A novel strategy towards cyclic aliphatic (co)polyesters

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Abstract. This feature article focuses on a novel strategy towards macrocyclic (co)polyesters that combines controlled ring-opening polymerization of lactones initiated by a cyclic tin(IV) dialkoxide and intramolecular cyclization by photo-cross-linking of pendant unsaturations next to the propagating sites. No linear species is ever involved in the polymerization and permanent cyclization steps, which allows higher molecular weight macrocycles to be prepared with high efficiency and no need for further purification. Moreover, this synthetic route is very flexible to the point where macrocyclic poly-esters with more complex although well-defined architectures, such as tadpole-shaped and sun-shaped copolyesters, can be tailored. Synthesis of well-defined eight-shaped polyesters and twin tadpole-shaped copolymers has also been explored by using a spirocyclic tin(IV) alkoxides as an initiator. When functional lactones were introduced, the 'click' copper-mediated cycloaddition [3+2] reaction was utilized to make the eight-shaped and twin tadpole-shaped copolyesters amphiphilic.

Keywords: polymer synthesis, ring-opening polymerization, cyclic polyesters, cross-linking by UV irradiation, 'click' chemistry

1. Introduction

Much attention was paid to cyclic polymers and much effort was devoted to their design and synthesis for the last decades because of distinct properties compared to the linear counterparts, such as glass transition temperature, order-disorder transition, hydrodynamic volume, intrinsic viscosity, and enhancement of fluorescence [1–4]. This interest is motivated by the appealing topology of the macrocycles, the stringent restrictions on the backbone conformation, and the absence of chain ends. The discovery of natural DNA ring [5], where the two strands of the double helix form a high order link, has stimulated the chemists to embark on the macromolecular engineering of cyclic polymers. It must be noted that living organisms produce numerous cyclic compounds, such as oligopeptides, polypeptides, and DNAs, whose molecular weight and ring size can change extensively. In protozoa, relatively small rings containing approximately 400 base pairs (equivalent to 2400 atoms in the ring) are known that have a molar mass of $1.2 \cdot 10^5$ g/mol. Importantly, it was found recently that cyclic DNA can be prepared *in-vitro* by using the enzyme ligase [6]. Therefore, synthesis of well-defined macrocycles, extending over a large range of macromolecular characteristic features is of the utmost importance for improving basic knowledge and ultimately mimicking compounds with a specific biological activity.

The main approaches to macrocycles are based on the end-to-end ring-closure (coupling) of homo- or hetero-difunctional linear precursors under very high dilution by any reaction known in the state of the art, such as nucleophilic substitution [7, 8], addition on unsaturations [9–13], metathesis reaction [14–16], amidification [17], 'click' reaction [18–22], and electrostatic interaction followed by covalent

fixation [23, 24]. Although the linear precursors prepared by living/controlled polymerization are well-defined, the unavoidable competition between intramolecular cyclization and intermolecular extension is the major problem to be solved. In order to increase the cyclization yield at the expense of the detrimental intermolecular polycondensation, the intramolecular cyclization must be performed at very high dilution. Nevertheless, even under optimized conditions, the efficiency of cyclization is inversely proportional to the molecular weight of the precursor. Anyway, the cyclization is not very effective, contamination by undesired polycondensates is a concern and requires an additional and tedious step of purification by fractionation. Therefore, the quest for more efficient cyclization methods remains a challenging priority, even though several clever strategies have been explored as reported in the literatures [25–28]. Remarkably, Bielawski *et al*. have initiated the ring-opening metathesis polymerization of cyclooctene by a cyclic ruthenium carbene, so leading to macrocyclic poly(cyclooctene) ($M_n = 6 \cdot 10^5 – 1.1 \cdot 10^6$ g/mol) by intramolecular chain transfer. Polymerization can be conducted at high concentration, even in the bulk and macrocycles with higher molecular weight can be achieved. Another route reported by He *et al*. [26] for the synthesis of macrocycles, relies on the controlled radical polymerization of methyl acrylate (MA) in THF (10 wt%) by using a cyclic initiator with a weak (C-S) bond upon ^{60}Co γ-ray irradiation. Cyclic poly(methyl acrylate) was accordingly formed with a predetermined molecular weight ($M_n = 8.2 \cdot 10^3$ g/mol) without high dilution by intramolecular chain termination. Kricheldorf *et al*. [27] initiated ring-opening polymerization of lactones and lactides by a series of cyclic tin dialkoxide and the growing chains are macrocycles linked by an endocyclic living tin dialkoxide. In a typical example, cyclization was stabilized by the insertion of 1,3-dithian-2-one into the Sn-O bond with formation of macrocyclic precursor. Finally, the cyclic 2-stanna-1,3-dithiane was selectively eliminated from the precursor. No need for high dilution is a substantial advantage [28]. Culkin *et al*. [29] reported a zwitterionic strategy for the kinetically controlled synthesis of high-molecular-weight cyclic PLA with narrow polydispersity by using N-hetreocyclic carbene as an initiator.

This feature article aims at summarizing recent developments in synthesizing macrocyclic poly(ε-caprolactone) with well-defined architectures designed through a novel strategy that combines controlled ring-opening polymerization of lactones initiated by a cyclic tin(IV) dialkoxide and intramolecular cyclization by photo-cross-linking of pendant unsaturations next to the propagating sites. No linear oligomer or polymer is ever involved in the polymerization and permanent cyclization steps, which allows higher molecular weight macrocycles to be prepared with high efficiency. Moreover, this synthetic route is very flexible to the point where macrocyclic polyesters with more complex although well-defined architectures, such as tadpole-shaped and sun-shaped copolyesters, can be tailored. When a spirocyclic tin(IV) alkoxides were employed as an initiator, well-defined eight-shaped polyesters and twin tadpole-shaped amphiphilic copolymers has been readily made available.

