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## REVIEW

# Sourcing, thermodynamics, and ring-opening (co)polymerization of substituted $\delta$ -lactones: a review

Peter McMichael,<sup>a</sup> Xavier Schultze,<sup>\*b</sup> Henri Cramail,<sup>\*a</sup> and Frédéric Peruch<sup>\*a</sup>

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Environmental concerns have escalated due to the extensive production of polymers from fossil resources and the resultant issues in waste management and environmental pollution. With the increased demand for more sustainable polymers, studies on the ring-opening polymerization of cyclic esters have risen for the obtention of aliphatic polyesters, a relevant class of polymers with good mechanical performance, potential biodegradation and biocompatibility. Among them, substituted  $\delta$ -lactones are interesting building blocks since a significant number of these monomers can be biobased and bring specific properties lacking in other lactones. Due to unfavorable ROP thermodynamic parameters, the polymerization of  $\delta$ -lactones is challenging. However, various (co)polyesters have been synthesized from these lactones leading to valuable applications in drug delivery or thermoplastic elastomers. This review focuses on the way to obtain these lactones, their particular thermodynamic parameters and the different catalytic systems such as organocatalysts, alkali metals or metal complexes used to perform their ring-opening (co)polymerization. By providing an in-depth understanding of the synthesis and polymerization of substituted  $\delta$ -lactones, this review aims at exploring sustainable polyesters with improved properties and minimal environmental impact

## 1. Introduction

Plastics are an indispensable class of materials that have tremendously increased our daily-life comfort. They are used in a wide range of applications including packaging (40% in weight of total non-fiber plastic), building and construction (20%), automotive (9%), electronics (6%), and household goods (4%).(1) From 1950 to 2019, plastics production is estimated to have increased by nearly 230-fold, representing nowadays a world-wide production of more than 438 Mt of polymer resins, fibers and additives.(2,3)

However, the rampant production of this class of materials, mainly petroleum-based and non-biodegradable, associated with the increase of wastes they generate, have led to major issues this past decade. Among them, waste management's issues have greatly participated to the environmental pollution.(4–9)

For some applications such as single-used plastics, one solution for reducing plastic wastes is the replacement of these non-degradable polymers by biodegradable ones. This is also an important target for polymers contained in cosmetic formula since they can be released in the environment through wastewater. Biodegradable polymers are able to degrade into  $H_2O$ ,  $CO_2$  or  $CH_4$  and biomass, through the action

of naturally occurring microorganisms.(10,11) These polymers usually contain a hydrolytically cleavable bond such as ester, thioester, acetal, or carbonate function.

In this regard, aliphatic polyesters have gained an uprising popularity in the course of biodegradable, bio-sourced and biocompatible polymers. Polyesters such as poly(lactide) (PLA) or poly(caprolactone) (PCL) are already commercialized and have indeed showed to be biodegradable under certain conditions.(12–16) Polyesters possess a wide variety of properties making them suitable for many applications such as biomedicine, electronics or packaging.(17–20)

Aliphatic polyesters are produced by two methodologies. First, polycondensation which is performed through (trans)esterification of diacids (diesters) with diols in the melt at high temperature to remove the co-products and produce high molar mass polyesters.(21) In these conditions, high-energy consumption and long reaction times are often needed which is not ideal in terms of green chemistry. These drastic experimental conditions together with a lack of molar mass control made the ring-opening polymerization method (ROP) an attractive alternative to synthesize aliphatic polyesters. Indeed, ROP can generally proceed under smooth conditions (22) and the mechanisms involved exhibit a living feature thus allowing a rather good control of the molar masses, dispersity and chain-end functionality.(23–26) Moreover, various architectures and microstructures have been obtained by the mean of ROP or Ring Opening coPolymerisation (ROcP) of lactones, increasing the potential of this methodology.(23,24,27–29)

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Among the variety of lactones used to produce polyesters by ROP, substituted  $\delta$ -lactones have attracted a growing attention due to their renewable nature. This monomer family leads to low  $T_g$  amorphous polyesters bearing alkyl side chain substituents. Several studies report the use of substituted  $\delta$ -lactones to reduce the crystallinity of (co)polyesters which improve their degradability under certain conditions.(30–32) These monomers were also used as soft hydrophobic block in multi-block thermoplastic elastomers or in amphiphilic block copolymers for drug delivery applications.(28,33,34) While increasing the biobased content in such (co)polyesters, poly(substituted  $\delta$ -lactone)s have proven to induce a better encapsulation of hydrophobic drugs easing their formulation in water.(35,36)

In comparison to the unsubstituted  $\delta$ -valerolactone, these lactones possess harsh thermodynamic parameters due to the larger negative entropic change upon polymerization (37). As a consequence, the equilibrium monomer conversions are lower, and are strongly affected by the polymerization temperature and experimental conditions (monomer concentration notably).

Among the catalysts used for the ROP of substituted  $\delta$ -lactones, organocatalysts have appeared to be the most valuable candidates as they offer some advantages over metallic catalysts such as the use of lower reaction temperatures to promote the ring-opening of monomers. (38–40) By using organocatalysts, higher monomer conversions were thus achieved and polyesters of controlled structures

were synthesized.

In this review, a state of the art of the homopolymerization and copolymerization of substituted  $\delta$ -lactones by different polymerization mechanisms will be presented, focusing on the monomer conversion and polyester molar masses and microstructures. Some other polymerization methods such as ATRP, RAFT or thiol-ene coupling will also be discussed for the obtention of functionalized poly(substituted  $\delta$ -lactone)s.

## 2. General aspects of substituted $\delta$ -lactones

Figure 1 lists the substituted  $\delta$ -lactones that were studied for the ROP and ROCp. These lactones can be divided according to the position of the substituent (respectively  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ ) and its nature. For simplification,  $\delta$ -substituted  $\delta$ -lactones will simply be called  $\delta$ -lactones.

### 2.1. Sourcing and production

#### 2.1.1. Alkyl $\delta$ -lactones

Alkyl substituted  $\delta$ -lactones appear in many natural compounds such as peach, coconut, heated milk fat or cashew apples.(41–44) They are used as flavor compounds in perfumes, food additives and were even tried as complexing agent for starch.(45)

The most reported alkyl  $\delta$ -lactone,  $\delta$ -decalactone,  $\delta$ -DL, is mainly derived from fatty acids transformation by enzymes, Baeyer-Villiger oxidation of delfone (46,47) or from biomass extraction (*Cryptocarya massaia* tree) (48,49) It is considered

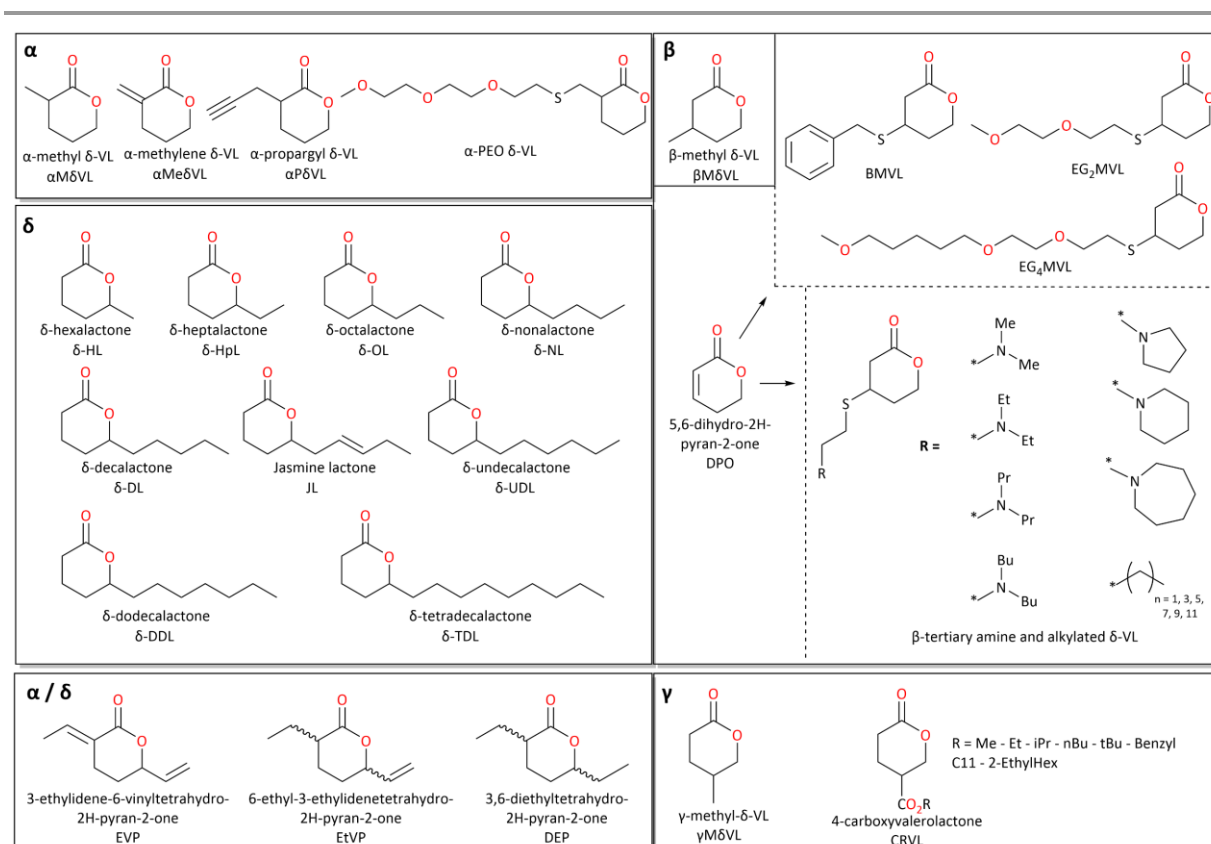


Figure 1 : Substituted  $\delta$ -lactones used in ROP.

to have a creamy, coconut, green and slightly fruity taste.

Among the strategies held to oxidize delfone, peroxyacids are mainly used (Figure 2). Environmentally more friendly solutions were also found with the use of hydrogen peroxide catalyzed by Sn-Beta zeolite with a yield of 86% of  $\delta$ -decalactone.(50)

Starting from a natural feedstock, a study performed by Rali *et al.* showed that hydro-distillation of the bark, heartwood and fruits of massoia tree afforded an oil with respectively 0.7, 1.2 and 1% yields containing up to 68.4% of C-10 massoia lactone (5,6-dihydro-6-pentyl-2H-pyran-2-one).(51) The double bond of this lactone can be reduced by enzymes, yeasts or isolated ene-reductase. High yields close to 100% can be achieved for the saturated massoia lactone (Figure 3).(52)

$\delta$ -dodecalactone can also be obtained from massoia trees, where the C-12 massoia lactone is present at a percentage of 17.4 and 13.4% in bark and heartwood oil, respectively. Another way to obtain  $\delta$ -DDL is by hydroxylation and lactonization of coriolic acid.(46)

$\delta$ -tetradecalactone can be obtained either by hydration of hydroxy or hydroperoxy linoleic acid, its  $\beta$ -oxidation and lactonization by enzymes,(53,54) or by extraction from coconut oil.(55)

$\delta$ -hexalactone,  $\delta$ -HL, can be derived from pineapple and is formed in Nature by acid-catalyzed intramolecular cyclization of  $\delta$ -hydroxycarboxylic acids as previously described.(56) Oxidation of 3-methyl-1,5-pentanediol by a laccase/TEMPO catalytic system could also lead to  $\delta$ -HL at >97% conversion and 92% yield.(57)

$\beta$ -methyl- $\delta$ -valerolactone ( $\beta$ M $\delta$ VL) has also been reported to be an interesting biosourced monomer. Hillmyer and coll. described a fully biochemical and a semisynthetic pathway to obtain this monomer readily for industrial applications (Figure 4).(58)  $\beta$ M $\delta$ VL can be obtained from direct fermentation of glucose and the dehydration and hydrogenation of mevalonate (an intermediate of fermentation). It can also be synthesized

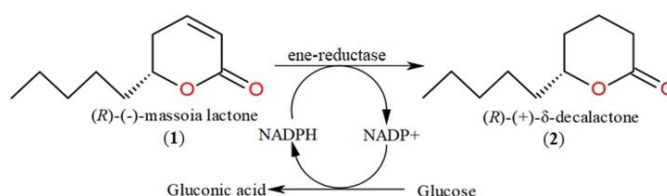


Figure 3 : OYE-mediated reduction of massoia lactone to (R)-(+)- $\delta$ -decalactone.(52)

from 3-methyl-1,5-pentanediol in presence of copper compounds at high temperature under hydrogen stream, yielding between 90 and 95% of  $\beta$ M $\delta$ VL.(59)

### 2.1.2. Functionalized substituted $\delta$ -lactones

Functionalized substituted  $\delta$ -lactones are also an interesting family of cyclic esters, as they can afford functional groups allowing various modifications and applications.

