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# *O*-Carboxyanhydrides: Useful Tools for the Preparation of Well-Defined Functionalized Polyesters

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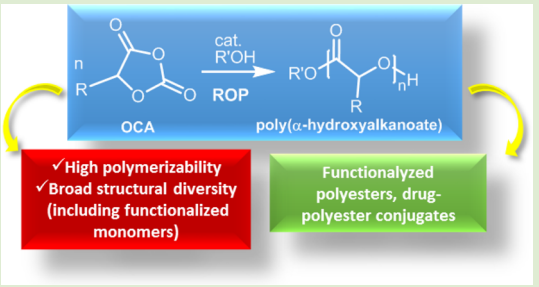
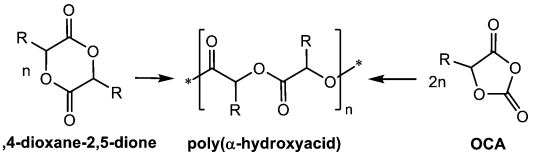
Supporting Information

**ABSTRACT:** Over the last ten years, *O*-carboxyanhydrides (OCA) have attracted increasing attention as ring-opening polymerization (ROP) monomers. They are readily available from $\alpha$-hydroxyacids and are significantly more reactive than 1,4-dioxane-2,5-diones. Thus, softer catalysts and milder reaction conditions can be used, allowing for a better control of the polymerization. Most attractive are the functionalized OCA that enable the introduction of functional groups along the polyester backbone and thereby vary and finely tune their physicochemical properties. In this viewpoint, the achievements made over the last years are critically overviewed. Particular attention is paid to the different catalytic approaches that have been reported for the ROP of these heterocycles and to the comparison with lactide ROP. In addition, the most representative examples of functionalized polyesters and polymer conjugates prepared from OCA are discussed.




Thanks to their biodegradable properties, synthetic polyesters have received increasing attention during the last three decades as resorbable biomaterials as well as commodity thermoplastics. In this area, poly($\alpha$-hydroxyacid) (PAHA) and, in particular, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers (PLGA), occupy a forefront position due to their biocompatible properties and their accessibility from renewable resources.[1] These polymers are typically prepared by ring-opening polymerization (ROP) of lactide and glycolide (the cyclic dimers of lactic and glycolic acid), a synthetic approach allowing much better control and tuning of the polymer properties than polycondensation. Different catalytic systems, including well-defined metal complexes and organocatalysts, have been developed to efficiently promote the ROP of these dilactones under mild conditions and in a highly controlled fashion.[2,3] Structural parameters of the polymers such as chain length, molar mass distribution, composition (lactide/glycolide ratio), and nature of the chain-end can be finely adjusted. However, the lack of structural diversity of the polyesters derived from lactide and glycolide appears as an important limitation, and increasing efforts have been devoted to the introduction of pendant groups along the polymer chain in order to modify and modulate the physicochemical properties of poly($\alpha$-hydroxyacid) and to expand thereby their applications.[4] These modulations can be achieved by the use of substituted 1,4-dioxane-2,5-diones (Scheme 1), but this strategy can be complicated by the moderate accessibility[5] and poor reactivity in ROP of the required 1,4-dioxane-2,5-diones.[2b,6−9] During the last years, *O*-carboxyanhydride (OCA) have emerged as suitable alternatives to 1,4-dioxane-2,5-diones for the efficient preparation of functionalized PAHA under mild conditions.

**Scheme 1. Preparation of Poly($\alpha$-hydroxyacid) by ROP of Substituted 1,4-Dioxane-2,5-diones and *O*-Carboxyanhydrides (OCA)**




This review aims to make the state-of-the-art of the achievements accomplished recently in this area. The structure and preparation of the OCA investigated in ROP will be discussed, followed by the presentation of the catalytic systems reported to promote their ROP. Both metallic and organic catalysts will be discussed. The last section of the review focuses on functionalized PAHA and their copolymers prepared using the OCA technology. Applications of these PAHA in gene and drug delivery are not covered, they have been discussed in a recent account.[10]