2. Synthesis of macrocyclic poly(ε-caprolactone)

The strategy for synthesis of cyclic PCL is based on the ring-opening polymerization of ε-caprolactone initiated by cyclic tin dialkoxides (DSDOP), followed by the sequential polymerization of a few functional units of α-(1-acryloxyethyl)-ε-caprolactone (αAεCL) [30]. As result of a coordination-insertion polymerization mechanism, no linear species is formed at any stage of the process. Moreover, polymerization being controlled, the molecular weight can be predicted by the monomer/initiator molar ratio and the monomer conversion. The growing chains are closed by two endocyclic tin alkoxides at least as long as they are protected from hydrolysis, which means the precursors to be stabilized are a living cyclic PCL (**CP**). Before cyclization, a sample was withdrawn and hydrolyzed into the parent linear copolyester ($M_{n,NMR} = 2.6 \cdot 10^4$ g/mol, $M_{n,SEC} = 2.4 \cdot 10^4$ g/mol, $M_w/M_n = 1.45$) for characterization. The intramolecular cross-linking of the pendant acrylic unsaturations of αAεCL units next to the propagating sites is performed by UV (350–420 nm, 1000 W) irradiation to result in macrocyclic polyesters ($M_{n,NMR} = 2.64 \cdot 10^4$ g/mol, $M_{n,SEC} = 2.08 \cdot 10^4$ g/mol, $M_w/M_n = 1.45$) free of any tin alkoxide after hydrolysis (Figure 1). ^{1}HNMR spectroscopy proved at least part of the double bonds in
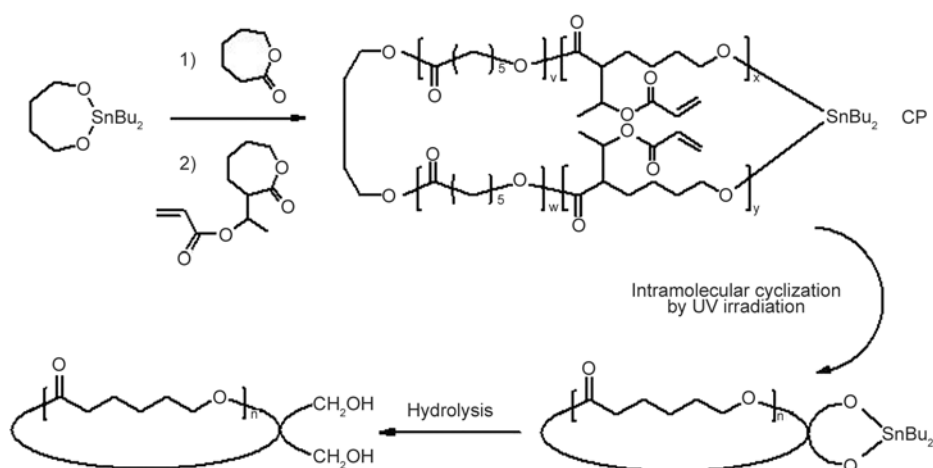
Figure 1. New strategy for the synthesis of macrocyclic polyester free from tin alkoxides

one block of the PCL chains react with double bonds in the second block. Remarkably, the concentration of the chains ($2.8 \cdot 10^{-4}$ M or ~ 0.78 wt%) at which the UV cyclization has been carried out, is at least one order of magnitude higher compared to cyclization of linear precursors ($<10^{-5}$ M). The average numbers of acrylic unsaturations per chain are key parameters for the success of cyclization. Indeed, gelation occurs as result of intermolecular cross-linking when either the chain concentration ($\geq 5.0 \cdot 10^{-3}$ M) or the number of acrylic units (more than 30) is too high. In contrast, whenever the average number of unsaturation is too low (less than 7), the apparent molecular weight measured by SEC remains unchanged, which indicated that intramolecular cross-linking does not take place and that no chain degradation is triggered by UV irradiation. Only chains of a medium molecular weight ($M_{n,theor.}$ = $2.6 \cdot 10^4$ g/mol) have been considered in relation to feasible characterization by NMR spectroscopy. The parameter $<G>$, i.e., the ratio of the molecular weights at the maximum of the elution peaks [$M_{p,SEC}$(cyclic)/$M_{p,SEC}$(linear)], is 0.76 and the ratio of the intrinsic viscosity of the polyester, g, ($g =$ [η]$_{cyclic}$/[η]$_{linear}$) is 0.69 in toluene at 25°C, in agreement with data published for other cyclic polymers [1]. Cyclization of PCL ($M_{n,NMR}$ = $2.64 \cdot 10^4$ g/mol) has only a minor effect on T_g, in contrast to the important impact on crystallization. Indeed, the melting temperature (T_m) of cyclic PCL decreased by 7°C compared to that of the linear counterpart and the degree of crystallinity (X_c) by at least a factor of two.

One advantage of the novel strategy for the synthesis of macrocycles is that there is no linear intermediate at any stage of the process, such that macrocyclic polyesters free of any knot are prepared. Indeed, whenever macrocycles are synthesized from a linear precursor, chains of high enough molecular weight can be entangled leading to physical cross-links or knots that impact the macroscopic properties of the macrocycles [31]. Moreover, the statistics of the cyclization is favourably changed because the probability for intra reaction (P_{intra}) is higher when the precursor is cyclic rather than linear, as result of the permanently close vicinity of the unsaturations to be crosslinked. Clearly, the new strategy is very well-suited to high molecular weight chains, whose macrocyclization from linear precursors is very challenging. The independence of P_{intra} on the chain molecular weight is the key feature, which makes the cyclization to depend mainly on the reactivity of the unsaturated units. In parallel, the probability for inter-reactions decreases upon increasing molecular weight which accounts for high cyclization yield can be observed at higher concentration.

3. Synthesis of functional ciclic copolyesters and amphiphilic sun-shaped copolymers
3.1. Functional cyclic copolyesters
In order to make a cyclic functional copolyesters available, a comonomer containing a protected hydroxyl group [32], i.e., γ-triethylsilyloxy-ε-caprolactone (γ-Et₃SiOεCL), has been random copolymerized with ε-caprolactone initiated by cyclic DSDOP in toluene, followed by the addition and sequential polymerization of a few units of αAεCL with formation of a cyclic precursor (**CP**) as shown in Figure 2, poly(γ-Et₃SiOεCL-co-εCL-b-αAεCL)
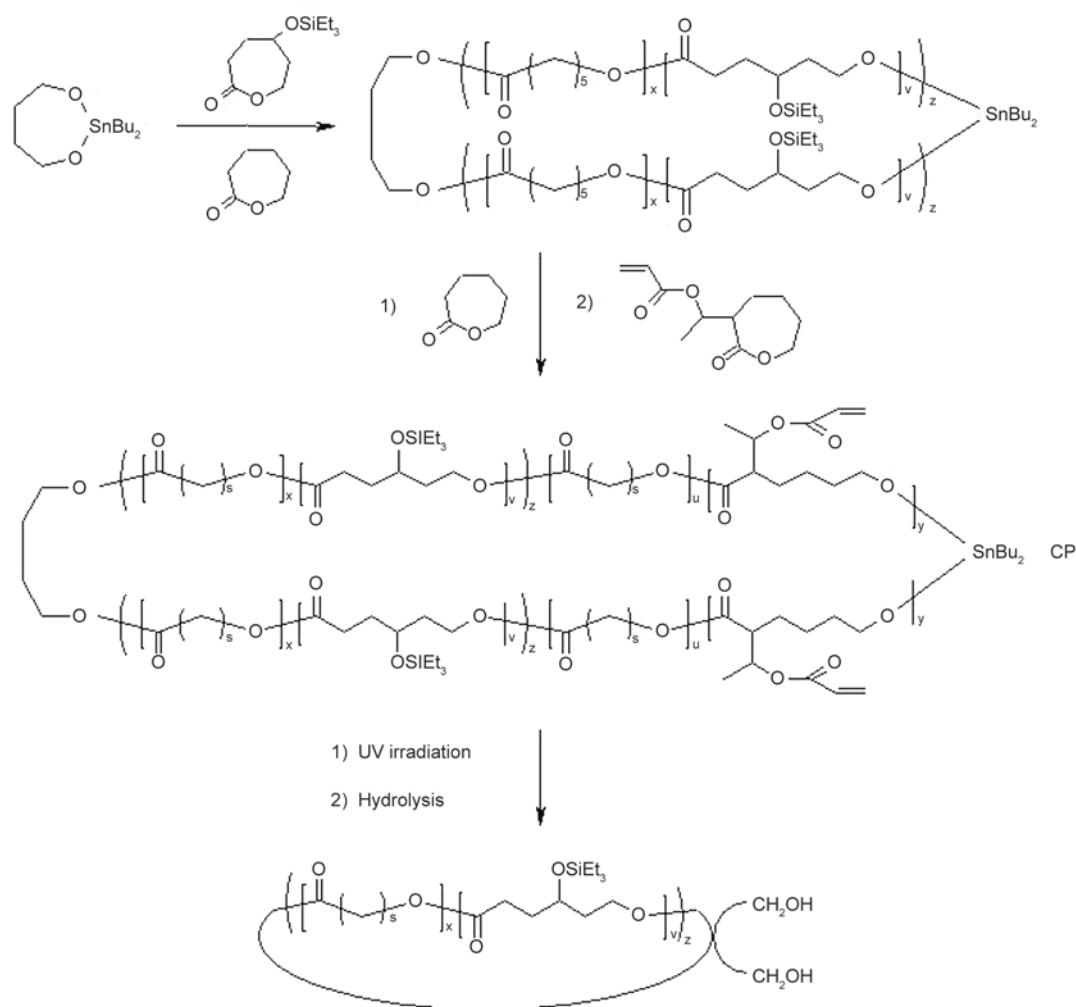
Figure 2. Synthesis of functional cyclic copolyesters