A fully synthetic method was performed to obtain  $\alpha$ -methylene- $\delta$ -VL from  $\delta$ -VL. Fastidious multiple steps reaction were needed to afford a colorless liquid with 56% yield after flash chromatography purification.(60,61) A PEO-functionalized lactone was synthesized using this lactone and a thiol functionalized PEO *via* thiol-ene addition in the presence of tributylphosphine. Yields between 85 and 95% were obtained.(62)

Other substituted  $\delta$ -lactones have been produced based on the modification of the  $\alpha,\beta$ -unsaturated  $\delta$ -valerolactone 5,6-dihydro-2H-pyran-2-one (DPO), that can be extensively found in plants, bacteria and fungi.(63)

A first example is the 3-mercaptovalerolactones synthesized by Waymouth and coll., by a one-step Michael addition of benzyl mercaptan and DPO at 80°C in presence of Et<sub>3</sub>N,

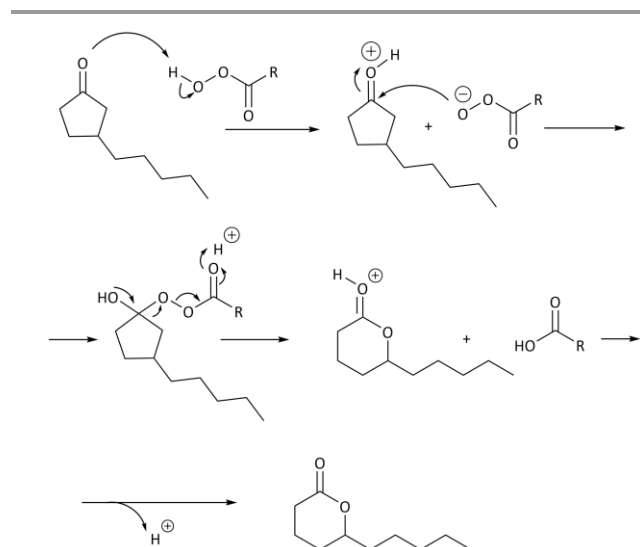


Figure 2 : Baeyer-Villiger oxidation of delfone into  $\delta$ -decalactone mediated by a peroxyacid.

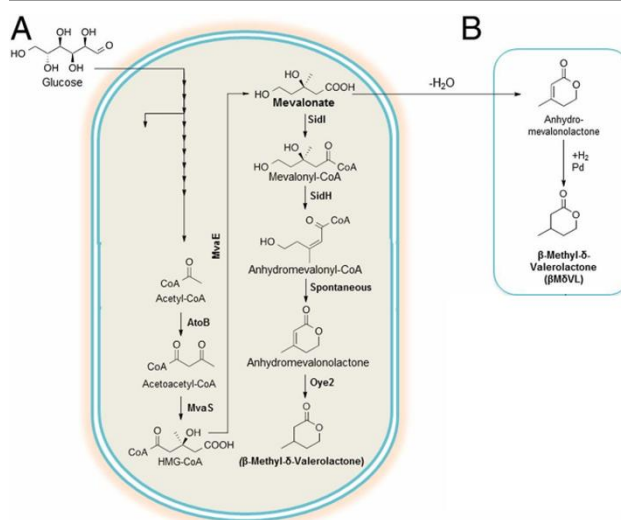


Figure 4 : (A) Total biosynthetic pathway for the production of  $\beta$ M $\delta$ VL. (B) A semisynthetic route to produce  $\beta$ M $\delta$ VL from mevalonate. Reproduced with permission from PNAS.

yielding 76% monomer.(64) 2 and 4 units of EO were also added on DPO for a respective yield of 54 and 44%.

Many  $\beta$ -substituted  $\delta$ -lactones with various tertiary amine and alkyl groups have also been synthesized (Figure 5). The synthesis pathway involved an equimolar reaction of DPO and aminothiol in the first case, and alkylthiol and DPO in presence of dimethylphenylphosphine (DMPP) in a second place, to obtain 100% conversion of functionalized  $\delta$ -lactones.

On  $\delta$ -position, the jasmine lactone is a  $\delta$ -decalactone with an unsaturation on the alkyl pendant chain which could be used for thiol-ene reaction. It is an FDA-approved food additive and can be found in Nature in jasmine flowers, tea, lily, ginger, or peach for example.(65) It can also be derived from  $\alpha$ -linoleic acid by enzymatic lactonization like alkyl  $\delta$ -lactones.(66–68)

Malic acid, an abundantly available renewable feedstock, has allowed the synthesis of gamma substituted  $\delta$ -VL with different carboalkoxy side chains (Figure 6).(69,70) 4-carboalkoxyvalerolactone with alkyl chain being methyl, ethyl, isopropyl, n-butyl and tert-butyl were synthesized in a multistep strategy. Coumalic acid was formed from a mixture of malic and sulfuric acids, then different alcohols were added, followed by a hydrogenation of the thus formed alkyl coumalate. Around 50% yield was obtained for each modification steps, meaning that only a low final amount of monomers can be recovered. 4-carbobenzyloxy, 4-carbo(2-ethylhexoxy), and 4-carboundecoxy- $\delta$ -valerolactones were also synthesized, from the reaction of methyleneglutaric acid with hydrobromic acid, cyclization with DIPEA and reaction with alkyl bromide in the presence of  $\text{Na}_2\text{CO}_3$ . Yields between 42 to 70% were obtained.

In the context of climate change,  $\text{CO}_2$  capture and valorization are two growing fields of investigation. An interesting approach has been described based on 3-ethylidene-6-vinyltetrahydro-2H-pyran-2-one (EVP) which has been synthesized *via* Pd-catalyzed telomerization of  $\text{CO}_2$  and butadiene (1,2 and 1,3) (produced from bio-based ethanol or butanediol) (Figure 7).(71–73) Moreover, the 2 alkene groups could be hydrogenated to give one alkene and one

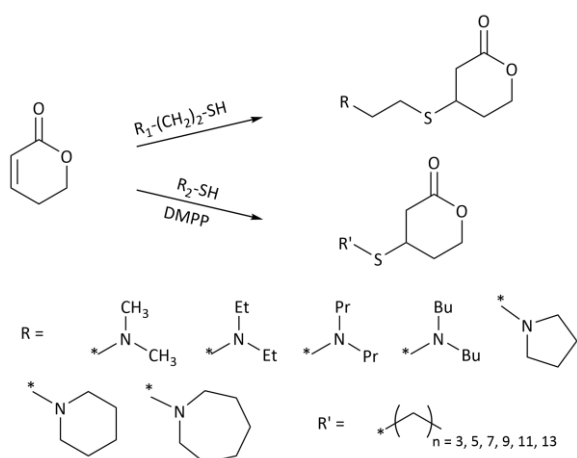


Figure 5 : One pot synthesis of  $\beta$ -tertiary aminated and alkylated substituted  $\delta$ -lactones.

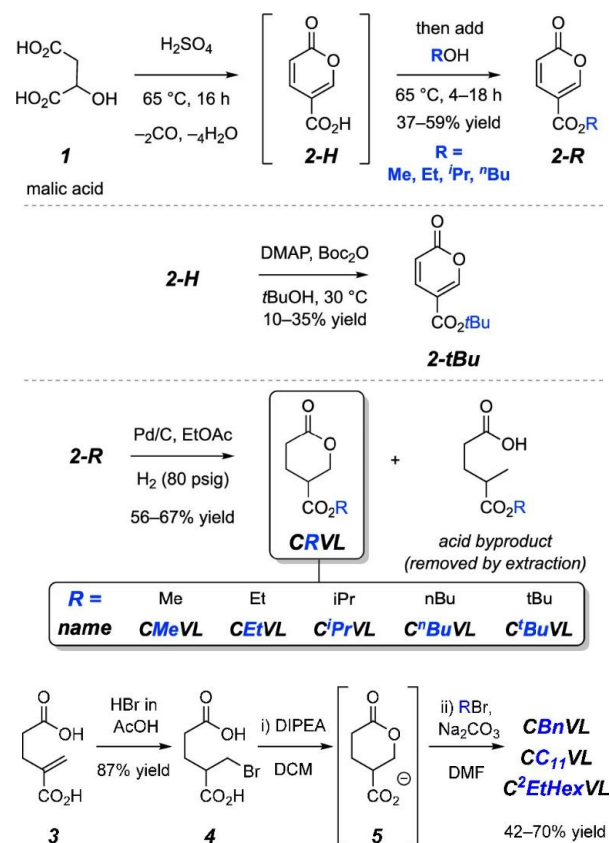


Figure 6 : Synthesis of 4-carboxyalkoxyvalerolactone. (69),(70)

Reprinted with permission from Fahnhorst GW, De Hoe GX, Hillmyer MA, Hoyer TR. 4-Carboalkoxylated Polyvalerolactones from Malic Acid: Tough and Degradable Polyesters. Copyright 2020 American Chemical Society

ethyl (EtVP) or a diethyl (DEP) lactone.(74,75) The first one could also be obtained through selectively reducing EVP using triethoxysilane and Stryker's reagent ( $[(\text{Ph}_3\text{P})\text{CuH}]_6$ ).(76)

A last interesting functionalized lactone is the propargyl functionalized  $\delta$ -VL ( $\alpha$ -propargyl- $\delta$ -VL,  $\alpha\text{P}\delta\text{VL}$ ).(77) Reaction of lithium N,N-diisopropylamide and  $\delta$ -VL in THF at  $-78^\circ\text{C}$  and the

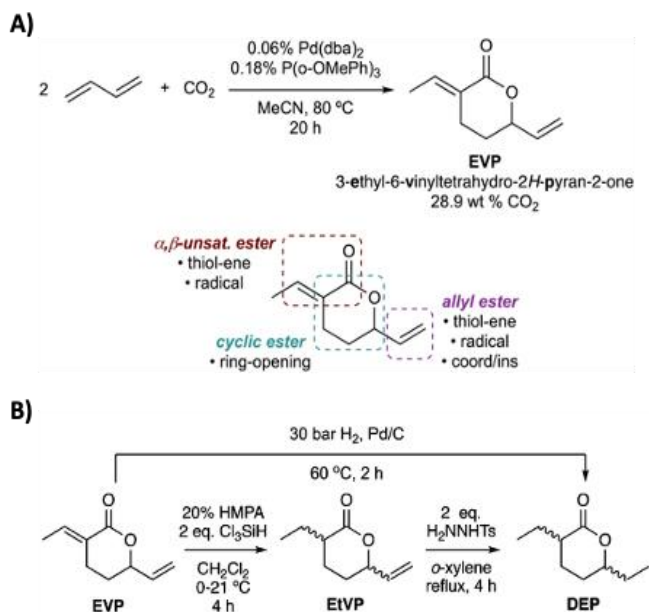


Figure 7 : (A) Synthesis of EVP from 1,3-butadiene and  $\text{CO}_2$ . (B) Examples of hydrogenation of EVP to yield EtVP and DEP. Reproduced from (75).

subsequent quenching with propargyl bromide solution in toluene allowed for the obtention of 74% yield of  $\alpha$ P $\delta$ VL, after distillation.

Noteworthy, substituted  $\epsilon$ -lactones have already shown to be interesting candidates as their polymerizability is close to non-substituted analogue.(78) However, compared to substituted  $\delta$ -lactones, few of them are biobased and industrially accessible.

## 2.2. ROP thermodynamics of substituted $\delta$ -lactones

The polymerization of cyclic monomers generally performed in solution is very sensitive to the monomer concentration, the type of catalysts and the temperature. A good tuning of these parameters is crucial to obtain high monomer conversion, control of the kinetics and of the polyester microstructure, notably. The polymerizability of a lactone is mainly governed by its ring size, as it drives its ring strain. Depending on the number of carbons in the ring, the nature and position of any substituent, the energy required to open the ring varies drastically. This energy is given by the Gibbs free energy of polymerization ( $\Delta G_p$ ) and indicates that a polymerization can occur thermodynamically when its sign is negative.

$$\Delta_{xy}G_p = \Delta_{xy}H_p - T\Delta_{xy}S_p$$

Where  $\Delta H_p$  and  $\Delta S_p$  are the enthalpy and entropy of polymerization and T the absolute temperature (in K). x and y denote the physical state of the monomer and polymer

This equation can be expressed under different forms to follow the feasibility of a reaction by including crucial parameters such as the equilibrium monomer concentration ( $[M]_{eq}$ , at  $\Delta G = 0$ ) and the ceiling temperature ( $T_c$ , temperature above which  $\Delta G > 0$ ). (37)

$$[M]_{eq} = \exp\left(\frac{\Delta H_p^\circ}{RT} - \frac{\Delta S_p^\circ}{R}\right)$$

$$T_c = \frac{\Delta H_p^\circ}{\Delta S_p^\circ + R \ln[M]_{eq}}$$

In the case of 6-membered lactones ( $\delta$ -lactones) such as  $\delta$ -valerolactone or D,L-Lactide, the enthalpy  $\Delta H_p$  is negative enough to enable the formation of polymer. Thereby, these monomers are readily polymerizable as demonstrated by the polymerization of lactide at an industrial scale to provide PLA (compostable in industrial compost). (79–81)

However, the presence of substituents on the 6-membered lactone disfavors the entropy of polymerization. Consequently, these lactones have a lower  $T_c$ , a higher equilibrium monomer concentration and thus a lower equilibrium monomer conversion. As reported by Schneiderman and Hillmyer, the presence and position of an alkyl chain substituent on the ring decreases the equilibrium conversion compared to  $\delta$ -VL (Figure 8). (82) Therefore, with respect to methyl substituted

$\delta$ -lactones, the equilibrium monomer conversions were calculated as a function of the substituent position as the following:  $\alpha$ M $\delta$ VL >  $\gamma$ M $\delta$ VL >  $\delta$ -HL >  $\beta$ M $\delta$ VL (96.5, 95.8, 92.1, 89.4% at RT and in bulk conditions; M $\delta$ VL stands for methyl- $\delta$ -valerolactone, HL for hexalactone).

In addition, as the molar mass of the monomers increase with the size of the substituent, the  $T_c$  in bulk decreases accordingly, to reach the lowest value of 116°C for  $\delta$ -tetradecalactone ( $\delta$ -TDL). At  $[M]_0 = 1M$ , because of close thermodynamic parameters of n-alkyl  $\delta$ -lactones, less difference of ceiling temperatures can be observed. However, at this concentration, ceiling temperatures are low and the equilibrium monomer conversions too (Figure 8 B). Key thermodynamic parameters and values of some alkyl  $\delta$ -lactones are summarized in Table 1.