***Preparation and Structure Diversity of OCA:*** **lacOCA**, the OCA derived from lactic acid, is the prototype OCA investigated in ROP.[11−13] Several other OCA prepared from $\alpha$-hydroxyacids naturally occurring or deriving from $\alpha$-amino-acids have also been reported for the synthesis of functionalized

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poly($\alpha$-hydroxyacid) via ROP (Figure 1): OCA deriving from mandelic acid,[11a,14] malic acid,[15] L-glutamic acid,[13,16] L-phenylalanine,[17] L-serine,[13,18] L-tyrosine,[19] and L-lysine.[13,20]

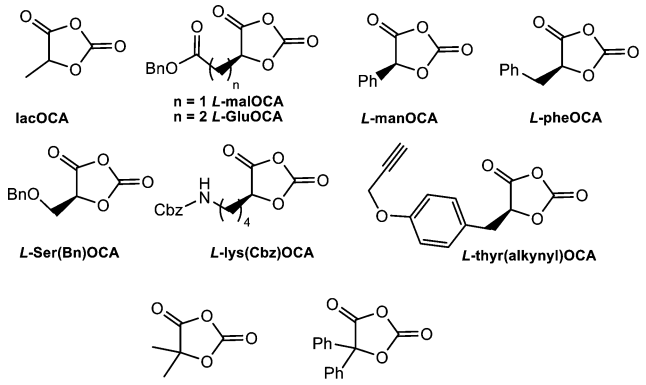
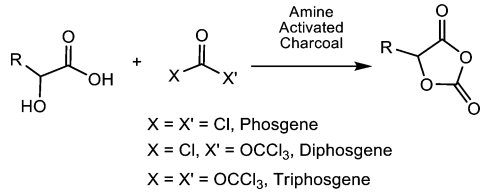



**Figure 1.** Structural diversity of OCA investigated in ROP.

OCA are typically prepared via carbonylation of $\alpha$-hydroxyacids. Phosgene and more frequently its surrogates diphosgene and triphosgene are used as cabonylating agents (Scheme 2).[21] When phosgene is used as carbonylating agent,

**Scheme 2. General Preparation of OCA**



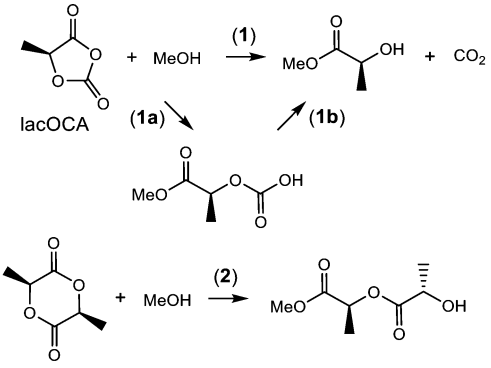

no basic additive is needed as acid scavenger,[11,18] whereas reactions with di- and triphosgene are most often carried out in the presence of activated charcoal, to promote their decomposition into phosgene, and a tertiary amine ($Et_3N$, Py, DMAP) to neutralize HCl.[12−17,19,20]

***Catalytic Systems for the ROP of OCA:*** Ring-opening of **lacOCA** by methanol to yield the corresponding lactate has been demonstrated to be thermodynamically much more favored than the ring-opening of lactide on both enthalpic and entropic points of view. As modelized by DFT, the ring-opening of **lacOCA** takes place in two steps: (1) the ring-opening itself provides the major part of the enthalpic term (**1a**, Scheme 3) and (2) the decarboxylation step plays a key role entropically (**1b**, Scheme 3).[22]

The fact that ring-opening **lacOCA** is more favored thermodynamically than that of lactide does not necessarily result in higher activity of **lacOCA** compared to lactide. The mode of action of the catalyst obviously comes into play. We can mention for instance HOTf as an organic catalyst capable to promote the ROP of lactide quite efficiently at r.t.,[23] while it is completely inactive toward **lacOCA** under similar conditions.