($M_{n,NMR}$ = 2.75·10^4 g/mol, $M_{n,SEC}$ = 2.55·10^4 g/mol, M_w/M_n = 1.45, $F_{γ-Et_3SiOεCL}$ = 8.8%). Then intramolecular photo cross-linking of the unsaturations next to the propagating sites is carried out, with formation of a functionalized macrocyclic random copolyester poly(γ-Et$_3$SiOεCL-co-εCL) after hydrolysis of tin alkoxides.

The apparent $M_{n,SEC}$ decreased indeed from 25 500 to 21 500 upon cross-linking, consistent with the lower hydrodynamic volume that the physically more compact cyclic macromolecules exhibit with respect to the linear counterparts [1]. This observation confirms that the macrocyclic copolyester is maintained after hydrolysis of the endocyclic tin alkoxide. The polydispersity index (1.45) before and after intramolecular crosslinking, remains unchanged and the ratio of the molecular weights at the maximum of the elution peaks [$M_{p,SEC}$(cyclic)/ $M_{p,SEC}$(linear)] is 0.79. An additional evidence for the successful cyclization is the ratio, g, of the intrinsic viscosity [$η$] of the copolyester after and before the UV treatment. This ratio (g = [$η$]$_{cyclic}$/[$η$]$_{linear}$) is 0.70 in toluene at 25°C, which is again quite consistent with observations reported in the scientific literature for other macrocyclic (co)polymers [1, 30]. All these observations support that the cyclization strategy is very effective.

The thermal properties of the cyclic random copolyester and the linear counterpart were also analyzed by differential scanning calorimetry. Both the samples are semi-crystalline, which indicates that the γ-Et$_3$SiOεCL co-units (8.8 mol%) do not prevent PCL from crystallizing. However, the crystallinity degree, X_c, and the melting temperature, T_m, are lower for the cyclic copolyester than for the linear chains. The reverse observation is found for the glass transition temperature, T_g, which is higher for the cyclic (–56.8°C) than for the linear chains (–64.5°C). Cyclization is thus responsible for a loss of chain mobility.

3.2. Amphiphilic sun-shaped copolymers

The deprotection of the triethylsilanolate groups released hydroxyl groups that were esterified by carboxylic acid end-capped PEO, with formation of an amphiphilic sun-shaped copolymer, i.e., macrocyclic copolyesters grafted with PEO as shown in Figure 3 [32]. The SEC traces could be superposed before and after deprotection, whereas the molar composition ($DP_{\gamma-HO\varepsilon CL} = 17$, $DP_{\varepsilon CL} = 178$) determined by ^{1}H NMR analysis remained unchanged after deprotection. The number of the grafted PEO chains (9.5 per cyclic chain, $M_{n,NMR} = 3.55 \cdot 10^4$ g/mol) was estimated from the relative integration of the ^{1}H NMR signals, such that the grafting efficiency was 50–60%.

Additional although qualitative evidence for the successful grafting of PEO onto the macrocycles may be found in the formation of water-soluble micelles by self-assembly of the amphiphilic grafted macrocycles in water. Spherical micelles are observed by TEM (Figure 4), that consist of a hydrophobic core formed by the cyclic copolyester and a hydrophilic corona of PEO.
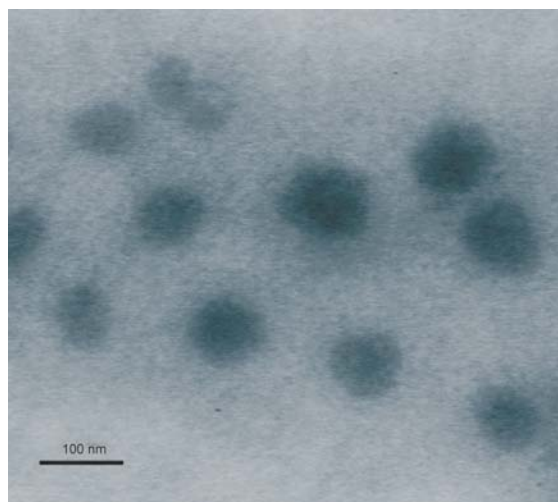

Figure 4. TEM picture of micelles of the cyclic poly(γ-HOεCL-co-εCL)-g-PEO in water