Interestingly, 4-carbomethoxyvalerolactone (CMeVL) has been found to possess similar thermodynamic parameters than  $\gamma$ M $\delta$ VL and thus, nearly identical equilibrium monomer conversion. (69)

Finally, valuable works on the thermodynamic parameters of EtVP and DEP, 6-membered lactones with two substituents, reported lower ceiling temperatures than  $\delta$ -HL in bulk conditions, with respectively 138°C and 110°C compared to 170°C. (76,83)

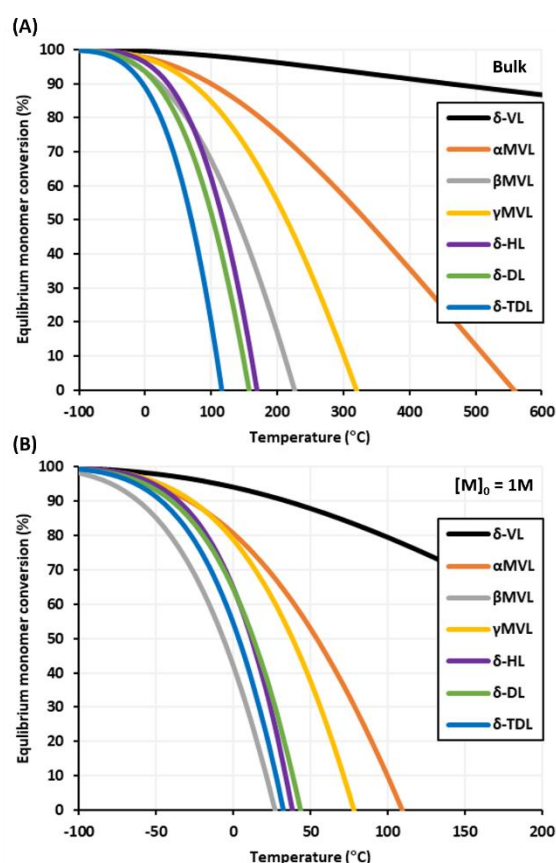


Figure 8 : Alkyl substituted  $\delta$ -lactones equilibrium monomer conversion as a function of the temperature, according to data from Schneiderman and Hillmyer (82). (A) Bulk (B) At  $[M]_0 = 1M$ .

Table 1 : Thermodynamic parameters of some alkyl  $\delta$ -lactones (82)<sup>a</sup>State refers to the state of monomer and polymer; l refers to liquid, g to glassy, a to amorphous, <sup>b</sup>T<sub>c</sub> calculated for bulk condition, <sup>c</sup>[M]<sub>eq</sub> calculated at 273K

	$\delta$ -VL	$\alpha$ M $\delta$ VL	$\beta$ M $\delta$ VL	$\gamma$ M $\delta$ VL	$\delta$ -HL	$\delta$ -DL	$\delta$ -TDL
Monomer							
State <sup>a</sup>	l-g	l-a	l-a	l-a	l-a	l-a	l-a
$\Delta H_p$ (kJ/mol)	-10.5	-13	-13.8	-15.8	-19.3	-17.1	-16.8
$\Delta S_p$ (J/mol·K)	-15	-34	-46	-45	-62	-54	-55
T <sub>c</sub> (°C) <sup>b</sup>	> 1000	558	226	330	170	158	116
[M] <sub>eq</sub> (mol/L) <sup>c</sup>	3.9·10 <sup>-2</sup>	0.314	0.963	0.381	0.717	0.74	0.85

The low T<sub>c</sub> of polyesters obtained from 6-membered lactones can be conveniently exploited to recycle the monomer by depolymerization at T>T<sub>c</sub>. Cederholm and Odellius showed that a polyester of  $\delta$ -DL that reached equilibrium monomer conversion, depolymerizes from 89% conversion to 30% conversion in 3h at 110°C.(84) The depolymerization can be limited even at high temperature by copolymerizing  $\delta$ -DL with higher T<sub>c</sub> monomers like  $\epsilon$ -CL or  $\epsilon$ -DL, allowing the end-capping of the polymer chains. In other words, the depolymerization of these monomers can be achieved on purpose to recycle polyesters by increasing the temperature and adding an external nucleophile.

### 3. Homopolymerization of substituted $\delta$ -lactones

$\delta$ -valerolactone is a 6-membered lactone that has commonly been used in homo and co-polymerizations. It has quite the same polymerizability than  $\epsilon$ -CL, which has however received much more attention in the field of ROP. Coordinative, enzymatic, cationic and anionic ROP of  $\delta$ -VL have all been reported to readily produce polyesters of high molar masses at high temperatures or under mild conditions.(85–93)

However, as mentioned in the second part, the introduction of a substituent on the  $\delta$ -VL ring induces a modification of the thermodynamic parameters, thus modifying the monomer polymerizability. Indeed, substituted  $\delta$ -lactones have low ceiling temperatures. Therefore, homopolymerization temperatures of these lactones should remain as low as possible to obtain the highest monomer conversion. In addition, polymerization in solution should be limited to high monomer concentrations due to high monomer equilibrium concentrations.

These crucial parameters have restricted the scope of catalysts used for the ROP of substituted  $\delta$ -lactones. Indeed, coordination catalysts often require high temperatures to be active and are hardly applicable for the homopolymerization of those lactones.

#### 3.1. Metal-based catalysts

The metal-based catalysts used for the ROP of substituted  $\delta$ -lactones are summarized in Figure 9.

##### 3.1.1. Coordination-insertion catalysts

ROP of  $\delta$ -HL has been described by Soum and coll, in the presence of lanthanum isopropoxide (La(OiPr)<sub>3</sub>).(94) Interestingly, this catalyst has proven to activate  $\delta$ -HL at 21°C in a 70:30 v/v mix of DCM/toluene. The conversion reached up to 78% within 23h, affording a p( $\delta$ -HL) with a maximum M<sub>n,exp</sub> of 5500 g/mol and a narrow dispersity ( $\bar{D}$  = 1.3), while 10000 g/mol was targeted.

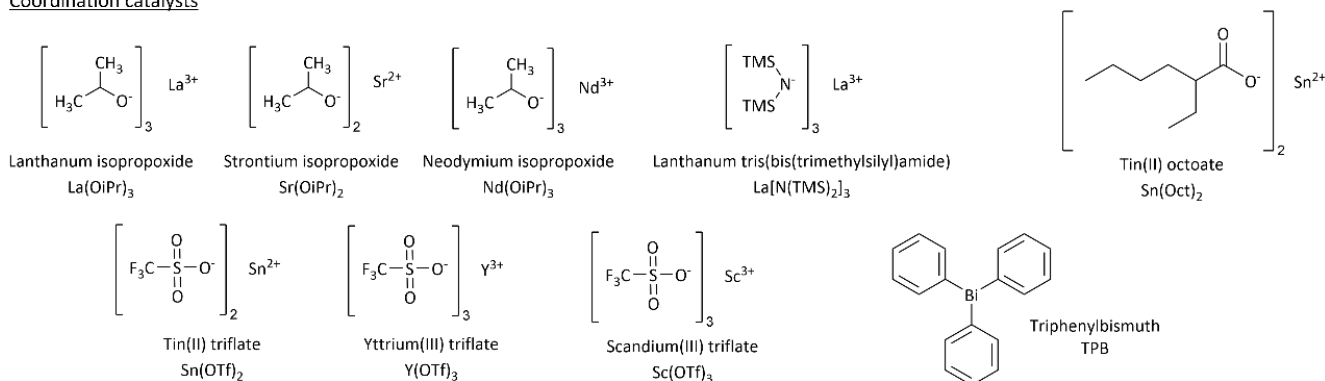
More recently, strontium isopropoxide was used as initiator/catalyst with or without n-dodecanol as co-initiator for the ROP of  $\delta$ -HL and  $\delta$ -DL at RT.(95) It has been shown to have a better activity than lanthanum isopropoxide for  $\delta$ -HL, as an 82% conversion and a molar mass of 5000 g/mol could be reached in 15 min using a co-initiator at a  $\delta$ -HL concentration of 4 mol/L in toluene. Furthermore, a dispersity of 1.16 was obtained. However, in the absence of the co-initiator, a poor conversion and a higher dispersity was obtained in the same reaction time.  $\delta$ -DL ROP with a co-initiator achieved 52% conversion in the same conditions as previously mentioned, with also a low dispersity ( $\bar{D}$  = 1.16). Noteworthy, with this catalyst,  $\delta$ -VL and  $\epsilon$ -CL ROP exhibited uncontrolled polymerization with dispersities above 5.

Y(OTf)<sub>3</sub> and La(N(TMS)<sub>2</sub>)<sub>3</sub> were also tried as catalysts for the ROP of  $\delta$ -HL.(96) No conversion at RT and less than 50% conversion were obtained in optimized conditions (31% for yttrium triflate at 100°C and 44% for La(N(TMS)<sub>2</sub>)<sub>3</sub> at 60°C).

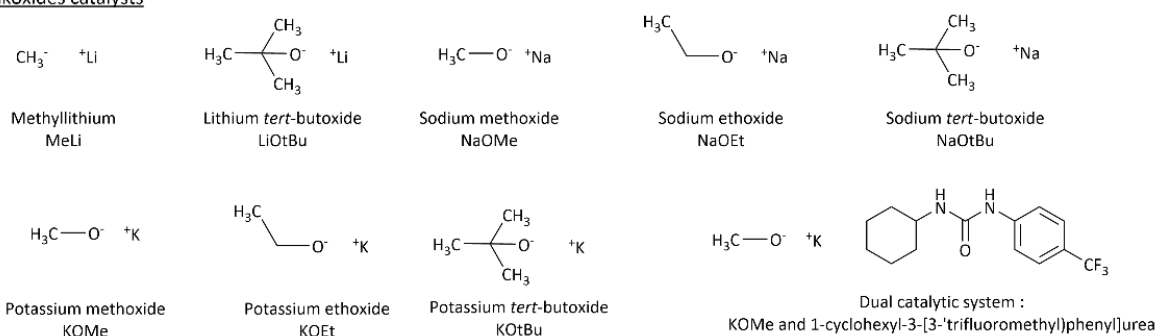
Neodymium isopropoxide (Nd(OiPr)<sub>3</sub>) has been described for the ROP of  $\delta$ -DL and  $\delta$ -DDL at 4°C.(97) Reactions proceeding with 150 eq. of monomer for 1 eq. of Nd(OiPr)<sub>3</sub> led to pDL and pDDL of 9 kg/mol ( $\bar{D}$  = 1.26) and 27 kg/mol ( $\bar{D}$  = 1.16) respectively after a long polymerization time (168h). Poor control of the molar masses was thus witnessed along with low conversion, close to 5% for  $\delta$ -DL and around 35% for  $\delta$ -DDL.

Sn(OTf)<sub>2</sub> was used at 3 mol% for the homopolymerization of  $\alpha$ -propargyl  $\delta$ -VL initiated by ethanol at RT in bulk.(77) More than 90% conversion was obtained in 48h, yielding polymers with molar masses ranging from 6 to 20 kg/mol and a narrow dispersity (1.13). The linear increase of molar masses against

## Coordination catalysts



## Alkali metal alkoxides catalysts

Figure 9 : Metal-based catalysts used for the ROP of substituted  $\delta$ -lactones.

conversion and the good agreement between theoretical and experimental molar masses demonstrated the control of the reaction. Extended reaction time enabled the full monomer conversion, with a slight increase of the polyester dispersity (1.3 – 1.4).

## 3.1.2. Alkali metal alkoxide catalysts

Alkali metal alkoxides have also been employed for the ROP of  $\delta$ -HL.<sup>(96)</sup> Sodium methoxide ( $\text{NaOMe}$ ), sodium *tert*-butoxide ( $\text{NaOtBu}$ ) and potassium methoxide ( $\text{KOMe}$ ) were used at 1 eq. for the ROP of 10 eq. of  $\delta$ -HL at different temperature in bulk.  $\text{NaOMe}$  has proven to be the most efficient catalyst as an astonishing full conversion could be obtained at RT, 60°C and 100°C within 18h. This result seems surprising considering the monomer equilibrium conversion being at around 80% conversion at 100°C. A higher monomer/catalyst ratio (i.e.  $[\text{M}]_0:[\text{Cat}] = 33:1$ ) led to a decrease of the conversion at RT (35% in 18h) and a lowered kinetic of polymerization, but still achieved a full conversion at 60°C and 100°C. Regarding molar masses and dispersity, it appeared that narrow dispersity and a good match between theoretical and experimental molar masses were obtained at RT, whereas the dispersity gradually increased with temperature increase. Furthermore, at 100:1 monomer to catalyst ratio, molar masses levelled off around 3000 g/mol due to transesterification side-reactions.  $\text{NaOtBu}$ ,  $\text{KOMe}$  and  $\text{KOtBu}$  catalysts enabled the conversion of respectively 88, 85

and 78% of  $\delta$ -HL within 18h for 10:1 ratio at RT. In all cases, molar masses remained below 3 kg/mol.

Interestingly, Li and coll. also investigated  $\text{KOMe}$  with or without urea for the room temperature ROP of  $\delta$ -HL at high concentration in THF (6M) (Figure 10).<sup>(33)</sup> 58% conversion was reached in 2h, leading to a polymer with dispersity of 1.42 with  $\text{KOMe}$  alone. By introducing an urea bearing a trifluoromethylphenyl substituent, 86% conversion could be obtained within 10 min and yielded a polymer of 12 kg/mol and narrow dispersity. A polymer of higher molar mass could also be obtained in bulk, with  $M_n = 42$  kg/mol and still narrow dispersity (1.1). Thus, a dual catalytic system seems to be an interesting tool to better control the ROP of  $\delta$ -substituted  $\delta$ -lactones and achieve high molar masses.