***Organocatalyzed ROP of OCA:*** The impressive progress of organocatalyzed ROP of lactones and lactide, in particular,[2] has enabled rapid development of organocatalyzed ROP of OCA. As mentioned before, acid catalysts do not promote the ROP of OCA, while bases/nucleophiles such as pyridines and NHC are capable to promote the ROP of OCA with good levels of control and selectivity (Table S1). Not surprisingly, most of the ROP investigations have been performed on **lacOCA**.

**Scheme 3. Thermodynamic Data Computed for the Ring-Opening of LacOCA and Lactide (298 K, kcal/mol)**




| 1 | 1a | 1b | 2 |
|---|---|---|---|
| ΔH = -15.4 | ΔH = -9.90 | ΔH = -5.4 | ΔH = -8.3 |
| ΔS = -4.70 | ΔS = -34.9 | ΔS = +30.2 | ΔS = -31.8 |
| ΔG = -14.0 | ΔG = +0.5 | ΔG = -14.5 | ΔG = -+1.2 |

Initial studies were reported by B. J. Tighe and H. R. Kricheldorf in the early 1980s using tertiary amines such as pyridine or triethylamine, or alkoxides (c.a. potassium *tert*-butoxide) as promoters for the ROP of **lacOCA**, **L-manOCA**, $\alpha$-diphenylated OCA, or $\alpha$-dimethylated OCA.[11,14b] Although these studies did not result in controlled preparation of polyesters from OCA, they represented an important starting point and stimulated future work.

In the middle of the 2000s, taking advantage of the progress achieved in organocatalyzed ROP of lactones, we reported the ROP of **lacOCA** using DMAP as organocatalyst in the presence of an alcohol as protic initiator and $M_n$ controlling agent.[12] According to $^1H/^{13}C$ NMR spectroscopy and MALDI-TOF MS analyses, ROP takes place with complete decarboxylation, leading to the formation of PLA. The polymerization reactions were carried out under mild conditions (25 °C, 1 mol/L, dichloromethane solutions), in a few minutes to several hours for $M/I$ ratios up to 600. PLA of $M_n$ values up to 62000 g/mol and narrow molar distributions ($Đ$ < 1.20) are obtained, attesting for the controlled character of the polymerization reaction. Notably, the reactions takes place under milder conditions that for lactide, (few hours at 25 °C versus few days in refluxing DCM, respectively).[24] The higher reactivity of **lacOCA** proved particularly beneficial when using as protic initiator a functionalized alcohol, such as 2-bromoethanol or cholesterol.

A detailed computational study of the polymerization mechanism supports basic activation of the initiating/propagating alcohol by DMAP as the most favored pathway, compared to nucleophilic activation of the monomer involving an acylpyridinium intermediate (Scheme 4).[22] Interestingly, the favored pathway involves also a weak nonclassical H-bond between the ester carbonyl of the OCA monomer and an *ortho* H of DMAP. Accordingly, DMAP can be considered to act as a bifunctional catalyst, with concomitant activation of the propagating chain end and monomer.[25]

The reaction conditions initially reported for **lacOCA** in 2006 have then been successfully applied to other OCA such as **L-gluOCA**,[16] **L-thyr(alkynyl)OCA**,[19] **L-ser(Bn)OCA**,[18] and **L-lys(Cbz)OCA**,[20] using primary or secondary alcohols as initiators (molecular alcohols, such as benzyl, pentyl, or isopropyl alcohols, or macromolecular alcohols, such as



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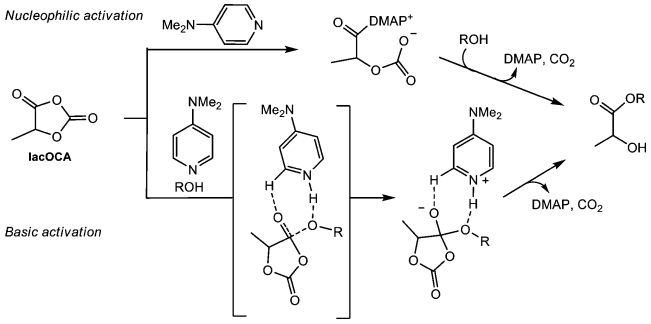
**Scheme 4. Proposed Bifunctional Mode of Action of DMAP in the ROP of LacOCA**




monohydroxylated PEG). Thanks to the mild conditions, the ROP are well-controlled in all cases, without side reactions caused by the lateral functional groups. Polyesters of tuned $M_n$ and narrow molecular distributions ($Đ$ < 1.20) were obtained. However, DMAP proved less efficient when a tertiary alcohol was used as initiator.[16] The steric demand of the alcohol slows down or even inhibits the initiation, and propagation becomes comparatively faster.