4. Synthesis of tadpole-shaped copolyesters

The novel strategy has been successfully tested for the synthesis of cyclic PCL [30] and cyclic functional copolyesters [32]. It relies on the intramolecular photo cross-linking of few acrylic unsaturations in the close vicinity of a cyclic precursor (**CP**)
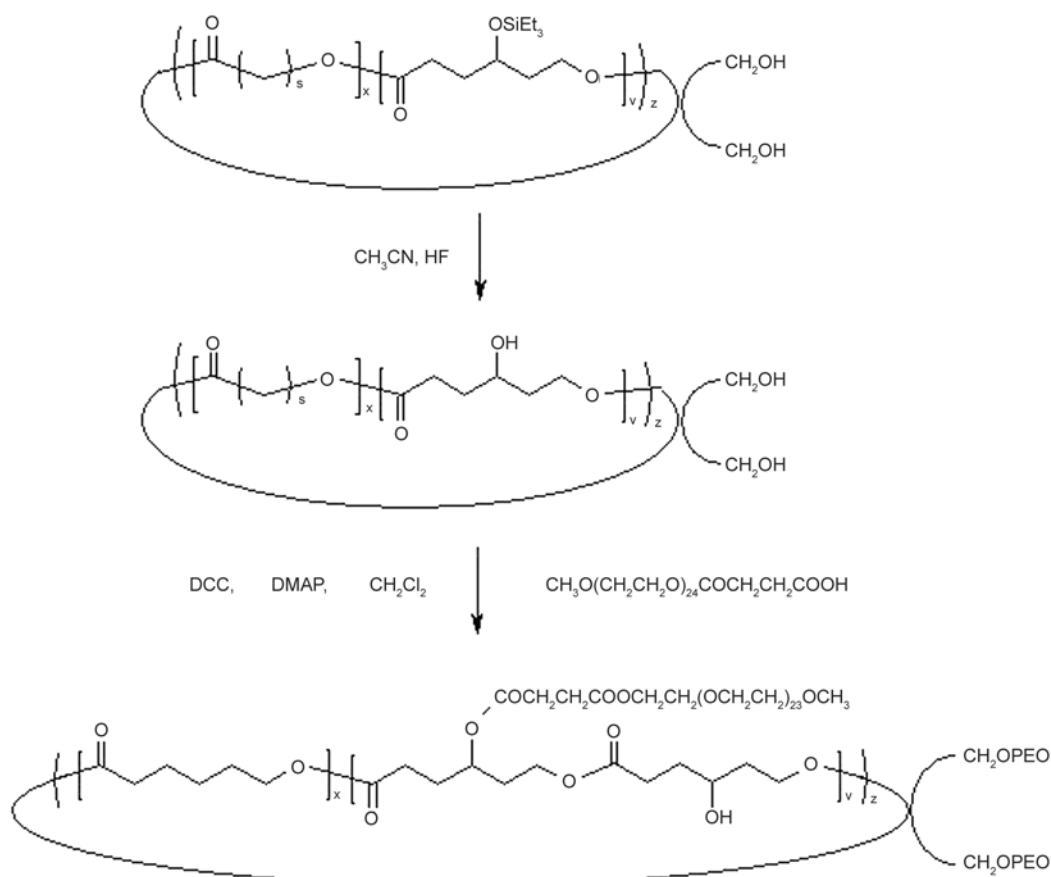

Figure 3. Synthesis of amphiphilic copolymer with a sun-shaped architecture

synthesized by ring-opening polymerization initiated by a cyclic tin alkoxide. This process is very well-suited to the synthesis of high molecular weight macrocycles. Remarkably, the propagating tin dialkoxides **1** (Figure 5) remain active after cyclization and available to further derivatization and macromolecular engineering.

As a very straightforward example [30], the εCL polymerization ($[CL]_0/[Sn]_0 = 108$, $M_{n,th} = 3.8 \cdot 10^4$ g/mol) has been resumed after cyclization, so leading to tadpole-shaped chains ($M_{n,NMR} = 3.84 \cdot 10^4$ g/mol, $M_{n,SEC} = 3.05 \cdot 10^4$ g/mol, $M_w/M_n = 1.45$), thus two adjacent tails grafted onto the macrocycles ($M_{n,NMR} = 2.64 \cdot 10^4$ g/mol, $M_{n,SEC} = 2.08 \cdot 10^4$ g/mol, $M_w/M_n = 1.45$) (Figure 5, path A).

In an alternative example [33], polymerization of L-lactide can be directly initiated by the macrocyclic initiator **1** after the UV treatment (intramolecular cyclization), with formation of two PLLA chains attached to the ring in the close vicinity one to each other (Figure 5, path B). The average polymerization degree of LLA was calculated from ^{1}H NMR analysis for each tail ($DP_{L-lactide} = 59$, $M_{n,NMR} = 8.5 \cdot 10^3$ g/mol). The apparent molecular weight measured by SEC was actually increased ($M_{n,SEC} = 2.45 \cdot 10^4$ g/mol, $M_w/M_n = 1.40$) after resumption polymerization, compared to the macrocyclic precursor ($M_{n,SEC} = 2.05 \cdot 10^4$ g/mol, $M_w/M_n = 1.40$). The molecular weight calculated from the integration of the ^{1}H NMR signals was $4.45 \cdot 10^4$ g/mol for the tadpole-shaped copolyesters and $2.75 \cdot 10^4$ g/mol for the macrocyclic PCL. Moreover, the absence of transesterification reaction was confirmed by ^{13}C NMR spectrum. Indeed, the expanded carbonyl region shows two peaks at 173.5 ppm for cyclic

PCL and at 169.5 ppm for the two PLLA tails, respectively. This observation of the PCL and PLLA homodiads without any additional signal is consistent with the coexistence of 'pure' macrocyclic PCL and linear PLLA tails. It can, thus, be concluded that the polymerization resumption is effective and that tadpole-shaped poly(ε-caprolactone) with two PLLA tails of a tunable length can be readily prepared.

The thermal behaviour of tadpole-shaped copolyester **3** (Figure 5, path B) was compared to cyclic PCL (precursor, i.e., after hydrolysis of macrocyclic initiator **1**) by differential scanning calorimetry. During cooling, crystallization peak is observed for the macrocyclic PCL at 15.0°C. When the tadpole-shaped copolyester is concerned, no crystallization is detected anymore, consistent with a much slower crystallization for the macrocyclic PCL as result of the grafting of two PLLA arms. Upon heating, a melting endotherm is clearly observed for the cyclic PCL (44°C, precursor) and a similar behavior is observed for the cyclic PCL in the tadpole-shaped copolyester. Indeed, the crystallization that did not occur during cooling, is observed during heating at –11.5°C, followed by melting at 39°C. The melting temperature of cyclic PCL is thus decreased by 5°C as result of the PLLA grafting. Although crystallization of PLLA could not be observed during the cooling and the heating steps (possibly because of a too low content of PLLA in the tadpole-shaped copolyester), a small melting endotherm was observed at a much lower temperature (132.5°C) compared to homo linear PLLA (148°C). In parallel to T_m, the crystallinity degree for cyclic PCL and PLLA is also decreased as result of incorporation into the
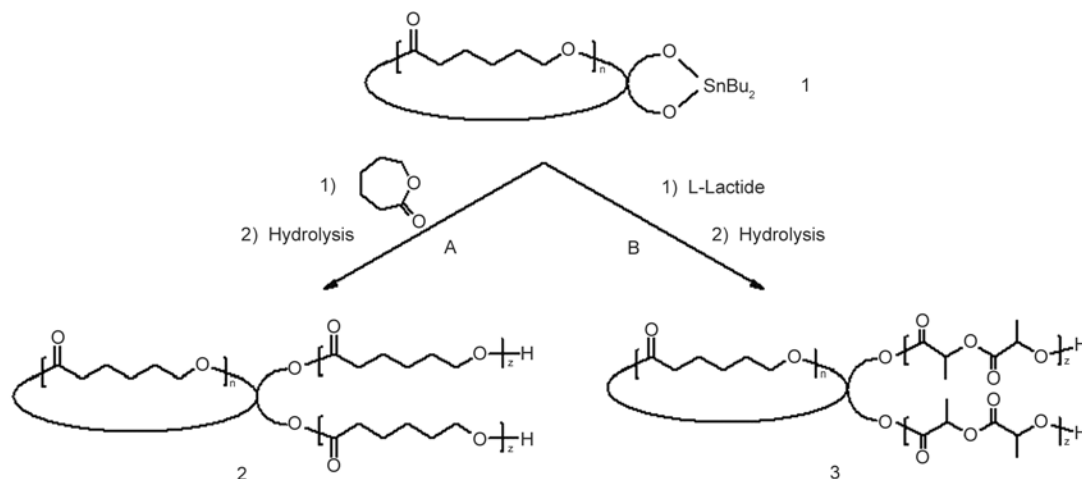