3-ethylidene-6-vinyltetrahydro-2H-pyran-2-one (EVP) and its hydrogenated conjugates have been the focus of several recent publications discussing their homopolymerization with different metal catalysts. Indeed,  $\text{Sc}(\text{OTf})_3$ <sup>(98)</sup>,  $\text{La}[(\text{N}(\text{TMS})_2)]_3$ ,  $\text{Sn}(\text{Oct})_2$ ,  $\text{Y}(\text{OTf})_3$ ,  $\text{Nd}(\text{OTf})_3$ ,  $\text{Y}[\text{N}(\text{TMS})_2]_3$ , and a zinc metal complex<sup>(96)</sup> failed to yield homopolymers from EVP. Interestingly, the hydrogenation of the  $\alpha,\beta$ -unsaturated group has given monomers with a different polymerization behavior. Sodium methoxide at high loading (10 mol%) has shown to allow the polymerization of EtVP at 72% conversion at RT.<sup>(74)</sup><sup>(75)</sup> However, only a low molar mass could be obtained due to the high quantity of catalyst/initiator needed. A low



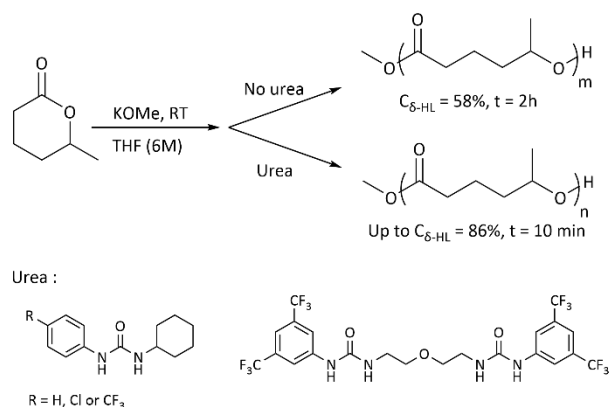


Figure 10 : ROP of  $\delta$ -hexalactone catalyzed by KOMe with or without an urea as co-catalyst.

glass transition ( $-39^\circ\text{C}$ ) was measured, close to other alkyl substituted  $\delta$ -lactone polymers.

Another study described the use of sodium and potassium methoxide as catalysts for the ROP of EtVP.(83) BnOH was used as initiator for a targeted DP of 50 and the reaction proceeded at  $-25^\circ\text{C}$  in a minimum volume of THF. 92 and 86% conversions were respectively achieved in 24h with surprising molar masses of 500 kg/mol and 70 kg/mol, respectively. The authors mentioned that only a small amount of catalyst was soluble in THF, leading to only few anionic species able to deprotonate alcohol moieties thus explaining the low initiation rate and the high molar masses obtained. NaOMe catalyzed ROP showed the narrowest dispersity ( $\mathcal{D} = 1.17$ ) while a bimodal distribution and a dispersity of 2.27 were obtained for KOMe catalysis, suggesting a competitive dual initiation of KOMe and BnOK. Without alcohol, KOMe catalyzed ROP of EtVP showed a 94% conversion resulting in a polymer with  $M_n = 440$  kg/mol and a narrow dispersity. This polymer appeared transparent, with excellent flexibility and ductility. Finally, complete recyclability of pEtVL could be obtained in a 1M solution of toluene in the presence of  $\text{La}[\text{N}(\text{TMS})_2]_3$  at  $120^\circ\text{C}$  in only 2h. Indeed, thermodynamic calculations highlighted a lower ceiling temperature than  $\delta$ -HL, reaching  $138^\circ\text{C}$  for EtVP and  $110^\circ\text{C}$  for DEP in bulk and  $18.3^\circ\text{C}$  at 1M for EtVP.

Potassium *tert*-butoxide ( $\text{KO}^t\text{Bu}$ ),  $\text{NaO}^t\text{Bu}$ , and lithium *tert*-butoxide ( $\text{LiO}^t\text{Bu}$ ) were also tried as catalysts for the ROP of EtVP under the same polymerization conditions as described above.(83) 86% conversion and molar masses of 214 and 31 kg/mol were obtained using the first two catalysts but led to bimodal distributions.  $\text{LiO}^t\text{Bu}$  was reported as a less reactive catalyst but with a good polymerization control as a conversion of 48% and a polymer of 12.7 kg/mol and 1.11 dispersity were obtained.

Alkali metal alkoxides have also been tested for the ROP of DEP in 48h under the previously reported conditions.(76) NaOMe and NaOEt showed to convert DEP at 88% and led to polymers with molar masses around 175 kg/mol and 1.15 dispersity. NaOtBu enabled the same conversion but led to polyester with a broader dispersity and lower molar mass ( $M_n = 25.8$  kg/mol and  $\mathcal{D} = 1.33$ ). Potassium-based catalysts also permitted conversions up to 88%. Molar masses

interestingly decreased with the size of the alkoxides ( $M_n$  for KOMe/KOEt/ $\text{KO}^t\text{Bu} = 330/98/28$  kg/mol). Lithium-based catalysts was reported as not effective for the ROP of DEP as a maximum of 16% conversion was obtained.

Finally, the use of 1-cyclohexyl-3-phenylurea as a co-catalyst with NaOMe at room temperature has been reported to be effective for the ROP of DEP.(74) 74% conversion was obtained in 24h using NaOMe/Urea = 3/1 and molar masses of 4.2 kg/mol were achieved.

To conclude, coordination-insertion mechanism has only afforded low molar masses polyesters of alkyl  $\delta$ -lactones ( $M_n < 6$  kg/mol) and, in most cases, monomer equilibrium conversion was not achieved (maximum of 82% conversion). On the other hand, alkali metal alkoxides appeared to allow for full monomer conversion within one day at room temperature but yield low molar mass polyester ( $M_n < 4$  kg/mol). Promising results came with the introduction of urea as a co-catalyst. It was shown to greatly enhance the control of the ROP and allowed for the synthesis of high molar masses polyesters ( $M_n = 41.7$  kg/mol). Moreover, recent works have shown the effective use of alkali metal alkoxides at  $-25^\circ\text{C}$  for the ROP of EtVP, giving in some cases high molar masses and narrow dispersity with and without initiator (up to 530 kg/mol and dispersity  $< 1.2$ ).

### 3.2. Organocatalyzed ROP of substituted $\delta$ -lactones

With the rise of organocatalysts, new possibilities appeared for the polymerization of substituted  $\delta$ -lactones in milder conditions. Catalysts used for the ROP of substituted  $\delta$ -lactones are summarized in Figure 11.

#### 3.2.1. Enzymatic ROP

The first enzymatic ROP of alkyl  $\delta$ -lactones was reported by Dong *et al.* in 1999 with lipase PSL (*Pseudomonas sp.*).(99) Both  $\delta$ -DL and  $\delta$ -DDL were polymerized in bulk at  $60^\circ\text{C}$ ; conversion reached respectively 87% and 78% to yield polymers with molar mass of 9000 and 7900 g/mol and dispersity values around 1.15-1.20 after 480h, respectively.

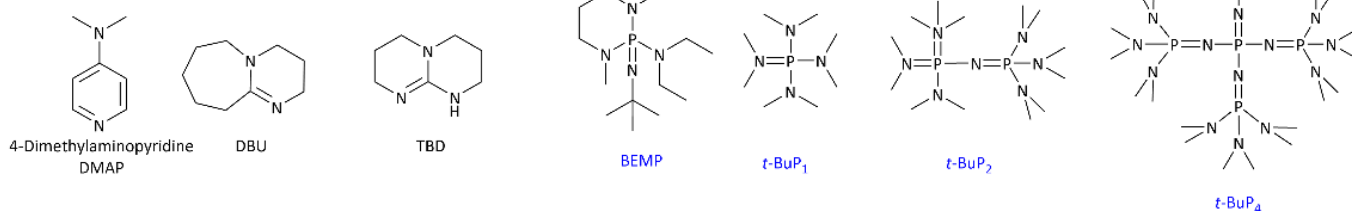
Similarly,  $\delta$ -HL was homopolymerized using *Candida Antarctica* enzyme.(100) Oligomers of 920 g/mol were obtained in bulk at  $60^\circ\text{C}$  in 24h, for a conversion of only 54%. In order to increase molar masses, copolymerization with  $\epsilon$ -caprolactone and other non-substituted monomers were performed in several organic solvents. The highest molar mass (9300 g/mol) was obtained in heptane at  $45^\circ\text{C}$ , using 12-dodecanolide as comonomer for a conversion of 46% of  $\delta$ -HL and of 100% of 12-dodecanolide in 8h. However, control of the reaction suffered from the presence of water initially brought by the lipase, which acted as an initiator. Thus, a dispersity of 2.3 was obtained.

#### 3.2.2. Organic bases

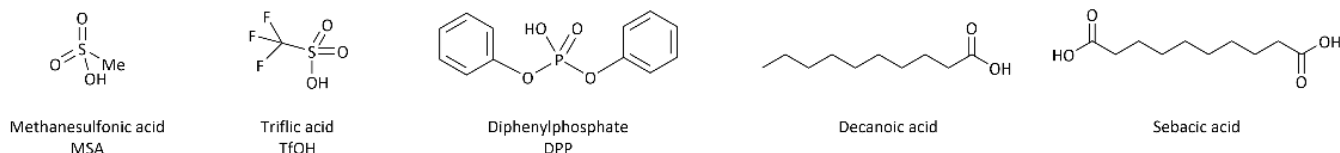
##### TBD catalyzed ROP of substituted $\delta$ -lactones

TBD is a strong guanidine base firstly reported by Hedrick, Waymouth and coll. in 2006 for the ROP of Lactide.(101) Contrary to a general base catalyst mechanism, TBD has been

## Organic bases

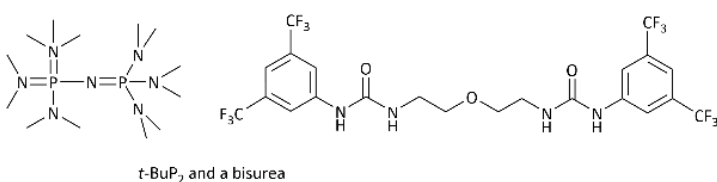


## Brønsted acids



## Phosphazene bases

## Dual catalytic system

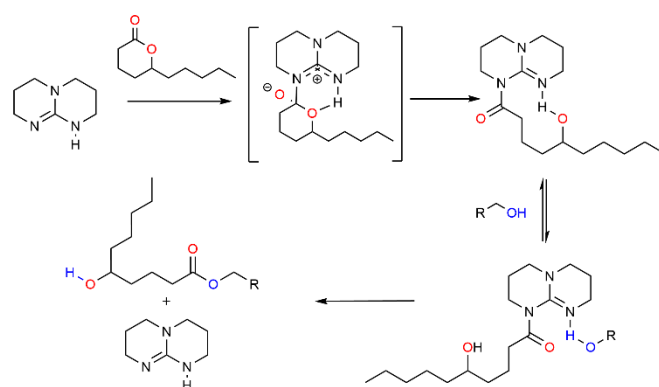
Figure 11 : Organic catalysts used for the ROP of substituted  $\delta$ -lactones.

described to be a bifunctional activator, performing a nucleophilic attack of the imine moieties on the carbonyl of the monomer to form a zwitterionic species, as the proton of the secondary amine transfers to the alkoxy oxygen. An amide is thus formed and hydrogen-bonding with an alcohol allows for the esterification of this amide to generate an ester and TBD (Figure 12).

This organocatalyst proved to be excellent for Lactide polymerization, reaching low dispersity and full conversion in 20 seconds in DCM for only 0.1 mol.% of catalyst vs the monomer. For  $\delta$ -valerolactone, 0.5 mol.% of catalyst was needed to obtain 91% conversion, still with a dispersity below 1.1 in 30 min. In addition to be highly active, a way to recover TBD by  $\text{CO}_2$  treatment was reported by Cota *et al.* allowing for a more eco-respectful synthesis.(102)

Consequently, in 2012, Martello *et al.* described the first ROP of  $\delta$ -DL using TBD.(103) The authors demonstrated the effectiveness of ROP of this lactone in bulk and at RT using benzenedimethanol (BDM) as initiator. First, an important study was performed to measure the equilibrium monomer concentration as a function of temperature and the overall thermodynamic and kinetic parameters. For instance, the equilibrium conversion was equal to 88% in bulk at room temperature. At  $100^\circ\text{C}$ , less than 50% conversion was obtained whereas 90% was reached at  $7^\circ\text{C}$ . From these reactions, the  $[\text{M}]_{\text{eq}}$  was calculated to be 0.74 M at room temperature. At RT, 80% conversion was reached within 10h.

Control of the molar masses at this stage of the reaction was confirmed by a linear relationship between molar masses and conversion, as monitored by  $^1\text{H}$  NMR. A pseudo-first order reaction was evidenced with a  $k_{\text{app}} = 0.249 \text{ h}^{-1}$ . Importantly, the

Figure 12 : Bifunctional mechanism of TBD during the ROP of  $\delta$ -decalactone.

molar mass dispersity measured by SEC in  $\text{CHCl}_3$  was kept below 1.25 in agreement with computational calculations that show the lower rate constant of intermolecular chain-transfer vs the polymerization one. This good polymerization control allowed the authors to achieve a high molar mass dihydroxytelechelic poly( $\delta$ -decalactone) (83 kg/mol).

Polymerization of  $\delta$ -HL has also been deeply studied by Schubert and coll. through TBD catalysis.(104) In toluene at RT, the authors varied the monomer concentration and the amount of catalyst. Unsurprisingly, conversion was higher for concentrated solution and levelled off at 83% for concentrations above 3 M. Monomer equilibrium concentration was determined to be 0.55 mol/L at RT. For a fixed concentration of 4 M and a targeted DP of 200, a maximum conversion of 73% was obtained in 2h for 8 eq. of

catalyst vs initiator, while 2 eq. gave 15% in 48h. A same molar mass of 9 kg/mol was obtained at 6 or 8 eq. of catalyst for a final conversion of 65%. While  $\delta$ -HL is a racemic mixture, low intensity scattering reflexes were obtained in WAXS analysis of a 6 kg/mol p( $\delta$ -HL). This feature demonstrates that the chains can pack to form crystalline domains (*i.e.*, 8%).

