$$\chi_c = \frac{A_c}{A_a + A_c} \quad (2)$$

Furthermore, the DSC thermograms also confirmed this tendency since the highest melting temperature ( $T_m = 135$  °C) was measured for the longest triblock copolymer  $T_{24}^{24}$ .

Thus, the architecture of the POx-based amphiphilic copolymers bearing coumarin units has a real impact on their physico-chemical properties. The photo-dimerization of coumarin groups before self-assembly favoured the crystallization and further the segregation between hydrophobic and hydrophilic blocks of  $T_x^x$ . The crystallization of the coumarin dimers and a part of the neighbouring POx chains seemed to occur according to a preferential direction producing non-spherical nanoparticles by  $\pi$ -stacking interactions between aromatic rings of coumarin dimers.

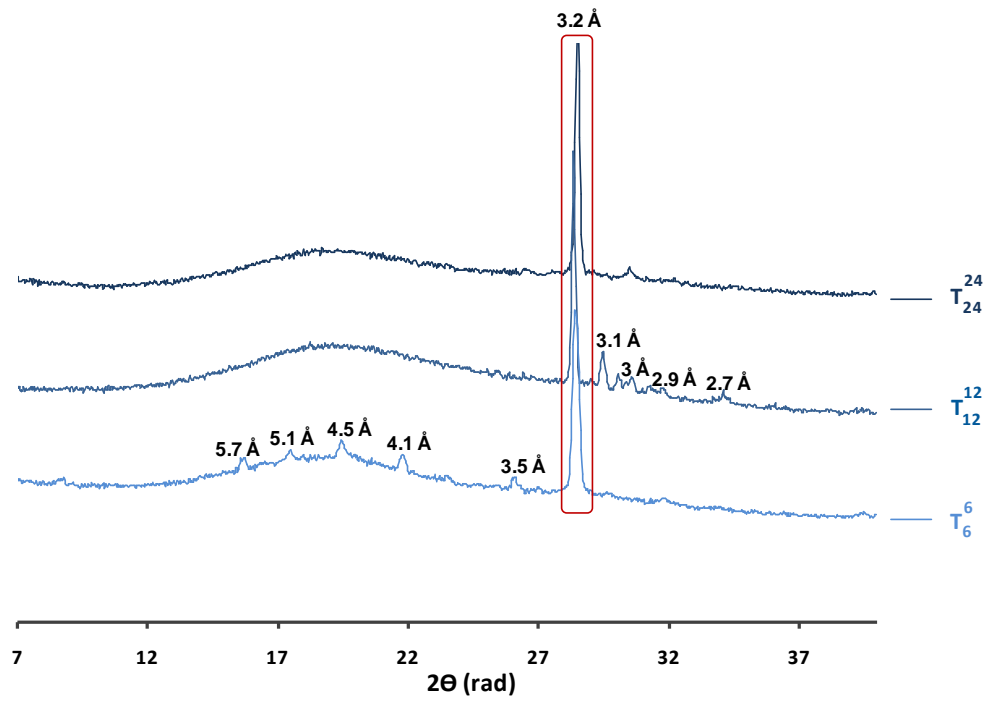


Figure 6: X-ray diffraction patterns measured by powder method for T<sub>6</sub><sup>6</sup>, T<sub>12</sub><sup>12</sup> and T<sub>24</sub><sup>24</sup>.

## Experimental

### *Materials*

2-Methyl-2-oxazoline (MOx) was dried and distilled from  $\text{CaH}_2$  and stored under dry nitrogen atmosphere. CmTs was synthesized according to a procedure previously described.<sup>[59]</sup> Anhydrous acetonitrile, diethylether, ethanol, methanol,  $\text{MgSO}_4$  and potash (KOH) were commercial products (Sigma Aldrich) and used without further purification.