Figure 5. Synthesis of a tadpole-shaped copolyester

tadpole-shaped architecture. It thus appears that the coexistence of two crystallizable constitutive components in the copolyester has a mutually detrimental impact on their crystallization. Finally, only T_g of the cyclic PCL could be observed by DSC, which remained unaffected by grafting of PLLA.

5. Synthesis of amphiphilic tadpole-shaped copolymers

In another version, the tadpole-shaped copolyester with a high molecular weight cyclic PCL head

($M_{n,NMR} = 2.45 \cdot 10^4$ g/mol, $M_{n,SEC} = 2.06 \cdot 10^4$ g/mol, $M_w/M_n = 1.40$) and two functionalized grafted tails, has been synthesized for the very first time [34]. The active macrocyclic initiator **1** (Figure 6) after intramolecular cyclization resumes a random copolymerization of εCL and αClεCL, so yielding a tadpole-shaped copolyester ($M_{n,NMR} = 6.76 \cdot 10^4$ g/mol, $M_{n,SEC} = 3.0 \cdot 10^4$ g/mol, $M_w/M_n = 1.40$) with two activated chloride containing tails poly(αClεCL-co-εCL) ($F_{\alpha Cl \varepsilon CL} = 0.53$). The chloride groups were then converted into azides i.e., poly(αN₃εCL-co-
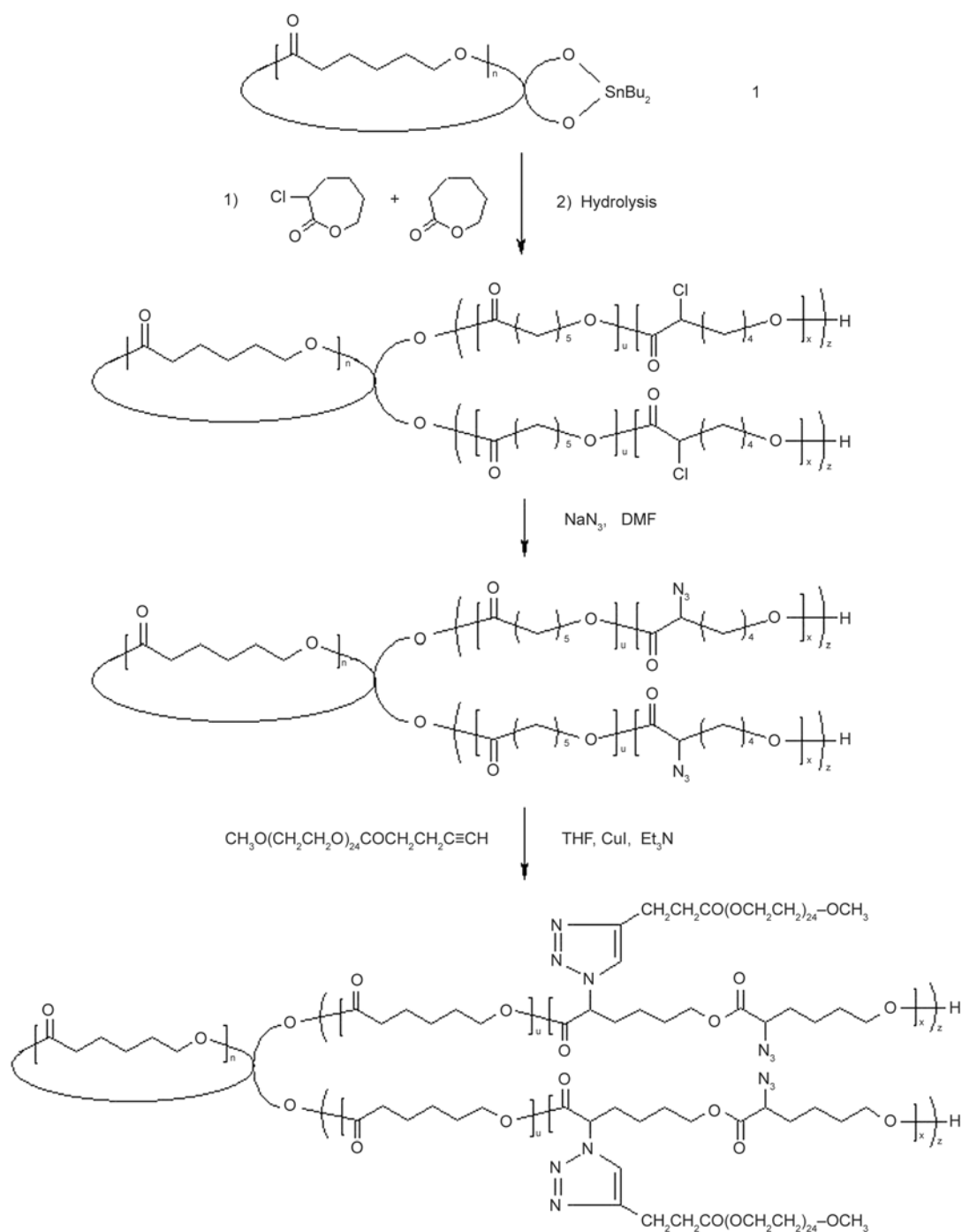

Figure 6. Synthesis of an amphiphilic copolymer by grafting of PEO onto functional tadpole-shaped copolyester

εCL) ($F_{\alpha N3\varepsilon CL}$ = 0.53), that were reacted with alkyne end-capped PEO by a 'click' copper mediated cycloaddition reaction in order to make tadpole-shaped copolyesters amphiphilic ($M_{n,NMR}$ = 1.81·10⁵ g/mol, $M_{n,SEC}$ = 2.62·10⁴ g/mol, M_w/M_n = 1.65). Each tail of the tadpole-shaped copolyester was grafted by 53 PEO chains and the grafting efficiency was 65% as determined by the ¹H NMR analysis.