Lower control over the polymerization have been identified in the ROP of L-**malOCA** and D-**malOCA** with DMAP.[14a,15] Dove observed some epimerization of the stereogenic carbon and the formation of a small amount of polymeric side products resulting from the nucleophilic addition of the propagating alcohol to the carbonate carbonyl of L-**malOCA** rather than to the ester one.[14] The catalytic activity of substituted pyridines was evaluated. Among them, 4-methoxypyridine displayed the best balance between selectivity and activity, although it did not totally inhibit the side reaction. Using this pyridine, poly($\beta$-benzyl-$\alpha$-L-malate), poly(L-BMA), of $M_n$ values up to 24500 g/mol and very narrow molar distributions ($Đ \sim 1.10$) could be prepared.[26]

Significant epimerization of the stereogenic center and loss of isotacticity were also observed for D-**manOCA** when using DMAP as catalyst, as deduced from $^1$H and $^{13}$C NMR spectroscopy.[14a] These problems come from the increased acidity of the proton in $\alpha$ position to the phenyl group. Reducing the basicity of the catalyst did not improve significantly the control of the polymerization. Much better results were obtained using the ion pair formed by the combination of pyridine with an equimolar amount of mandelic acid.[27] The ammonium-carboxylate ion pair promotes the ROP of D-**manOCA** at room temperature, the hydroxyl group of the mandelate anion acting as initiator. Under these conditions, poly(mandelic acid) of $M_n$ values up to 48000 g/mol (in agreement with the $M/I$ values) and very narrow molar distributions ($Đ$ < 1.10) were obtained.[28] Furthermore, all the poly(mandelic acid) samples prepared using the pyridinium/mandelate ion pair combination as catalyst showed high levels of isotacticity, supporting the absence of epimerization under these conditions.

Very recently, NHC organocatalysts that are highly efficient for lactide ROP via nucleophilic activation of the monomer,[2] have been applied to the ROP of **lacOCA** and **manOCA** using alcohols as initiators.[29] Similarly to lactide, the best results in terms of activity and polymerization control were obtained with the carbene **IMes**. However, in contrast to what was observed with DMAP, polymerization times are slightly longer for L-**lacOCA** than for lactide: 200 equiv of L-**lacOCA** could be converted in 1 h at r.t., whereas only 25 min were needed for lactide. According to NMR and MALDI-TOF MS analyses, the ROP of L-**lacOCA** proceeds with complete decarboxylation yielding PLA samples. SEC analyses revealed $M_n$ values close to the targeted ones and narrow molar distributions ($Đ$ < 1.16). A mechanism equivalent to the one generally accepted for the ROP of lactide has been proposed. This mechanism is reminiscent to the one proposed in Scheme 4 in which DMAP acts as a nucleophile.[2] A similar behavior was observed for the ROP of L-**manOCA**. **IMes** did not induce significant amount of epimerization, on the contrary to what was observed with DMAP.[30] Moreover, the living and controlled character of the polymerization allowed for the preparation of 4-armed star-shaped diblock copolymers via sequential ROP of L-**lacOCA** and L-**manOCA** monomers using pentaerythritol [C-$(CH_2CH_2OH)_4$] as initiator.