### *Measurements*

The UV-dimerization of the CmTs was performed in a cylindrical photochemical reactor “RayonnetRPR-200” equipped with 16 symmetrically placed lamps with emission in 350 nm (UV-B). The samples were irradiated in quartz flasks placed on a circular rotating holder. The polymerization reactions were performed in capped reaction vials specially designed for the single-mode microwave. The microwave reactor system used was a Monowave 300 from Anton-Paar. These hot vials, allowed to cool to room temperature, and filled with argon prior to use. All experiments were performed on 30 mL solutions; the polymerization reactions were terminated by adding methanolic potash to the reaction mixture at room temperature outside the microwave system. Nuclear magnetic resonance (NMR) spectra were recorded on a NMR BrukerAvance I 300 MHz or on a BrukerAvance III 600 MHz spectrometers. The chemical shifts were in part per million (ppm) where (s) means a singlet, (d) a doublet, (t) a triplet, (m) a multiplet and (dd) a doublet of doublet. Chemical shifts ( $^1\text{H}$  NMR) were referenced to the peak of residual  $\text{CHCl}_3$  at 7.26 ppm. Size exclusion chromatography (SEC) with N,N-dimethylacetamide (DMAc) (with 0.1 w/w% LiCl) as eluent at a flow rate of 0.8  $\text{mL min}^{-1}$ , calibrated with poly(methylmethacrylate) (PMMA) standards, was performed on a PL-GPC 50 Plus equipped with a Varian model 410 autosampler. The SEC apparatus

comprised a refractive index detector and was filled with a 8  $\mu\text{m}$  PolarGel-M pre-column ( $7.5 \times 50$  mm) and two 8  $\mu\text{m}$  PolarGel-M columns ( $7.5 \times 300$  mm) thermostated at  $50^\circ\text{C}$ . Dynamic light scattering (DLS) measurements were performed using an ALV/CGS-8FS/N069 apparatus (from ALV) equipped with an ALV/LSE-5004 multiple  $\tau$  digital correlator with a 125 ns initial sampling time (from ALV) and a 35mW red He-Ne linearly polarized laser operating at a wavelength of 632.8 nm (from JDSU). The copolymer suspensions in water were obtained by direct copolymer dissolution in Milli-Q water (characterized by a resistivity of  $18.2 \text{ M}\Omega\cdot\text{cm}$ ) at a concentration of  $4 \text{ mg}\cdot\text{mL}^{-1}$  without filtration, loaded in 10 mm diameter cylindrical cells and then maintained at a constant temperature of  $25.0 \pm 0.1^\circ\text{C}$  prior to measurement. In DLS, the relaxation time distribution was obtained using CONTIN analysis of the autocorrelation function ( $g^{(2)}-1$ ). Sample preparation for TEM analysis was done as follows: 10  $\mu\text{L}$  of aqueous copolymer suspensions concentrated at  $0.04 \text{ mg}\cdot\text{mL}^{-1}$  were dropped onto glow discharged carbon-coated copper grids (Agar scientific, Cu-300) and the excess liquid was blotted thanks to filter paper. Then, 10  $\mu\text{L}$  of a 4 w/v % aqueous uranyl acetate negative stain solution was added. After 30 seconds, the excess of liquid was again blotted. TEM imaging was performed using a JEOL, JEM – 2200FS microscope operating at 200kV. Statistical treatment of the images carried out on more than 300 objects gives the main diameter. Calorimetric analyses were carried out at  $10^\circ\text{C}/\text{min}$  under nitrogen atmosphere using a Star1 differential scanning calorimeter (DSC) from Mettler Toledo. X-ray diffraction (XRD) analysis were performed on a X-pert powder diffractometer with a 10 mm mask, a divergent fente of  $1/4^\circ$  on silicium surface to avoid noise signal. UV-visible analyses were conducted with a Perkin Elmer – lambda 35 UV/Vis spectrometer equipped with PTP-1+1 Peltier System in vial quartz ( $l=1\text{cm}$ ).