The copolymerization step is controlled and the substitution (conversion of chlorides into azides) and the 'click' cycloaddition [3+2] reactions are easily implemented and quasi quantitative. The 'click' chemistry used for the grafting of the tails of the tadpole-shaped PCL is very tolerant to many functional groups and no cumbersome protection/deprotection reaction is required. It may be noted that all these copolymers consist of two biocompatible components and that PEO is known for protein repellent properties.

The thermal behavior of cyclic PCL, α-chloro-functionalized tadpole-shaped copolyester, α-azide-substituted derivative, PEO-grafted copolymer, and homo-PEO (reference) was characterized by DSC. Upon cooling, a crystallization peak was observed at 12.0°C for the macrocyclic PCL (macroinitiator **1** after hydrolysis of the tin dialkoxide), in contrast to a faint peak at a lower temperature (–12°C and –11°C) for the tadpole-shaped copolyesters with two amorphous tails poly(αClεCL-co-εCL) ($F_{\alpha Cl\varepsilon CL}$ = 0.53) and poly(αN₃εCL-co-εCL) ($F_{\alpha N_3\varepsilon CL}$ = 0.53), respectively. The crystallization enthalpy (ΔH_c) decreased by at least a factor of two upon the grafting of two functional tails onto the macrocyclic PCL. The same observation was also observed in case of grafting of two semi-crystalline poly(L-lactide) arms [33]. As a rule, the two tails of the tadpole-shaped copolyesters have a depressive effect on the crystallization of PCL, whatever they are amorphous or not. Crystallization of the PEO grafts of the PEO-grafted tadpole-shaped copolymer was observed although at a much lower temperature and to a lesser extent than homo PEO. During heating, a melting endotherm was noted for the cyclic PCL at 42°C with a melting enthalpy of 34.5 J/g. Once again, the negative impact of the tails was reported to an extent that depends on the substituents, thus chlorides versus azides. The melting temperature of PCL was indeed decreased by 6.5°C in case of α-chlorides and by 10.5°C for the α-azide pendant
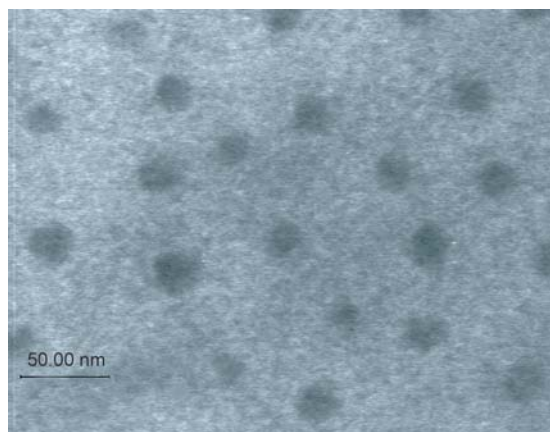

Figure 7. Micelles of PEO-grafted tadpole-shaped copolyester in water observed by TEM

groups. In parallel to T_m, the melting enthalpy for PCL was also decreased by 7.5 J/g for the α-chloride substituted copolyester and by 10.5 J/g for the α-azide version. When PEO is part of the copolymer, only this constitutive component crystallizes, although with restrictions imposed by the complex architecture, as testified by a substantial decrease in T_m (by 17°C) and ΔH_m (by 112 J/g) compared to linear PEO.

The micellization in water as result of the amphiphilicity and self-assembly of this new well-defined copolymer was testified by transmission electron microscopy (Figure 7). Spherical micelles were indeed observed, that are supposed to consist of a hydrophobic polyester core surrounded by a hydrophilic corona of PEO.

6. Synthesis of eight-shaped and twin tadpole-shaped amphiphilic copolymers by using a spirocyclic tin initiator

6.1. Eight-shaped polyester

The novel strategy which allows going a step further in the complexity of the eight-shaped and twin tadpole-shaped architecture is less demanding in terms of dilution and size of the rings. Briefly, the sequential ring-opening polymerization of εCL and αAεCL units was initiated by a spirocyclic initiator (**a**, Figure 8), followed by the intramolecular photo-cross-linking of the acrylate unsaturations, thus the covalent stabilization of rather high molecular weight eight-shaped PCL **d** ($M_{n,NMR}$ = 4.12·10⁴ g/mol, $M_{n,SEC}$ = 2.40·10⁴ g/mol, M_w/M_n = 1.45) [35]. Before cyclization, the living chain **b** was hydrolyzed into the parent star-shaped copolyester ($M_{n,NMR}$ = 4.26·10⁴ g/mol, $M_{n,SEC}$ = 2.90·10⁴ g/mol, M_w/M_n =
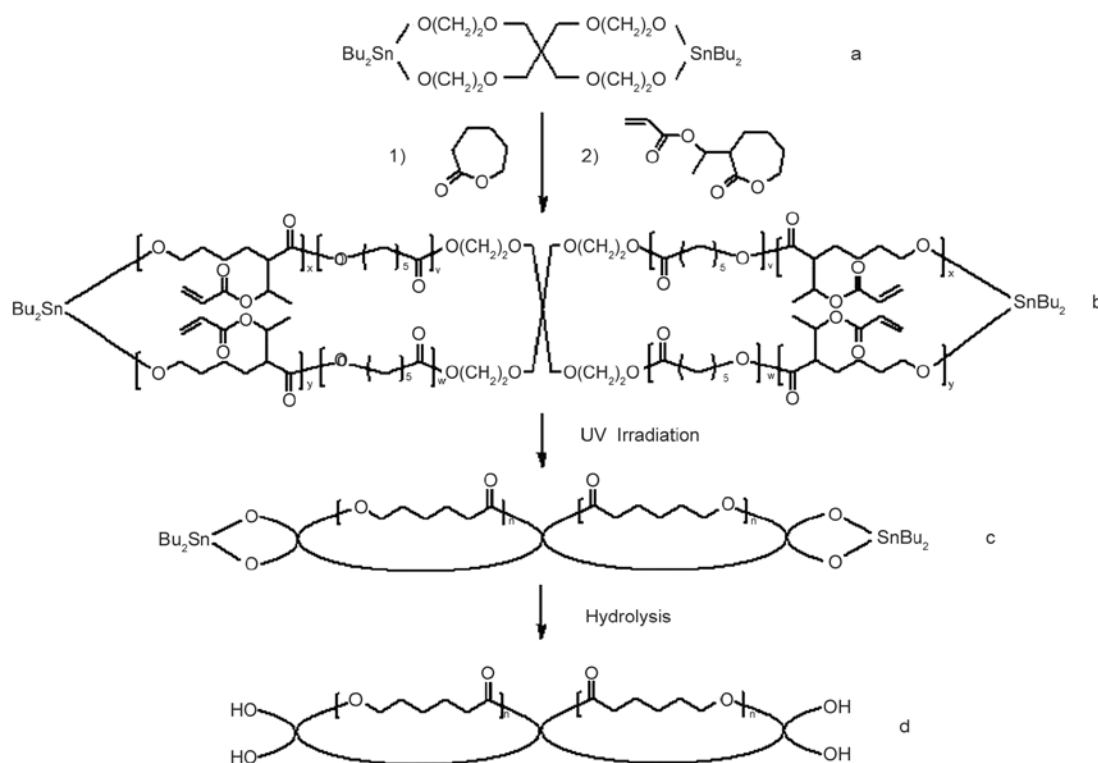
Figure 8. Synthesis of eight-shaped PCL by a spirocyclic initiator