***Metal Promoted ROP of OCA:*** In marked contrast with organocatalysts, metallic derivatives have been scarcely investigated toward OCA ROP (Table S2). Very few examples can be found in the literature, whereas countless examples of metallic promoters have been applied to lactide.[3]

The first report dealing with a well-defined metallic promoter for OCA ROP dates back only to 2011.[31] H. Nishide and X. Chen evaluated the activity of several metallic derivatives toward **lacOCA** (Table S2). Cobalt−salen complexes bearing nitrophenoxide coligands were evaluated as promoters of the ROP of **lacOCA**. ROP was observed regardless of the use of an external protic initiator. It is worth noting that these cobalt−salen do not promote the ROP of lactide,[32] which support again the higher reactivity of **lacOCA** related to lactide. The different complexes evaluated (varying the linker of the salen ligand and the phenoxide coligand) promote the formation of PLA from **lacOCA**, NMR spectroscopic analyses confirming complete decarboxylation. The $M_n$ values of the obtained PLA are lower than targeted, with the exception of those prepared with one complex featuring the diphenylethylene linker and the dinitrophenxide coligand. The $M_n$ values do not depend on the presence or not of an external protic initiator.

Tin benzoate and tin octanoate (which is the most frequently ROP promoter for lactide)[3] have also been evaluated in the **lacOCA** ROP.[31] Although PLA can indeed be prepared using these metal carboxylates under reaction conditions similar to those used with lactide (70 °C in toluene solution), the absence of $M_n$ control upon the addition of an external protic initiator ($i$-PrOH) indicates again poor control of the polymerization. With Nd($i$-PrO)$_3$,[33] complete conversion of **lacOCA** was obtained in less than 4 h at 25 °C. $^1$H NMR spectroscopy strongly supports the formation of PLA (and thus complete decarboxylation) and the incorporation of the $i$-PrO groups as ester chain-end. However, the $M_n$ of the obtained PLA upon varying the monomer/initiator ratios from 27 to 200 remain relatively uniform (around 11000−16000 g/mol), revealing a lack of control in the polymerization process. The tendency of these alkoxide species to be involved in aggregation equilibria and the growth of several polymer chains per metallic center might be at the origin of this lack of control. Better results should be expected from the use of single-site mono alkoxide-catalysts with ancillary ligands, as already demonstrated for lactide.

Up to now, the best results in terms of activity and polymerization control have been reported by J. Cheng using the well-defined single-site Zn complex (BDI-EI)Zn−N-$(TMS)_2$ combined with an external protic initiator.[17] This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complex, known to efficiently promote the controlled ROP of lactide,[34] has not been applied to **lacOCA**, but to two functionalized OCA: L-**pheOCA** and L-**thyr(alkynyl)OCA**. (BDI-EI)Zn−N(TMS)$_2$ proves particularly indicated for the controlled ROP of these OCA mediated by a bulky tertiary alcohol, since DMAP fails to promote efficient ROP of the OCA in that case. Using a tertiary alcohol (camptothecin, see below) as external protic initiator, (BDI-EI)Zn−N(TMS$_2$) promotes the ROP of these two OCA leading to the corresponding polyesters whose structure has been assessed by NMR and IR as well as by MALDI-TOF MS.[35] The $M_n$ values of the prepared polymers match nicely with those targeted for M/I ratios ranging from 10 to 100 and the molar distributions are particularly narrow ($Đ$ < 1.19 for L-**PheOCA**[17] and 1.10 for L-**thyr(alkynyl)OCA**).[19]

***Enzyme Promoted ROP of OCA:*** Higher polymerizability of **lacOCA** compared to lactide has also been evidenced in the enzymatic polymerization promoted by lipases.[36] Two commercially available lipases, *Pseudomonas cepacia* PS and Novozyme 435 (lipase B from *Candida Antartica* supported on polymethacrylate beads), have been used to promote the ROP of **lacOCA**.[37] Among these lipases, only PS is able to produce PLA of significant $M_n$ from lactide.[38] Although high molecular weights and very low $Đ$ (<1.10) can be achieved, harsh polymerization conditions are required (typically 5−7 days in bulk at 80−130 °C) and the yield of recovered PLA are usually low (<16%). In contrasts, PLA with relatively high molecular weights (up to 38000 g/mol) can be obtained by ROP of **lacOCA** with PS and Novozyme 435 (3.8 mol/L toluene solution, 80 °C) in less than 24 h with isolated yields ∼90%. PLA formation with complete decarboxylation was confirmed by NMR and MALDI-TOF MS. Variation of the amount of *Pseudomonas cepacia* lipase PS does not result in the variation of the molar masses of the obtained PLA. Polymers of $M_n$ values between 20000 and 30000 g/mol are obtained whatever the loading of enzyme used (% in weight related to the monomer, ranging from 19 to 1%). On the contrary, Novozyme 435 allows for the preparation of PLA of different molar masses by adjusting the amount of enzyme (Figure 2). An important