Polymerization of PEO functionalized  $\delta$ -VL (substituted in  $\beta$  position) was performed using TBD as a catalyst. Benzyl mercaptan, EG<sub>2</sub> and EG<sub>4</sub> substituted  $\delta$ -VL were polymerized in the presence of benzyl alcohol with 5 mol% TBD in DCM, toluene and in bulk. Polymerization in DCM led to no conversion even at high monomer concentration. Ring-opening polymerization at a concentration of 1M in toluene, afforded low conversions ranging from 20 to 58% with molar masses between 2.5 and 4.6 kg/mol in accordance with the unfavored thermodynamic parameters of substituted  $\delta$ -lactones. Higher conversions were obtained in bulk at 25°C with 60 to 70% monomer conversions. However, retro-Michael reactions occurred and led to lower molar masses than the targeted ones. Indeed, thiol-ene reaction on the endomethylene cyclic  $\delta$ -VL did not afford stable adduct. As reported by Li *et al.*, the use of exo-methylene cyclic  $\delta$ -lactone led to the formation of a stable adduct and the controlled ROP of PEO-functionalized  $\delta$ -lactone (described in 3.2.3).(62)

Due to its biosourced nature and large-scale production,  $\beta$ M $\delta$ VL received more attention than  $\alpha$  and  $\gamma$ M $\delta$ VL. p( $\beta$ M $\delta$ VL) with molar masses between 4 and 70 kg/mol and dispersities below 1.3 could be obtained in 1h at RT in presence of TBD and benzyl alcohol.(58) According to DSC analysis, an amorphous polymer was obtained even for the isotactic p((-)- $\beta$ M $\delta$ VL).(105)

The first homopolymerization of EVL was reported by Eagan and coll. who managed to form a pEVL using TBD as a catalyst (

Figure 13 A).(106) Various amounts of catalyst were tested in bulk conditions and at room temperature. Quite similar results were obtained with yields ranging from 15 to 57%. In addition, the authors described a competition between vinylogous 1,4-conjugate Michael addition and ROP leading to a hybrid brush-like polymer. Consequently, low molar masses and high dispersity were obtained.

EtVP has shown to polymerize in bulk using TBD with 3-phenylpropanol (PPA) as initiator at RT ([TBD]:[PPA]=5:0.5) (Figure 13 B).(74,75) TBD catalysis afforded a pEtVP of 13.6 kg/mol ( $\bar{M}_w/\bar{M}_n = 1.32$ ) with 78% conversion in 3 days.  $T_g$  of pEtVP was reported to be -39°C. Lower conversion were observed for DEP in the same conditions with a 46% conversion. A lower molar mass of 5.8 kg/mol was obtained.

### Other organic bases

As TBD is an effective catalyst for the ROP of substituted  $\delta$ -lactones, few reports mentioned the use of other organic bases.

The phosphazene base BEMP was tried for the bulk homopolymerization of  $\delta$ -HL initiated by BnOH.(96) No conversion was obtained at room temperature and only a low

conversion of 15% was achieved at 60°C in 2h, with no further reaction after this time.

Another phosphazene base was used in association with an urea for the homopolymerization of  $\delta$ -HL initiated by BDM in a minimum volume of THF. Interestingly, the dual catalytic system *t* BuP<sub>2</sub>/Urea was reported to be highly effective and to achieve high molar masses poly( $\delta$ -HL).(33) Indeed, compared to other catalytic systems, 86% conversion could be reached in 20 min, affording a polymer of 100 kg/mol and 1.09 dispersity. Dual catalytic systems based on a strong base and an urea or a thiourea have been deeply studied for the catalysis of lactide, leading to fast reaction with excellent control.(107–109) This recent work might allow the more common use of such catalytic system for the obtention of high molar masses  $\delta$ -substituted  $\delta$ -VL polymers.

As a consequence of the unfavored thermodynamic parameters brought by its two stabilizing substituents, EVP has failed to form a polymer using DMAP, DBU, BEMP, or *t*-Bu-P<sub>4</sub>.(96)

*t*-BuP<sub>4</sub> was however an effective catalyst for the ROP of EtVP.(83) In a small quantity of THF ([EtVP]<sub>0</sub> = 5.82M) using benzyl alcohol at -25°C, ROP of EtVP with P<sub>4</sub>-*t*-Bu was achieved with a 92% conversion affording a polymer with a molar mass of 11.5 kg/mol and a dispersity of 1.16 within 12h. Without initiator, a polymer with a  $M_n$  of 246 kg/mol was obtained but the reaction seemed uncontrolled as the dispersity was 2.4. Authors hypothesized that deprotonation of acidic proton of EtVP by *t*-BuP<sub>4</sub> could have generated reactive anionic species able to initiate the ROP of EtVP.

The fully saturated DEP was also polymerized in the

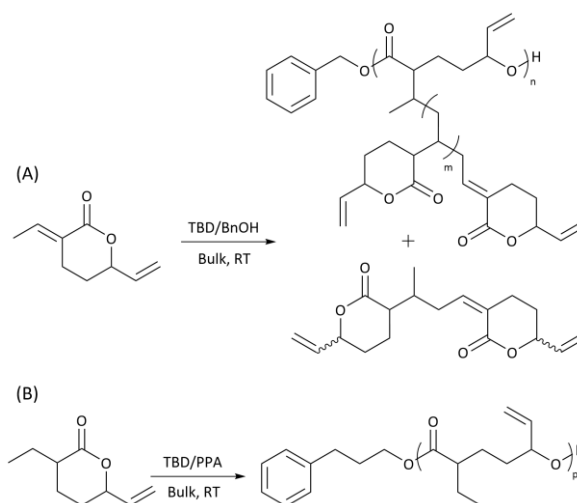


Figure 13 : Effective ROP of EVP and EtVP catalyzed by TBD.

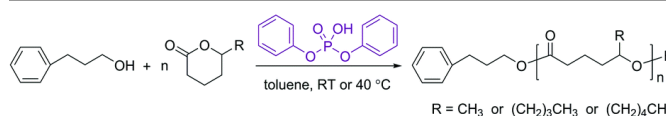


Figure 14 : Schematic illustration of DPP-catalyzed ROP of alkyl  $\delta$ -lactones. (112)

presence of *tert*-Bu-P4 in the same conditions as described above.(76) Controlled ROP was achieved using BnOH as initiator, giving an experimental molar mass close to theoretical one, but limited to 20 kg/mol. A maximum of 88% conversion could be obtained at -25°C and was in accordance with the lower ceiling temperature of DEP compared to EtVP. The less basic *t*-Bu-P<sub>1</sub> and *t*-Bu-P<sub>2</sub> have respectively shown no conversion and 41% conversion. Only P<sub>4</sub>-*t*-Bu gave polymers without initiator with molar masses up to 600 kg/mol and a dispersity of 1.45. MALDI-ToF of shorter p(DEP) synthesized in the same way showed the formation of only cyclic polymers. T<sub>g</sub> of either linear or cyclic pDEP was found to be -30°C.

### 3.2.3. Organic acids

#### DPP catalyzed ROP of substituted $\delta$ -lactones

Another well-described catalyst for the ROP of substituted  $\delta$ -lactones is diphenyl phosphate (DPP). Like TBD, a monomer/chain-end dual activation mechanism takes place during ring-opening polymerization performed by this organic acid catalyst.(110,111)

Zhao and Hadjichristidis investigated the DPP-catalyzed homopolymerization and chain-extension of  $\delta$ -HL,  $\delta$ -NL and  $\delta$ -DL at RT in toluene (Figure 14).(112) 3-phenyl-1-propanol at a ratio of [DPP]<sub>0</sub>/[OH]<sub>0</sub> = 1, led to polymers with a degree of polymerization ranging from 40 to 107. Excellent control of the reactions was maintained with a good agreement between theoretical and experimental molar masses, a dispersity below 1.2 and a linear correlation of M<sub>n,SEC</sub> with conversion. The authors achieved a maximum molar mass of 15 kg/mol of pDL (but did not report if any higher molar masses were achievable). <sup>1</sup>H NMR analysis highlighted the impact of concentration over conversion. In accordance with thermodynamic parameters of these lactones, a concentration of 1.5 M of  $\delta$ -DL gave a 6% conversion after 48h while a concentration over 3 M led to 70% conversion within 48h. In addition, increasing the temperature from RT to 40°C improved the polymerization kinetics but resulted in a lower final conversion and a slightly higher dispersity. A comparison of the three lactones at 3.5 M showed a higher conversion and faster polymerization for  $\delta$ -HL (85% within 24h) while a reaction time of 3 days was necessary to reach 80% conversion for  $\delta$ -NL and  $\delta$ -DL. Finally, a living polymerization behavior was confirmed by chain extension, which resulted in the same control of dispersity and increased molar masses.

Additional study on  $\delta$ -methyl to nonyl  $\delta$ -lactones initiated by BnOH using the same catalyst was done by Schneiderman and Hillmyer.(105,113) The authors demonstrated the effective polymerization of all these alkyl  $\delta$ -lactones in bulk and room temperature. The polymerization rate was shown to

decrease with an increase of the size of the substituent and its position on the ring. Indeed,  $\alpha$ ,  $\beta$ , and  $\gamma$ M $\delta$ VL appeared to have the same rate of polymerization than  $\delta$ -VL, with a complete conversion at equilibrium within 10 hours. In the case of  $\delta$ -HL, it took at least 2 days in the same conditions ( $\alpha$  and  $\gamma$ M $\delta$ VL reached 98% conversion,  $\beta$ M $\delta$ VL 91% and  $\delta$ -HL 89% conversion, Table 2).(105) This feature could be explained by the secondary alcohol propagation for the  $\delta$ -position, slowing the polymerization rate. Moreover, the size of the substituent did not affect the glass transition temperature but modified the solubility parameters. This feature would be of interest to increase the hydrophobicity or favoring the segregation phenomenon without changing the T<sub>g</sub>, contrary to what is observed with poly(*n*-alkyl acrylate)s.

PEO functionalized  $\delta$ -VL in  $\alpha$ -position was polymerized using DPP in bulk at RT for 24h (Figure 15).(62) The benzyl alcohol/DPP ratio was set to 1/1 and DP was varied from 20 to 100. A conversion up to 89% was obtained, as well as molar masses between 5.4 and 23.7 kg/mol according to <sup>1</sup>H NMR analysis, which was in good agreement with SEC and theoretical values. 3-mercaptopropan-1-ol was also found to be a good initiator, leading to a polymer with a thiol chain-end of 5 kg/mol and a dispersity of 1.01. This polymer demonstrated excellent protein resistance and anti-cell adhesion capabilities, making it a good anti-fouling polymer.

Substituted in gamma position, 4-carbomethoxyvalerolactone (CMeVL) was homopolymerized in bulk using DPP at RT.(69) 1 eq. of benzenedimethanol was used as initiator with 200 and 500 eq. of monomer. Polymers of 31 and 71 kg/mol were obtained at 98% conversion and in a

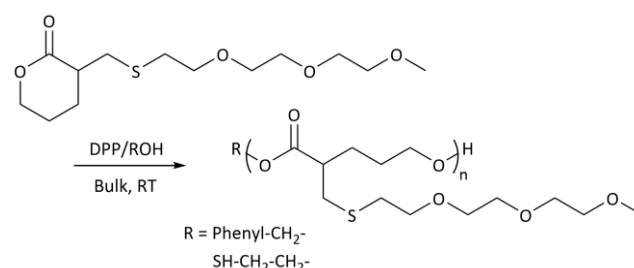


Figure 15 : ROP of PEO functionalized  $\delta$ -VL catalyzed by DPP and initiated by benzyl alcohol or 3-mercaptopropan-1-ol.

controlled manner with a dispersity of 1.2. Surprisingly, despite the racemic nature of the monomer, a semicrystalline polymer was obtained with a T<sub>g</sub> = 18°C and T<sub>m</sub> values at 68 and 86°C. A valuable thermodynamic and kinetic study was performed to compare this lactone with its methyl analogue. The authors could determine that both lactones had the same thermodynamic parameters, and thus, nearly identical

Table 2 : Characteristic values of some alkyl  $\delta$ -lactones. k<sub>p</sub>: rate constant of polymerization, M<sub>e</sub>: Entanglement molar mass

Monomer	$\alpha$ M $\delta$ VL	$\beta$ M $\delta$ VL	$\gamma$ M $\delta$ VL	$\delta$ -HL	$\delta$ -DL	$\delta$ -TDL
k <sub>p</sub> (M <sup>-1</sup> min)	1.1	2.8	7.7	0.4	0.029	0.057
Conversion (%)	98	91	98	89	-	-
T <sub>g</sub> (°C)	-51	-52	-51	-51	-51	-54
M <sub>e</sub> (kg/mol)	7.7	4.3	2.1	3.4	13.5	-

equilibrium monomer conversion. Concerning the rate of polymerization, it appeared that CMeVL had a 2.5 times slower rate of polymerization than  $\gamma$ -M $\delta$ VL. Extensive studies showed two routes to chemically recycle this polymer, the first one *via* reverse ring-opening transesterification using Sn(Oct)<sub>2</sub> at 150°C and reduced pressure to retrieve CMeVL. The second one involved DBU-induced eliminative degradation of the polymer to a methacrylate analogue, usable for polymerization.

The same authors also reported the DPP-catalyzed ROP of other 4-carboalkoxyvalerolactones with different alkyl side chains.<sup>(70)</sup> A series of polymers were synthesized in bulk, affording 97 to 99% conversions, good control and well-defined polymers with dispersity below 1.2. Depending on the nature of the alkyl substituent,  $T_g$  from -7°C to below -75°C were achieved. All the polymers exhibited a semi-crystalline feature. Higher targeted molar mass polymers needed higher temperature (70°C) to afford 90% conversion within 24h. However, the presence of chain transfer and intramolecular cyclization side reactions were proved through MALDI-ToF and SEC analyses which revealed the presence of bimodal distributions. Among the polymers tested in uniaxial tensile tests, pCMVL showed mechanical properties comparable to the ones of LDPE (with respect to Young modulus and elongation) and HDPE (strain at break).