1.45) for comparison characterization. The apparent $M_{n,SEC}$ decreased from $2.90 \cdot 10^4$ to $2.40 \cdot 10^4$ g/mol upon cross-linking, merely because of the successful conversion of star into bicyclic macromolecules. Meanwhile, the cyclization reaction did not change the molar mass distribution ($M_w/M_n = 1.45$), which is evidence for the well-controlled formation of eight-shaped macrocycles. The ratio of the molecular weights at the maximum of the elution peaks [$M_{p,SEC}$(bicyclic)/$M_{p,SEC}$(star)] was 0.65, thus smaller than the value (0.76) for monocyclic PCL ($M_{n,NMR} = 2.60 \cdot 10^4$ g/mol) [30].

The thermal behavior of the star-shaped (parent) and eight-shaped PCL ($M_{n,NMR} = 4.12 \cdot 10^4$ g/mol) was compared by DSC. The crystallinity of the eight-shaped PCL decreased from 50.0 to 22.0% upon cyclization, and the melting temperature (T_m) decreased by 17°C compared to the star-shaped PCL. In contrast, cyclization of PCL of high molecular weight had only a minor effect on T_g. The same evolution was previously observed for the impact of the cyclization of linear PCL on the thermal properties [30].

6.2. Twin tadpole-shaped amphiphilic copolymers

After UV irradiation, the bicyclic polyester without hydrolysis was nothing but a new macroinitiator **c**

(Figure 9) able to resume the ring-opening polymerization of a mixture of εCL and αClεCL, so imparting a functional twin tadpole structure **e**. This was the first example of an eight-shaped architecture substituted at the same place by two dangling chains to the individual macrocycles. Indeed, the average polymerization degrees of εCL and αClεCL in the four tails of the bicyclic chains were 246 and 190, respectively, which indicates the molecular weight of the twin tadpole-shaped copolyesters was very high ($M_{n,NMR} = 1.0 \cdot 10^5$ g/mol). The apparent molecular weight of e measured by SEC was actually increased ($M_{n,SEC} = 3.48 \cdot 10^4$ g/mol) while keeping the polydispersity index unchanged ($M_w/M_n = 1.45$), compared to the spirocyclic PCL ($M_{n,SEC} = 2.40 \cdot 10^4$ g/mol, $M_w/M_n = 1.45$).

The pendant chloride groups of the functional twin tadpole-shaped copolyesters **e** were converted into azides under a very mild condition. The completeness of the derivatization reaction was confirmed by ^{1}H NMR and IR analysis. Moreover, the azide content of the tails in **f** ($F_{\alpha N_3 \varepsilon CL} = 0.43$) was found in good agreement with the composition of the precursors **e** ($F_{\alpha Cl \varepsilon CL} = 0.43$). Meanwhile, the molecular weight and the polydispersity index before and after the derivatization remain unchanged.

Finally, the copper mediated 'click' chemistry was used to attach alkyne end-capped PEO ($M_n = $
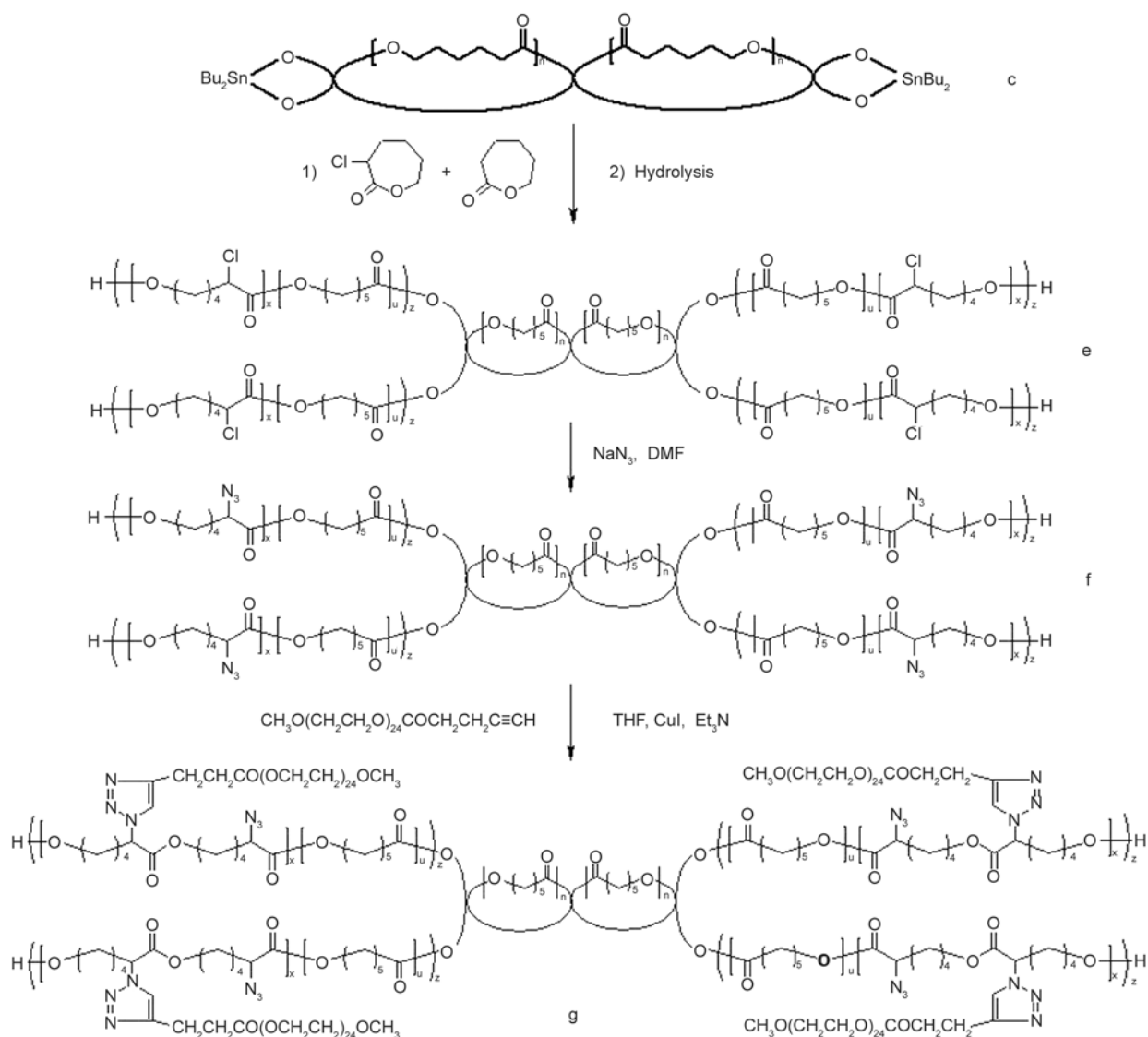
Figure 9. Synthesis of amphiphilic twin tadpole-shaped copolymers