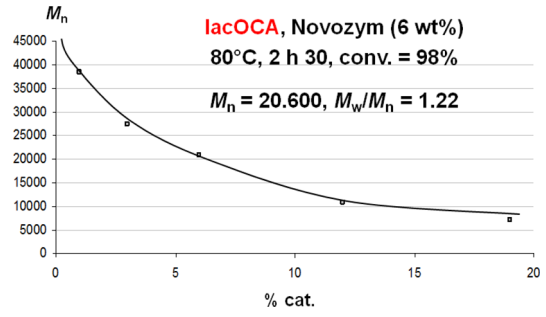


**Figure 2.** Influence of the Novozyme 435 loading on the $M_n$ values of the PLA prepared by ROP of lacOCA.

drawback of the enzymatic ROP of **lacOCA** is the inability to incorporate protic initiators as ester chain end, since only $H_2O$ initiation is observed even in the presence of an external alcohol. This contrasts with ROP of lactide with PS that can be initiated by mono and poly alcohols, with yields of recovered PLA around 60%.[36d]

***Focus on Functionalized Polymers:*** As discussed previously, the high reactivity of OCA as acylating agents enables their ROP at low temperature using smooth catalysts. Thanks to these very mild conditions, these monomers are particularly suitable for the introduction of functional groups along the polyester backbone or in the initiating group, without the occurrence of side reactions. The preparation and polymerization of OCA deriving from natural $\alpha$-amino acids has allowed for the synthesis of various poly($\alpha$-hydroxyalkanoates) bearing pendant functional groups (carboxylic acid, amine or alcohol). The first functionalized OCA applied in ROP was L-**gluOCA**.[16] Using this OCA derived from glutamic acid, poly($\alpha$-hydroxyacids) of tuned $M_n$ and bearing carboxylic acid groups were efficiently prepared by DMAP promoted ROP followed by deprotection. The same approach was applied later on by Dove for the preparation of poly($\alpha$-malic acid) via ROP of L-**malOCA** promoted by *p*-methoxypyridine.[15] In both cases, the deprotection of the benzyl ester by hydrogenolysis did not affect the polymer backbone, but the polymer properties (solubility, thermal stability, and hydrolytic degradation) were strongly impacted by the carboxylic acid functions. The high reactivity of OCA reduces the impact of the steric hindrance associated with the lateral group, something that has been shown to strongly reduce the reactivity of substituted 1,4-dioxan-2,5-diones.[2b] Indeed, among the two corresponding symmetric 1,4-dioxan-2,5-diones, only that deriving from malic acid (malide, Figure 3) has been studied up to now, and ROP

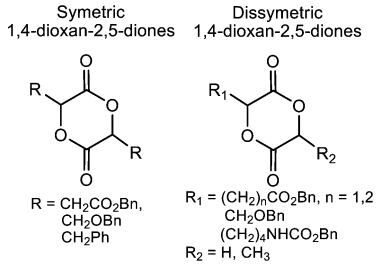


**Figure 3.** Symmetric and dissymmetric 1,4-dioxan-2,5-diones derived from natural $\alpha$-amino acids.

could not be achieved efficiently, even under forcing conditions (ROP with SnOct$_2$ as catalyst at 180 °C hardly reached 15% monomer conversion after 8 h).[6] To favor ROP, dissymmetric 1,4-dioxan-2,5-diones combining the functionalized hydroxyalkanoate unit with a glycolic or lactic unit have been used. But even with these less-encumbered monomers, the polymerization conditions can be harsh, in particular those bearing the lactic unit (most often in bulk at 140 °C using SnOct$_2$ as catalyst).[9] The best results were obtained with 1,4-dioxan-2,5-diones bearing a glycolic unit whose ROP has been achieved efficiently using the thiourea/sparteine pair at room temperature.[39,40] However, ROP of these dissymmetric 1,4-dioxan-2,5-diones lead to functionalization ratios of the polymer backbone only half of that accessible from OCA.