Within the EVP family of monomers, only EtVP polymerization was reported, using PPA as initiator at room temperature.<sup>(74,75)</sup> The polymerization rate constant using DPP appeared to be 50 times lower than the one with TBD (0.029 vs. 1.44 M/h). Moreover, only 40% conversion was achieved (compared to 78% for TBD), but a polymer of 7.8 kg/mol was still obtained.

#### Other Brønsted acids

Bourissou and coll. reported the ROP of  $\delta$ -DL using methane sulfonic acid (MSA) in bulk and in toluene at 30°C.<sup>(114)</sup>  $\delta$ -DL was dried over molecular sieves, filtered and stored under argon. Like the previous systems involving DPP as catalyst, a high catalytic activity was also observed in this case, producing pDL with  $\bar{D} = 1.13$  and molar masses up to 6100 g/mol in 18h in the conditions:  $[\delta\text{-DL}]_0/[\text{n-Pentanol}]_0/[\text{MSA}]_0 = 40/1/1$ . To decrease the viscosity, the syntheses were also held at 1 M and 4 M in toluene but as expected, lower conversion and higher reaction time were observed; the more concentrated assay showing 74% conversion in 23h. Higher DP could be achieved in 25 vol.% of toluene, affording a polymer of  $M_n = 9400$  g/mol and  $\bar{D} = 1.16$ . This value was lower than the theoretical one due to side-initiations, highlighting the need to highly purify the monomer.

In the same work, triflic acid was also used for the bulk ROP of  $\delta$ -DL, leading to 81% monomer conversion. However, a slightly slower kinetic was obtained leading to polymer with  $M_n$  of 5 kg/mol and  $\bar{D} = 1.22$  in 22h at  $[\delta\text{-DL}]_0/[\text{n-Pentanol}]_0/[\text{HOTf}]_0 = 40/1/1$ .

Decanoic and sebacic acids were tried for the ROP of  $\delta$ -HL but no conversion was obtained even at 230°C.<sup>(96)</sup>

Thanks to organocatalysis, a better control was obtained under milder conditions for the ROP of substituted  $\delta$ -lactones. Also,  $\delta$ -lactones substituted in  $\alpha$ ,  $\beta$  and  $\gamma$ -positions showed higher polymerization rates and conversions than  $\delta$ -substituted  $\delta$ -lactones, in accordance with thermodynamic and kinetic parameters. Interestingly, the introduction of a dual catalytic system has greatly enhanced the catalytic activity and reaction control of the formerly slow ROP of  $\delta$ -HL, also enabling the obtention of high molar masses.

## 4. Copolymerization of substituted $\delta$ -lactones

The high interest of substituted  $\delta$ -lactones comes from their pendant chain, that generally brings to the corresponding polymers an amorphous feature with low  $T_g$  values and some specific properties such as the compatibility with hydrophobic media. Studies on the polymerization of substituted  $\delta$ -lactones have pointed out the thermodynamic issues with this family in comparison to  $\epsilon$ -lactone counterparts and mainly dealt with their random copolymerization. The more recent works on the ring-opening copolymerization (ROcP) of substituted  $\delta$ -lactones are discussed thereafter.

### 4.1. Statistical copolymerization of substituted $\delta$ -lactones

#### 4.1.1. Organometallic catalyzed statistical ROcP

A first example describing the synthesis of random copolyesters to tune the crystallinity ratio was reported by Fernández and coll.<sup>(31)</sup> Indeed,  $\omega$ -pentadecalactone ( $\omega$ -PDL) and  $\delta$ -HL were copolymerized in bulk at different ratios using triphenyl bismuth (TPB) as a catalyst (Figure 16 A). 100 eq. of comonomers were polymerized with 1 eq. of catalyst for 6 days at 130°C without any initiator, using only the protic impurities contained in the monomers to initiate the polymerization. Molar masses ranging from 62 to 249 kg/mol (and dispersity from 1.81 to 2.03) were obtained, which increased proportionally with  $\omega$ -PDL feed ratio. The copolyester composition determined by <sup>1</sup>H NMR, revealed a  $\delta$ -HL incorporation of 61.3% to 17.6% and a lower conversion of  $\delta$ -HL compared to  $\omega$ -PDL. The authors also reported the use of <sup>13</sup>C NMR to assign the different dyads. Interestingly, the average number of sequence lengths could be estimated and compared to the calculated Bernoullian values allowing them to determine the randomness character value (R) of this random copolymerization. A gradient microstructure was noticed with a slightly higher randomness for higher  $\omega$ -PDL content (R = 0.85). According to DSC measurements, high ratio of  $\omega$ -PDL led to higher melting temperature and higher crystallinity fraction, in agreement with higher content of  $\omega$ -PDL- $\omega$ -PDL sequences. Compared to the blockier p( $\epsilon$ -DL-co- $\omega$ -PDL) reported by the same group<sup>(115)</sup>, p( $\delta$ -HL-co- $\omega$ -PDL) exhibited, surprisingly, a less reduced crystallinity ratio (21 to 41%) but a lower melting temperature, explained by the shorter size of the alkyl substituent. Degradation tests at 37°C in buffer solution were finally held to show the influence of lower crystallinity ratios together with increased ratios of ester linkages in the copolymer, on hydrolytic degradability. After 6 months, the degradation rate value, ( $K_{Mw}$ ) and the half

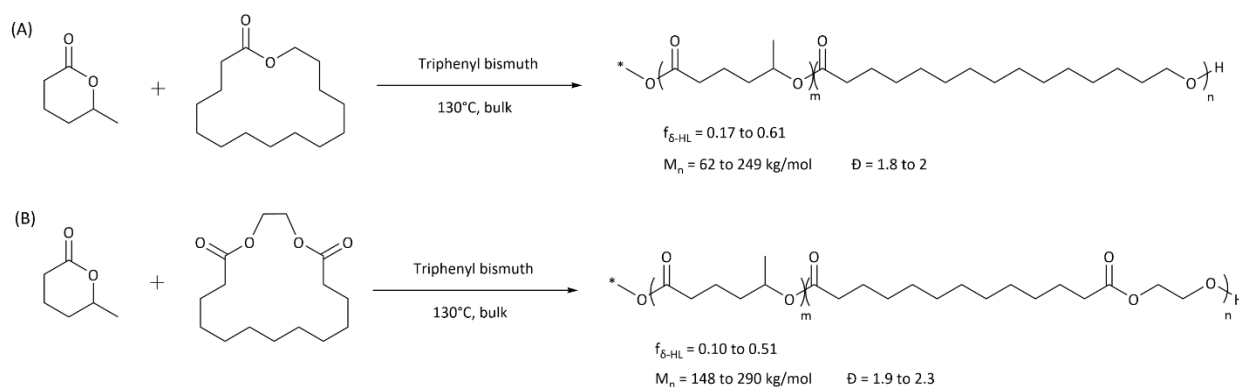


Figure 16 : ROcP of  $\delta$ -hexalactone and  $\omega$ -pentadecalactone or ethylene brassylate catalyzed by triphenyl bismuth.

degradation times were calculated through the change of  $\ln(M_w)$  over time. A higher degradation value was only observed for the copolymer containing the highest  $\delta$ -HL content (0.0019  $\text{d}^{-1}$ ). This observation can be explained by the competition between the ester function content and the randomness of the copolymer, with also a non-negligible effect of the initial average molar masses. Where pPDL needed more than 9.5 years to degrade to half of his molar mass, 1.4 to 1 years were sufficient for these copolymers.

Following this work, ethylene-brassylate (EB) was also considered as a comonomer in the same conditions, to evaluate its impact on the copolymer composition (Figure 16 B).<sup>(32)</sup> Copolymer composition varied from 10 to 51% mole fraction of  $\delta$ -HL and a similar randomness value was obtained whatever the comonomer feed. Remarkably, a 3-day reaction time gave close to full conversion for EB but lower conversion for  $\delta$ -HL (<50%), highlighting the lower reactivity of  $\delta$ -HL and the gradient structure obtained for longer reaction times. Calorimetric and diffraction analyses confirmed a decrease of  $T_g$ , crystallinity ratio and melting temperature with an increase of  $\delta$ -HL content. Similarly, a degradation study was performed and showed almost a 4 times higher degradation rates of the copolymers compared to PCL. Mechanical tests were performed on copolymers with  $f_{\text{EB}} \geq 63\%$ . Copolymer films showed an improvement in flexibility without losing ductility compared to pEB homopolymer. Finally, despite the high residual content of bismuth, no cytotoxicity was found for these copolymers.

Guillaume and coll. reported the use of NaOMe at 1 and 2.5 mol% for the copolymerization of  $\delta$ -HL and  $\delta$ -VL at 60°C.<sup>(96)</sup> Feed ratios were varied ( $[\delta\text{-HL}]_0/[\delta\text{-VL}]_0 = 1/1, 1/3$  and  $3/1$ ). A better control of the copolymerization was achieved with 2.5 mol% of catalyst. A conversion between 91 and 98% was obtained for  $\delta$ -VL and between 72 and 87% for  $\delta$ -HL, with  $\delta$ -VL appearing to be more reactive. Gradient copolymers were thus achieved in these conditions.

Neodymium isopropoxide ( $\text{Nd}(\text{OiPr})_3$ ) was also used for the copolymerizations of  $\epsilon$ -CL/ $\delta$ -DL,  $\epsilon$ -CL/ $\delta$ -DDL and  $\epsilon$ -DL/ $\delta$ -DDL.<sup>(97)</sup> Polymerizations proceeded in 168 h with 150 eq. of monomers for 1 eq. of  $\text{Nd}(\text{OiPr})_3$  in bulk at 4°C. Five copolymerizations per series were launched with molar ratios of 20-40-50-60-80 mol%. Only global conversion of monomers

could be given by the authors, certainly due to overlapping in  $^1\text{H}$  NMR signals. The final comonomer contents could be calculated. For the first set of comonomers ( $\epsilon$ -CL/ $\delta$ -DL), low  $\delta$ -DL incorporation in the copolymer was obtained for  $f_{\delta\text{-DL}} < 80\%$  ( $F_{\delta\text{-DL}} < 11\%$ ). Copolymers with 20 to 25 kg/mol and dispersity in the range of 1.3 to 1.6 were obtained. For the copolymer of  $f_{\delta\text{-DL}} = 80\%$ , a nearly equal incorporation of both monomers was achieved. A p( $\epsilon$ -CL-co- $\delta$ -DL) with  $M_n$  of 22 kg/mol and  $\bar{D} = 2$  was obtained in this case. Global monomer conversions remained below 60% and no clear correlation between feed ratios and conversions could be made.

For  $\epsilon$ -CL/ $\delta$ -DDL copolymers, an increase of  $f_{\delta\text{-DDL}}$  led to a decrease of conversions and molar masses (from 37.4 to 15.5 kg/mol). It however increased the incorporation of  $\delta$ -DDL units in the copolymers up to 31 mol% incorporation for  $f_{\delta\text{-DDL}} = 0.8$ . Dispersities showed no particular tendency and ranged between 1.3 and 1.6.

$\epsilon$ -DL/ $\delta$ -DDL copolymers showed better control of the dispersity, remaining below 1.2. A better accuracy between targeted and experimental monomer incorporation ratios were obtained, as proved by  $^{13}\text{C}$  NMR analysis. Molar masses around 27 kg/mol were obtained with a global conversion around 60%. Only these fully substituted copolymers revealed to be amorphous, with  $T_g$  increasing for higher  $\epsilon$ -DL amount, accordingly to the  $T_g$  of p( $\epsilon$ -DL) which is higher than that p( $\delta$ -DDL). Other copolymers only showed a significative decrease of the crystallinity ratio and melting enthalpy for copolymers of  $f_{\text{substituted } \delta\text{-lactone}} = 0.8$  (i.e. for the better incorporation of substituted  $\delta$ -lactone units in the copolymer).

Another purpose of a random copolymerization could be the insertion of functional groups along the copolymer backbone.<sup>(77)</sup> In this way,  $\alpha$ -propargyl- $\delta$ -VL was copolymerized with  $\epsilon$ -CL to tune the number of pendent alkyne moieties in the final copolymer (Figure 17 A).  $\text{Sn}(\text{OTf})_2$  was used as a catalyst at room temperature to achieve, in 48h, narrow dispersity copolymers with 10 to 47 mol% insertion of  $\alpha$ -propargyl- $\delta$ -VL (in accordance with feed ratios) and molar masses around 8 kg/mol. Random distributions of both monomers were confirmed by  $^{13}\text{C}$  NMR spectroscopy, showing several overlapping carbonyl signals. Moreover, the crystallinity of pCL was inhibited above 25 mol% incorporation of the functional lactone. Successful click reaction of the

functionalized copolyester with azide-terminated PEG was achieved, leading to graft copolymers with different number of PEG grafts (Figure 17 B). These new copolymers were soluble in ethanol, water, and in most common organic solvents.

Both monomers were also copolymerized in presence of  $\text{Sn}(\text{Oct})_2$  at  $100^\circ\text{C}$  using benzyl alcohol as an initiator.(116) A copolymer containing 33 mol% of functionalized monomer was obtained in 16h with a narrow dispersity and a  $M_n$  of 14.6 kg/mol. No further data were given for the synthesized copolymers. Photopatterned cross-linked films were formed and showed to degrade under enzymatic stimulus.