1050 g/mol) onto those azide functionalized tails, so leading to an amphiphilic eight-shaped copolyester, whose constitutive macrocycles were grafted by four PCL-g-PEO tails. The grafting efficiency was 61% as calculated from the relative intensity of the ^{1}H NMR signals. Each tail of the copolymer **g** was grafted by 29 PEO chains and M_n was $1.95 \cdot 10^5$ g/mol as determined by ^{1}H NMR. The polydispersity of the amphiphilic twin tadpole-shaped copolymer was slightly increased (from 1.45 to 1.75) as result of the PEO-grafting in line with the chromatograms that remained monomodal and symmetrical and with the data for the PEO grafted tadpole-shaped copolymer [34].

Dependence of the crystallization on conversion of the chlorinated tails of the eight-shaped PCL (**e**) to the azide containing tails (**f**) and finally to the PEO grafted tails (**g**) was also investigated by DSC.

Comparison of data shows that the crystallization temperature and enthalpy decreased by 12.5°C and 8 J/g, respectively, upon the grafting of four poly (αClεCL-co-εCL) tails onto the spirocyclic PCL. The same observation was reported when cyclic PCL was grafted by two semi-crystalline poly(L-lactide) tails [33] and by two amorphous poly (αClεCL-co-εCL) tails [34], respectively. As a rule, the grafting of mono/spiro-cyclic PCL by two/four polymeric tails, amorphous or not, has a depressive effect on the crystallization of PCL.

Conversion of the chlorinated chains into the azide containing version decreased ΔH_c by 14.5 J/g for spirocyclic PCL (**f** vs **e**). Crystallization of the PEO grafts was observed for the copolymer **g**, although at a much lower temperature (T_c decreased by 42.5°C) and to a lesser extent (ΔH_c decreased by 121.5 J/g) than homo PEO.
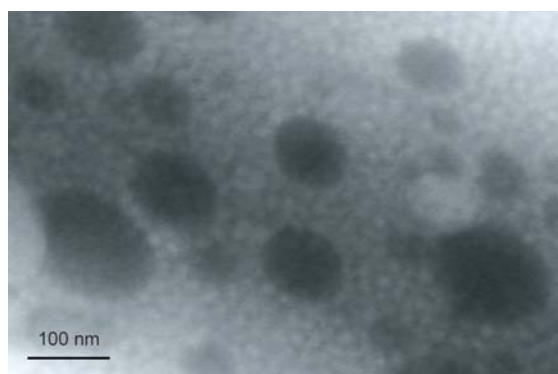
Figure 10. TEM of micelles of amphiphilic twin tadpole-shaped copolymers (Figure 9, **g**)

Comparison of T_m and ΔH_m for the spirocyclic PCL and the samples **e** and **f** confirms the negative impact of the tails on the PCL crystallization to an extent that depends on the tail substituents, thus chlorides versus azides. The melting temperature of PCL was indeed decreased by 3.5°C in case of α-chlorides and by 10.0°C for the α-azide pendant groups. In parallel to T_m, the melting enthalpy for PCL was also decreased by 5.0 J/g upon grafting of the chlorinated tails **e** and by 16.0 J/g when the tails contained azides **f** rather than chlorides. Once again, there is a clear relationship between property and macromolecular architecture. When PEO was part of the copolymer, only this constitutive component crystallized, although with some restriction imposed by the complex architecture, as testified by a substantial decrease in T_m (by 16°C) and ΔH_m (by 109.5 J/g) compared to linear PEO and in agreement with the PEO-grafting of tadpole-shaped PCL [34].

Micellization in water as result of the amphiphilicity and self-assembly of the grafted copolymer **g** was an additional although qualitative evidence for the successful grafting of PEO onto the twin tadpole-shaped macrocycles. Ellipsoidal micelles were observed by TEM (Figure 10), that are supposed to consist of a hydrophobic polyester core surrounded by a hydrophilic corona of PEO. The size of the micelles formed by the eight-shaped amphiphilic PCL/PEO copolymer **g** (Figure 9) was larger than by the monocyclic amphiphilic PCL/PEO copolymer (Figure 6) [34].

7. Conclusions

This review has highlighted the novel and efficient strategies for the synthesis of well-defined macro-cyclic aliphatic polyesters, to which steadily more complex topologies can be imparted. In this respect, combination of controlled ring-opening polymerization initiated by cyclic/spirocyclic tin(IV) dialkoxides and intramolecular photo cross-linking of unsaturations close to the propagating site proved to be successful. Compared to the traditional techniques of cyclization of linear precursors by the end-to-end coupling at very high dilution, this process has the substantial advantage that linear species are never involved while cyclic precursors (**CP**) are concerned. Accordingly, the new strategy is very well-suited to the synthesis of high molecular weight macrocycles ($2.4 \cdot 10^4$–$4.2 \cdot 10^4$) under moderate dilution, which is a sizeable improvement. Very importantly, the macrocyclic/macrobicyclic polyesters prepared in these routes, can be accommodated into more complex architectures as part of a macromolecular engineering effort of the basic macrocycles/macrobicycles. Indeed, the propagating tin alkoxides remain active after cyclization and available to further derivatization, so leading to the functional tadpole-shaped and twin tadpole-shaped architectures, both the size and composition of which can be extensively tuned. In another version, when a copper mediated 'click' reaction was employed, new amphiphilic PEO/macrocyclic-PCL copolymers with tadpole architecture and amphiphilic PEO/macrospirocyclic-PCL copolymers with twin tadpole architecture were accordingly made available. Another engineering route was pioneered to novel functional macrocyclic copolyesters, so resulting in amphiphilic sun-shaped copolymers.

The research effort is now devoted to the synthesis of polyesters with novel architectures based on macrocyclic/macrospirocyclic building blocks. In order to shed light on the impact of the architectures on the macroscopic properties and the self-assembly both in solution and in bulk, synthesis of a wider range of macrocyclic polyesters with different compositions and different molecular weights will be explored in the future.

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