Block and random copolymerization of L-**gluOCA** with **lacOCA** allowed for the preparation of polymers of different compositions and distributions of the carboxylic acid groups along the polymer chain.[16] The controlled character of the polymerization, with transesterification side reaction occurring in very low extent if any, enabled the clean formation of block copolymers. The close reactivity of the two monomers resulted in regular distribution of the functional groups along the polymer chains in the random copolymers. Furthermore, the initiation of the ROP of L-**malOCA** and D-**malOCA** with PEG−OH led to the formation of amphiphilic block


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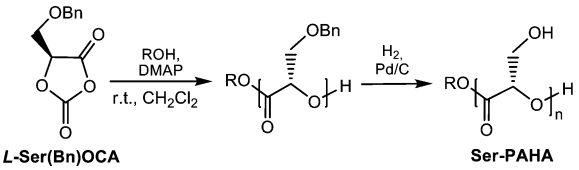
copolymers PEG-*b*-P(L-BMA) and PEG-*b*-P(D-BMA) capable of forming micelles in water.[41] The self-assembly of equimolar mixtures of these copolymers resulted in the formation of micelles of higher stability (CMC of $5.53 \times 10^{-3}$ mol/L compared to $1.23 \times 10^{-2}$ mol/L and $9.80 \times 10^{-3}$ mol/L for PEG-*b*-P(L-BMA) and PEG-*b*-P(D-BMA), respectively), thanks to the formation of stereocomplexes between the P(L-BMA) and P(D-BMA) enentiomeric blocks.

Water-soluble poly(α-hydroxyalkanoates) bearing lateral hydroxyl groups (**Ser-PAHA**) have been prepared by DMAP promoted ROP of **L-ser(Bn)OCA** initiated by an alcohol (molecular of macromolecular), followed by the deprotection of the pendant hydroxyl groups (Scheme 5).[18] Similarly to L-

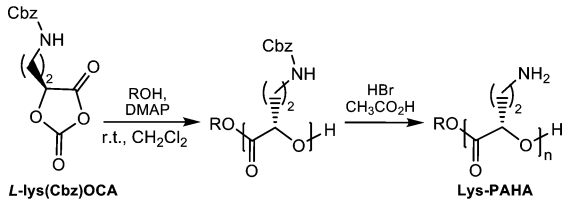
**Scheme 5. Preparation of Poly(α-hydroxyalkanoates) Bearing Lateral Hydroxyl Groups (Ser-PAHA) by ROP of L-ser(Bn)OCA**




**gluOCA** and **L-malOCA**, the polymerization is well controlled, leading to polymers of narrow molar distributions, including block copolymers with **lacOCA**. These highly hydroxylated poly(α-hydroxyalkanoate) are hardly available from the corresponding dioxanediones. The symmetric monomer could only copolymerize with lactide, and the amount of functionalized monomer incorporated was low (5%).[7] Better results were obtained with the corresponding dissymmetric 1,4-dioxane-2,5-dione, but as mentioned above, this approach enabled to introduce only one lateral hydroxyl group every two lactic acid units.[9]

The OCA derived from lysine (**L-lys(Cbz)OCA**) was similarly applied to the preparation of a poly(α-hydroxyalkanoate) featuring high concentration of pendant amino groups along the polymer backbone after deprotection in acidic conditions (Scheme 6).[20] The low solubility of this polymer

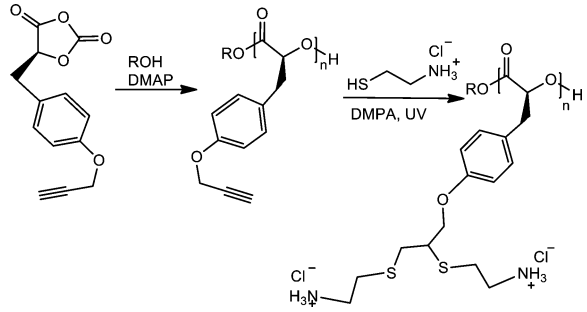
**Scheme 6. Preparation of Poly(α-hydroxyalkanoate) Bearing Lateral Amino Groups by ROP of L-lys(Cbz)OCA**




precluded characterization by SEC. However, the integrity of the polymer chains was supported by the relative integration of the chain end signals related to the polymer backbone in the $^1$H NMR spectrum.