Successful copolymerization of  $\alpha$ -Methylene- $\delta$ -VL ( $\alpha$ -MeVL) and  $\delta$ -VL in presence of 1 mol% of  $\text{Sn}(\text{Oct})_2$  was achieved without initiator at  $130^\circ\text{C}$  in 72h (Figure 18).(60) 25 to 10 mol% feed ratio of  $\alpha$ -MeVL were used with a final ratio in the copolymer of 18 to 6 mol%. Low molar masses were obtained with quite high dispersity (1.65). Interestingly, the higher the amount of  $\alpha$ -MeVL in the copolymer, the lower the melting temperature. Crosslinking of these copolymers, mediated by 2,2'-azobis(2,4-dimethyl)valeronitrile, were performed with 90 wt% of either ethyl methacrylate (EMA), 2-hydroxyethyl methacrylate or  $\alpha$ -MeVL. A network, with loss of crystallinity, and exhibiting a single  $T_g$  at  $72^\circ\text{C}$  was obtained for EMA based

copolymer while two  $T_g$  were obtained as well as some crystallinity phases for the two other crosslinked polymers.

The synthesis of 139 lipocationic copolyesters were reported using methyl lithium as catalyst (Figure 19).(38) The purpose of this work was to perform different combinations of functionalized  $\beta$ -substituted lactones at different mole ratios in the feed and analyze their impact on siRNA delivery. Globally, 90% conversion was obtained with molar masses between 3 and 12 kg/mol and dispersity between 1.3 and 2. Incorporation of monomers were close to feed ratios allowing for the formation of copolyesters with tunable hydrophobicity and pKa (6.1 to 4.0).

Yue *et al.* described the first polymerization of EVL through its copolymerization with the strained  $\beta$ -Butyrolactone.(98)  $\text{Sc}(\text{OTf})_3$  was used at temperatures between  $40$  and  $70^\circ\text{C}$  in the following conditions:  $[\text{M}]_0:[\text{Cat}] = 100:1$  with  $[\text{M}]_0$  being the sum of the two monomer concentrations. Feed ratio of EVL varied from 19 to 69% and its final incorporation went up to 50% with 80% conversion of the monomer. Molar masses could not reach more than 4.1 kg/mol with dispersity over 2, due to high chain transfer. No EVL-EVL diad was observed neither through  $^{13}\text{C}$  NMR nor MALDI-ToF analysis. Kinetics revealed a random propagation of the two monomers. Indeed, the so-formed copolymer revealed a single diffusion in  $^1\text{H}$  NMR-DOSY and one  $T_g$  through DSC analyses.

To conclude,  $\delta$ -substituted  $\delta$ -lactones are difficult to copolymerize, and their conversion remain low using organometallic catalysts, thus mainly leading to gradient-type copolymers. The other substituent positions led to higher conversions and random copolymers but still with low molar masses.

#### 4.1.2. Organocatalyzed ROcP

As substituted  $\delta$ -lactones belong to "Thermodynamic intermediate monomers" as defined by Albertsson and coll. (37), organocatalysis and its mild reaction conditions offers the possibility to reach higher conversions. However, as depicted in the homopolymerization part, few organocatalysts were reported for the ROP of substituted  $\delta$ -lactones, lowering the possibility to tune the reactivity ratios and the copolymer microstructure.

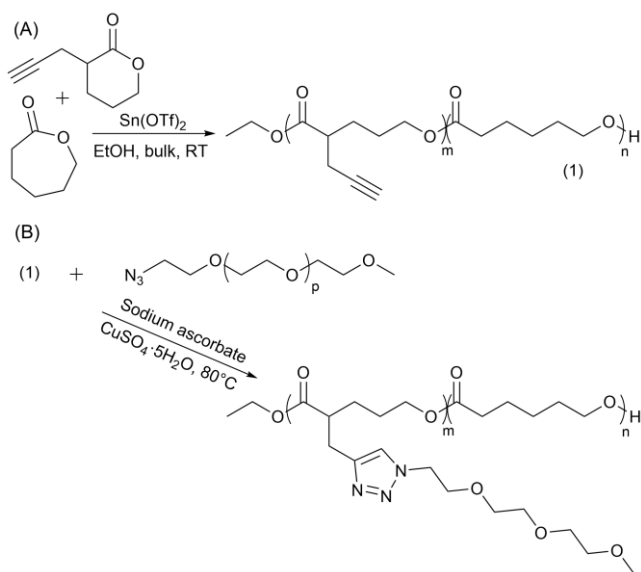


Figure 17 : (A) ROcP of  $\alpha$ -P6VL and  $\epsilon$ -CL catalyzed by  $\text{Sn}(\text{OTf})_2$ .(B) Click reaction of (1) and azide-terminated PEG

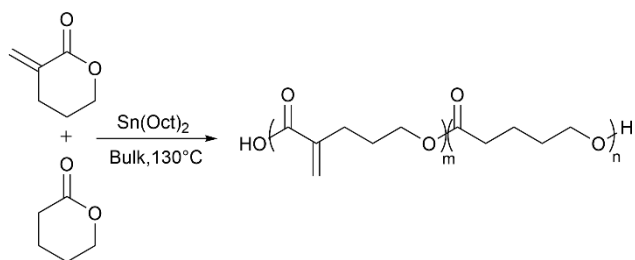


Figure 18 : ROcP of  $\alpha$ -Me $\delta$ VL and  $\delta$ -VL catalyzed by  $\text{Sn}(\text{Oct})_2$ .

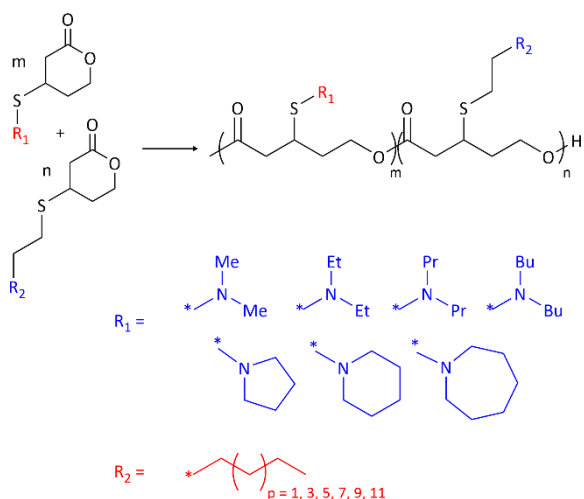


Figure 19 : ROcP of tertiary amine-bearing valerolactone and alkylated valerolactone monomers for the obtention of 139 lipocationic copolymers

Song *et al.* described the organocatalyzed DPP-ROcP of  $\epsilon$ -caprolactone ( $\epsilon$ -CL) and  $\delta$ -HL at 100°C.(30) A series of copolymers with 5, 12 and 38 mol% incorporation of  $\delta$ -HL was achieved in 17h for monomer feeds of 10, 20 and 50 mol% of  $\delta$ -HL, respectively. As previously reported, unfavorable thermodynamics of  $\delta$ -HL afforded only 62 to 67% conversion of this monomer at 100°C. Still, copolymers with molar masses from 18 to 25 kg/mol were obtained with dispersities decreasing from 1.75 to 1.38 with higher  $\delta$ -HL amounts. Contrary to  $\omega$ -PDL copolymerization, close resemblance of the two monomeric units did not enable the distinct proton shifts in the different dyads. By  $^{13}\text{C}$  NMR analysis, four carbonyl groups could however be observed, leading to the conclusion that at least all 4 dyads exist. Significantly, only one  $T_g$  at -55°C was observed for the copolymer containing the highest  $\delta$ -HL content. Indeed, for this copolymer, neither a melting of crystalline phases nor the presence of crystals under polarized light could be observed, meaning that the successful synthesis of an amorphous copolymer was achieved. The authors thus assume that the two monomeric units are well dispersed within the copolymer, notably thanks to a redistribution by transesterification reactions of the monomer units which occurred at 100°C. As a comparison with PCL, degradation of copolymer films was performed using Lipase PS. The authors showed the significant improvement of enzymatic degradation of p(CL-*co*-HL) compared to PCL, by the introduction of at least 5 mol% of  $\delta$ -HL in the copolymer to reduce the crystallinity ratio.

As already mentioned in 2.2, Cederholm and Odelius described the copolymerization of  $\delta$ -DL with  $\epsilon$ -CL or  $\epsilon$ -DL mediated by DPP at RT.(84) Bulk copolymerizations with a molar content of  $[\text{M}]_0/[\text{DPP}]/[\text{BDM}] = 100/5/1$  were performed with a ratio of  $\delta$ -DL varying from 97.5 to 80 mol%. Monomer equilibrium conversion was reached after 5 to 7 days. Copolymerization kinetics were monitored by  $^1\text{H}$ ,  $^{13}\text{C}$  and 2D HSQC NMR spectroscopy, showing quite a similar reaction rate of monomer insertion for p( $\delta$ -DL<sub>80</sub>-*co*- $\epsilon$ -CL<sub>20</sub>), while homopolymerization of  $\epsilon$ -CL was found to be 10 times faster

than the one of  $\delta$ -DL. Gradient copolymers were obtained for the copolymerization of  $\delta$ -DL and  $\epsilon$ -DL as a consequence of a slower reaction rate of  $\epsilon$ -DL incorporation in comparison to  $\delta$ -DL one. Upon heating at 110°C, depolymerization was found to be less efficient for higher contents of thermodynamically stable  $\epsilon$ -lactones. Moreover, the latter was found even lower for  $\epsilon$ -DL because of the higher number of  $\epsilon$ -DL units in the copolymer. The use of DPP seems more appropriate than  $\text{Nd}(\text{O}i\text{Pr})_3$  for the copolymerization of these lactones, as higher conversions and narrower dispersities are obtained.

Schubert and coll. tried the association of  $\delta$ -DL with  $\delta$ -VL in statistical and block copolymerizations.(117) Statistical copolymerizations were performed in bulk at RT using TBD as catalyst, a molar ratio of  $\delta$ -DL in the feed between 20 and 50% and  $[\text{M}]_0/[\text{TBD}]/[\text{BnOH}] = 100/1/1$  (Figure 20 A). Reactions proceeded in 16h and gave rather high dispersity copolymers ranging from 1.6 to 2.4.  $^1\text{H}$  NMR kinetic studies revealed that  $\delta$ -VL converted faster than  $\delta$ -DL, thus forming a block-gradient copolymer. Block copolymerization was also performed, starting from a purified pVL of 7.7 kg/mol, followed by the addition of  $\delta$ -DL and TBD. 17% conversion was obtained for this 2<sup>nd</sup> step reaching a final composition of 80/20 mol%  $\delta$ -VL/ $\delta$ -DL and a diblock copolymer molar mass of 11 kg/mol with 1.35 dispersity. Regarding the microstructure-thermal properties relationship, incorporation of  $\delta$ -DL slightly decreased the crystallinity of pVL as a gradient copolymer exhibited 34% crystallinity ratio in comparison to 43% crystallinity for a diblock copolymer. Moreover, the gradient copolymer induced a different surface structure with shorter and randomly oriented crystals in comparison to the long and parallel lamellar crystals observed for the homopolymer and diblock copolymers. Thus, the authors could compare 2 copolymers exhibiting different crystallinity ratios but similar hydrophobicity than pCL. Nanoprecipitation in water of the copolymers and pCL solutions in THF allowed for the formation of stable nanoparticles of around 170 nm with negatively charged surface. Interestingly, AFM of these particles logically showed stiffer particles for higher crystallinity ratios. Cellular uptake being related to the stiffness and the release rate of a drug being slower for crystalline nanoparticles, drug delivery could be adjusted with the crystallinity ratio of these copolymers.

In a same manner, Schubert and coll. copolymerized  $\epsilon$ -CL and  $\delta$ -HL, isomers that would give similar hydrophobicity than pCL (Figure 20 B).(104) Compared to Song's work(30), the authors used TBD as catalyst and reported kinetics to better understand the microstructure of this polymer. Feed ratio of  $\delta$ -HL was varied from 20 to 50% to reduce the crystallinity of pCL and the following conditions were applied for the five copolymers:  $[\text{M}]_0/[\text{BnOH}]_0/[\text{TBD}]_0 = 100/1/2$  with  $[\text{M}]_0 = 4$  mol/L in toluene.

Copolymerization kinetics were experimentally measured and theoretically calculated with Meyer-Lowry and Beckingham models. All results suggested the presence of random copolymers as the reactivity ratios of  $\delta$ -HL remained around 0.5 and that of  $\epsilon$ -CL varied from 0.77 for 80 mol% and 0.49 for 50 mol% of  $\delta$ -HL. Interestingly, the polymerization was



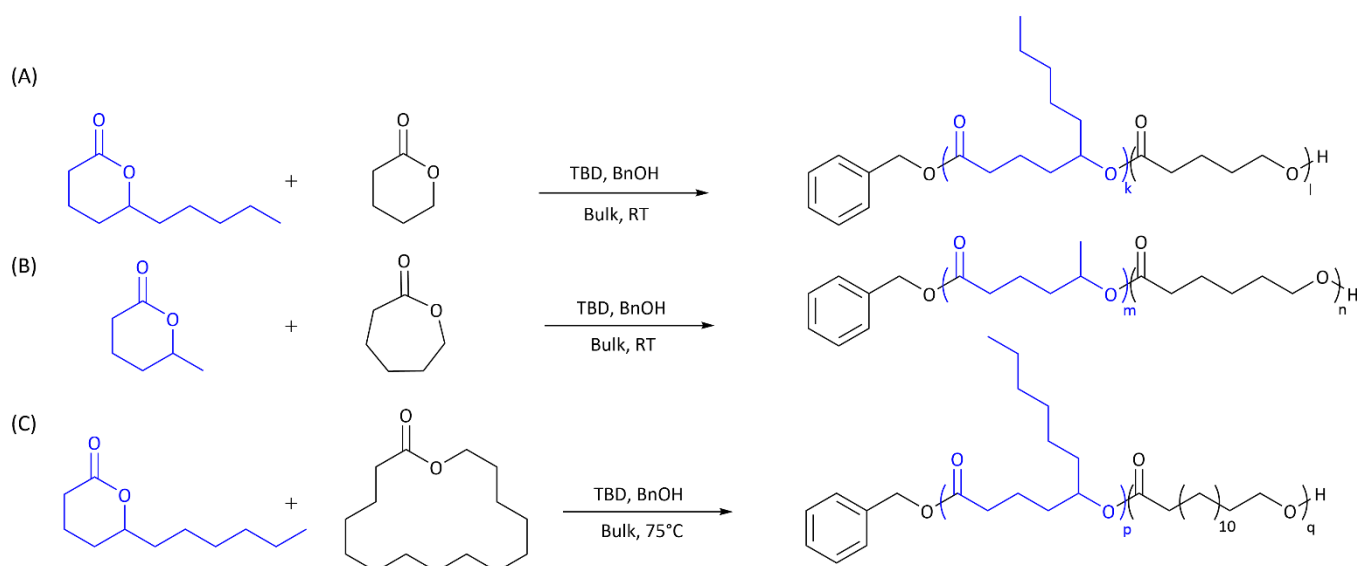


Figure 20 : TBD catalyzed ROcP of various alkyl  $\delta$ -lactones with common lactones. (A)  $\delta$ -DL and  $\delta$ -VL, (B)  $\delta$ -HL and  $\epsilon$ -CL, (C)  $\delta$ -UDL and  $\omega$ -PDL

stopped on purpose before  $\delta$ -HL reached its equilibrium conversion (a bit higher than 60%) to avoid any pCL block at the end of the copolymerization. Conversion of  $\epsilon$ -CL decreased linearly with decreased feed ratio of  $\epsilon$ -CL from 89 to 51%. As described by Song, bulk crystallinity and melting temperature decreased linearly with  $\delta$ -HL fraction.