*Dimerized initiator: CmTs<sub>2</sub>*

In a quartz closed flask, a solution of the initiator CmTs (10 g, 20 mmol) in chloroform (30 mL) was exposed to UV irradiation at  $\lambda=350$  nm (UV-B) for one hour in cylindrical photochemical reactor. The dimer was separated to the corresponding unimer by recrystallization from ethanol (four times). The white powder corresponding to the unimer was removed giving CmTs<sub>2</sub> in a 72% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 7.8 (d, 4H, CH<sub>aroTs</sub>), 7.3 (d, 4H, CH<sub>aroTs</sub>), 7.0 (d, 2H, H<sub>2\*</sub>), 6.6 (m, 4H, H<sub>7\*</sub> and H<sub>9\*</sub>), 5.8 (s, 2H, H<sub>6\*</sub>), 3.9 (m, 4H, CH<sub>2-O-</sub>), 3.5 (m, 8H, H<sub>11</sub> and H<sub>21</sub>), 2.4 (s, 6H, CH<sub>3Ts</sub>), 2.3 (s, 6H, H<sub>4</sub>), 1.8 (m, 4H, H<sub>12</sub>), 1.5-1.2 (m, 32H, H<sub>13</sub>-H<sub>20</sub>).m<sub>p</sub> = 80°C

*Linear triblock copolymers: T<sub>x</sub><sup>x</sup>*

A typical procedure for the synthesis of T<sub>12</sub><sup>12</sup> with a targeted molecularweight of 4000 g.mol<sup>-1</sup> was described here. The dimerized initiator CmTs<sub>2</sub> (2.44 g, 3 mmol) and MO<sub>x</sub> (10 g, 118 mmol) were dissolved in 30 mL of dry acetonitrile in a quartz closed vial. The solution was vigorously stirred under microwave conditions at 140 °C for 30 min at constant pressure. The polymerization was terminated by addition of an adequate amount of methanolic potassium hydroxide (0.7 g, 13 mmol, 5M). The flask was maintained at 30 °C for 4 h. After cooling, the polymer was isolated by slow precipitation into cold diethylether and dried under vacuum overnight.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 7.0 (d, 2H, H<sub>2\*</sub>), 6.6 (dxd, 4H, H<sub>7\*</sub> and H<sub>9\*</sub>), 5.9 (s, 2H, H<sub>6\*</sub>), 4 (t, 4H, H<sub>11</sub>), 3.7-3.2 (m, 8nH, H<sub>a</sub> and H<sub>b</sub>), 3.5 (m, 4H, H<sub>21</sub>), 2.5 (s, 6H, H<sub>d1</sub>), 2.25 (s, 6H, H<sub>4</sub>), 2.2-1.8 (m, 6nH, H<sub>d</sub>), 1.75-1.2 (m, 36H, H<sub>12</sub>-H<sub>20</sub>).



## **Conclusion**

This study demonstrates the potential interest of the photo-dimerization of amphiphilic linear copolymers related to the photo-crosslinking of nanoparticle core using amphiphilic grafted copolymers. Otherwise, the benefits of the self-assembly of amphiphilic triblock copolymers, previously prepared by photo-dimerization can be summarized as follows: i) high photo-conversion of coumarins without any unfavourable de-dimerization and retro-formation of diblock copolymers during the CROP process, ii) few aggregations of nanoparticles showing a sharp segregation phase between hydrophilic and hydrophobic blocks, and iii) original morphology of nanoparticles with non-spherical shape that can be attributed to the crystallization of the coumarin moieties until 26%. More studies are underway in our laboratory to demonstrate the difference in term of stability, loading and release of active molecules between different nano-objects based on polyoxazoline and coumarin (photo-dimerized spherical nanoparticles using the diblock route, photo-dimerized ovalic nanoparticles using the triblock route and photo-crosslinked spherical nanoparticles using grafted copolymers).

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