Postpolymerization functionalization via click reactions is another practical use of the pendant functional groups that may be introduced thanks to OCA. In this respect, **L-thyr(alkynyl)-OCA** has been prepared and polymerized with DMAP as catalyst and an alcohol as initiator.[19a] The alkynyl group has been exploited to achieve chemical modifications, in particular via "click" reactions. A water-soluble polymer bearing a high concentration of ammonium groups is thus prepared via thiol−yne reaction, using 2 equiv of 2-aminoethanethiol hydrochloride (Scheme 7). Using PEG−OH to initiate the ROP of L-

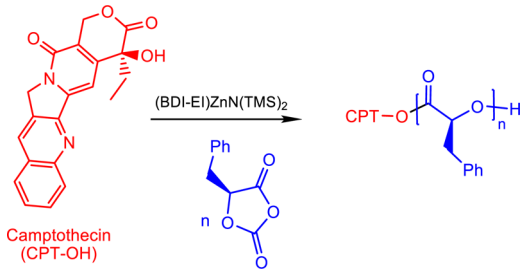
**Scheme 7. Preparation of the Polycationic Polyester from L-thyr(alkynyl)OCA**




**thyr(alkynyl)OCA**, amphiphilic block copolymers have also been prepared.[19b] The alkynyl lateral groups were also derivatized by Cu(I)-catalyzed azide−alkyne cycloaddition.

The mild conditions under which OCA polymerize have also been exploited to prepare drug-polymer conjugates by direct ROP mediated by a hydroxyl function of the drug. Such drug−polymer conjugates are attractive in drug delivery as they increase the encapsulation efficiency of hydrophobic drugs and reduce the initial burst. A conjugate of camptothecin (Cpt, an anticancer drug) and a polyester was prepared from L-**phenOCA** by ROP promoted by the combination of the drug and the complex (BDI-EI)Zn−N(TMS)$_2$ (Scheme 8). As

**Scheme 8. (BDI-EI)Zn−N(TMS)2/Cpt Mediated ROP of L-pheOCA**




mentioned before, successful ROP of the OCA is achieved with the tertiary alcohol function of camptothecin using the Zn derivative, enabling the preparation of conjugates with tuned properties.[17] ROP of the corresponding 1,4-dioxan-2,5-diones (phenyllactide) requires bulk polymerization at 180 °C with $SnOct_2$ in order to achieve high monomer conversions,[8] reaction conditions hardly compatible with the lactone function of camptothecin.

In conclusion, OCA appear as valuable alternatives to substituted 1,4-dioxan-2,5-diones for the preparation of well-defined and highly functionalized poly(α-hydroxyalkanoates). The first report of controlled ROP of an OCA, namely, **lacOCA**, dates back to less than 10 years. But a number of functionalized OCA deriving from natural hydroxy-acids or amino acids have already been reported, and their ROP has been achieved in a controlled manner, using different catalytic systems (mainly DMAP). Thanks to the high reactivity of OCA with nucleophiles, leading to ring opening followed by decarboxylation under very mild conditions, ROP occurs with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exceptional functional compatibility. A wide range of poly(α-hydroxyalkanoate) and copolymers thereof, bearing high ratios of functional groups (carboxylic acid, hydroxyl, amino), and drug−polymer conjugates have been reported.

The OCA technology already seems mature enough to be employed broadly. It is likely that it will be developed further in near future to prepare PAHA of diverse architectures and functionalities. Biological applications of these advanced materials will certainly continue to progress, in particular, in the field of nanomedicine.[10]

## ■ ASSOCIATED CONTENT

### Supporting Information

Tables S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.orgThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00376.

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### Notes

The authors declare no competing financial interest.

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