An interesting work by Bernaerts group, described a way to increase the solubility of the highly crystalline poly( $\omega$ -pentadecalactone).<sup>(118)</sup> By copolymerizing  $\delta$ -undecalactone ( $\delta$ -UDL) with  $\omega$ -PDL, the authors reported the formation of random-like structures that showed decreased crystallinity compared to p( $\omega$ -PDL), unlike copolymerization with other substituted lactones like  $\epsilon$ -DL or  $\delta$ -HL (Figure 20 C).<sup>(119,120)</sup>

For this purpose, a solvent-free ROcP was conducted in the presence of benzyl alcohol initiator ( $[\omega\text{-PDL}]_0/[\delta\text{-UDL}]_0/[\text{BnOH}] = 8/8/1$ ) and TBD (1 eq.) at 75°C. One-pot and sequential additions of one monomer into the other one have also been investigated, showing random-like structure only for  $[\omega\text{-PDL}]_0/[\delta\text{-UDL}]_0$  4/12 ratio but for both processes. This can be explained by the different thermodynamic parameters of each lactone.  $\delta$ -UDL is a more strained lactone than  $\omega$ -PDL and requires lower temperatures to achieve high conversion, while  $\omega$ -PDL needs high temperature to increase the entropy factor ( $-T\Delta S$ ) and allow its polymerization. Due to the ring strain,  $\delta$ -UDL polymerized faster at 75°C than  $\omega$ -PDL, thus forming block-like structures. Even when  $\delta$ -UDL was gradually added in 4h on  $\omega$ -PDL forming polyester, a copolymer with high  $\omega$ -PDL molar ratio was obtained and led to block-like structures with alternating sequences. Surprisingly, crystallinity was still observed for random-like structures but the increase of  $\delta$ -UDL ratio was found to decrease the melting temperature as less  $\omega$ -PDL- $\omega$ -PDL dyads were formed.

The  $\beta$ -substituted 3-mercaptopvalerolactones (MVL) synthesized by Waymouth and coll. were copolymerized with  $\epsilon$ -CL in 1:1 mixture of comonomers with 5 mol% TBD in

toluene solution at room temperature.<sup>(64)</sup> 76 to 94% conversions were obtained in 1h, faster reactions and higher conversions than homopolymerized MVL. Final compositions were close to the feed ratio and random structures were assigned by  $^{13}\text{C}$  NMR spectroscopy. Final copolymers ranged from 5.8 to 6.9 kg/mol with quite narrow dispersities. Moreover, no crystallinity and a single glass transition temperature were obtained for all copolymers, all below the  $T_g$  of pMVL, accounting for the sole formation of amorphous copolymers.

Finally, crystallinity inhibition of pCL was investigated by Bourissou and coll. by employing several substituted lactones among which  $\delta$ -DL.<sup>(114)</sup> As for the homopolymerization of  $\delta$ -DL, MSA were used as catalyst for the *n*-pentanol initiated ROcP of  $\epsilon$ -CL and  $\delta$ -DL in toluene with the conditions:  $[\epsilon\text{-CL} + \delta\text{-DL}]_0/[I]/[\text{Cat}] = 40/1/1$  and  $120/1/1$ . Change in molar ratio was operated for  $\text{DP}_{120}$  copolymers, targeting  $\delta$ -DL molar ratios of 33, 50 and 66%. Full conversion of  $\epsilon$ -CL was obtained for each copolymer while 54 to 73% conversion was reached for  $\delta$ -DL, increasing with higher feed ratio of the latter. Kinetics monitoring by  $^1\text{H}$  NMR spectroscopy showed close reactivity of both monomers, thus leading to random copolymers. Control of the reaction *via* this catalytic system remained good as SEC revealed molar masses close to the theoretical ones with dispersity values below 1.2. Last, only one  $T_g$  appeared in DSC and an amorphous copolymer was obtained for a copolymer containing 42% of  $\delta$ -DL.

To conclude, higher conversions but still low molar masses were obtained using organocatalysts. However, a larger variety of copolymer structures could be achieved and the crystallinity of homopolyesters could be inhibited by random copolymerization with alkyl-substituted  $\delta$ -VL.

Table 3 summarizes all the copolymerizations performed. From this table, it can be observed that the catalyst has no

Table 3 : Summary of different monomer association with substituted  $\delta$ -lactones for their statistical ring opening copolymerization using various catalysts (n.d.: not defined, - : no initiator used)

Ref.	M1	M2	Structure	Catalyst	Solvent (Concentration)	Temp.	Initiator	Conversion M1 (%)	Conversion M2 (%)	Molar masses (kg/mol)	Dispersity	Crystallinity
96	$\delta$ -HL	$\delta$ -VL	Gradient	NaOMe	Bulk	60°C	-	72 - 88	91 - 98	2.4 - 9.2	1.2 - 1.4	n.d.
30		$\epsilon$ -CL	Random	DPP	Bulk	100°C	BnOH	62 - 67	100	18 - 25	1.4 - 1.75	No / Yes
104			Random	TBD	Toluene (4M)	RT	BnOH	62 - 67	51 - 89	7 - 11	1.2 - 1.6	No / Yes
31		$\omega$ -PDL	Gradient	TPB	Bulk	130°C	Impurities	38 - 50	62 - 85	62 - 249	2	Yes
32		EB	Gradient	TPB	Bulk	130°C	Impurities	30 - 48		148 - 290	2	Yes
117	$\delta$ -DL	$\delta$ -VL	Gradient	TBD	Bulk	RT	BnOH	82 - 85	98 - 99	11 - 14	1.6 - 2.4	Yes
97		$\epsilon$ -CL	Random	Nd(iPr) <sub>3</sub>	Bulk	4°C	-	nd	nd	20 - 25	1.3 - 2	Yes
84			Random	DPP	Bulk	RT	BDM	88 - 91		9 - 12	1.3 - 1.4	n.d.
114			Random	MSA	Toluene (1-4M)	30°C	n-pentanol	54 - 73	100	5 - 16	< 1.2	No / Yes
84		$\epsilon$ -DL	Gradient	DPP	Bulk	RT	BDM	87 - 90		10	1.3 - 1.4	nd
118	$\delta$ -UDL	$\omega$ -PDL	Random / grad.	TBD	Bulk	75°C	BnOH	38 - 90	96 - 100	2 - 7	1.4 - 2.2	Yes
97	$\delta$ -DDL	$\epsilon$ -CL	n.d.	Nd(iPr) <sub>3</sub>	Bulk	4°C	-	nd	nd	15 - 37	1.3 - 1.6	n.d.
97	$\delta$ -DDL	$\epsilon$ -DL	n.d.	Nd(iPr) <sub>3</sub>	Bulk	4°C	-	nd	nd	23 - 27	< 1.2	n.d.
77	$\alpha$ -propargyl- $\delta$ -VL	$\epsilon$ -CL	Random	Sn(Oct) <sub>2</sub>	Bulk	RT	EtOH	> 90		8	< 1.11	No / Yes
116	$\alpha$ -propargyl- $\delta$ -VL		Random	Sn(Oct) <sub>2</sub>	Bulk	100°C	BnOH	90		15	< 1.2	n.d.
60	$\alpha$ -methylene- $\delta$ -VL		n.d.	Sn(Oct) <sub>2</sub>	Bulk	130°C	-	53 - 88 (yield)		3 - 6	1.65	Yes
38	$\beta$ -subs. $\delta$ -VL	$\beta$ -subs. $\delta$ -VL	Random	MeLi	Bulk	RT	-	90		3 - 12	1.3 - 2	n.d.
64	$\beta$ -subs. $\delta$ -VL	$\epsilon$ -CL	Random	TBD	Toluene (1M)	RT	BnOH	76 - 94	83 - 94	6 - 7	1.2 - 1.5	No
98	EVL	$\beta$ -BL	Random	Sc(OTf) <sub>3</sub>	Bulk	70°C	-	22 - 98	17 - 100	0.5 - 4.1	1.9 - 3.7	No

influence on the randomness of the copolymers, the latter being essentially governed by the type of monomers involved.

## 4.2. Block copolymerization of substituted $\delta$ -lactones

### 4.2.1. Thermoplastic elastomers made of polyesters and poly(substituted $\delta$ -lactones)

Thermoplastic elastomers are a class of linear polymers that combine properties of thermoplastic polymers (reprocessability) and of elastomer networks (elasticity). As previously mentioned, a main interest of polymerizing substituted lactones in addition to their biobased nature is their ability to yield amorphous polyesters with low  $T_g$ , making them potential candidates for soft segments of thermoplastic elastomers.

As discussed earlier, Martello *et al.* gave an overview of triblock copolymers synthesis using pDL as mid-block and pLA as hard block.(103) In a room temperature one-pot synthesis strategy, the authors added a DCM solution of 35 wt% of D,L-Lactide to a TBD-catalyzed polymerization of  $\delta$ -DL reaching equilibrium conversion. Theoretical molar masses of pDL and pLA, respectively 90kg/mol and 20kg/mol, were achieved as proved by <sup>1</sup>H NMR and SEC analyses. Furthermore, no depolymerization phenomenon was observed for  $\delta$ -DL, a potential side reaction caused by dilution of pDL in the presence of catalyst. To finally confirm the triblock structure, DSC analysis of the copolymer showed two  $T_g$  corresponding to the pDL and pLA blocks, respectively at -51 and 54°C.

In the same conditions, telechelic p( $\beta$ M $\delta$ VL) was also copolymerized with L and D,L-Lactide in a two-step/one-pot strategy to achieve a triblock copolymer.(58) A series of triblock copolymers of different sizes were synthesized and

characterized. An increase of molar masses was clearly observed by MALS-SEC and the clean formation of triblock copolymers was also confirmed by <sup>13</sup>C NMR. In addition, microphase separation and self-assembled nanostructures were evidenced by SAXS and DSC analyses, the latter also showing a separate  $T_g$  and  $T_m$  for L-LA based triblocks. Tough plastics could be obtained at high ratios of lactide ( $F_{LA} = 0.59$ ) whereas elastomer behaviors were obtained at lower volume fraction of LA ( $F_{LA} = 0.29$ ). Moreover, L-LA based triblocks showed to form elastomers with high stress at break, 1700% elongation at break and nearly complete recovery of the applied strain, competing with the best elastomer used nowadays like Kraton.

Another catalytic pathway was used for the triblock formation of D,L-LA using telechelic p( $\beta$ M $\delta$ VL) of 100 kg/mol as macroinitiator.(121) Stannous octoate at 0.01 wt% relative to the monomer was used to form a triblock copolymer of 0.23  $F_{PLA}$  with very low dispersity in toluene. This copolymer was then mixed with varying amounts of rosin ester tackifier and the mixture characterized by rheology, peel adhesion, loop tack and shear resistance tests. Results varied a lot but globally exhibited a pressure-sensitive adhesive behavior for this blend.

Using the same monomers, molar ratio of both monomers were adjusted in order to obtain an elastomer of 1 MPa Young modulus, a value close to the elastic moduli of soft tissues.(17) For this purpose, a 100 kg/mol soft midblock and 10 kg/mol hard blocks were designed using a higher temperature (140°C) for the Sn(Oct)<sub>2</sub> mediated triblock formation. Films were casted to perform tensile tests on dry and wet specimens and *in vitro/in vivo* degradation and cytocompatibility. Compared to poly(glycerol sebacate), one of the most reported materials

for this application, this triblock exhibited better tensile properties and cytocompatibility, and similar *in vivo* biocompatibility. It can thus be potentially used in implantable material, material devices and tissue engineering scaffold.

$\epsilon$ -CL was also used to form a triblock copolymer with  $\beta$ M $\delta$ VL in order to obtain low melting temperature copolymers processable at lower temperature than their PLA-based analogues.(122) The same procedure as mentioned above was performed, using Sn(Oct)<sub>2</sub> as catalyst for the triblock copolymer synthesis. 85%  $\epsilon$ -CL were converted and well-defined triblock copolymers of 82.3 to 100 kg/mol with different fractions of pCL were obtained (from 0.24 to 0.37). Crystalline phases and melting temperatures showed to increase with pCL fraction. Tensile strength followed the same tendency with Young moduli increasing from 1.4 to 13.6 MPa. These materials were reported to be highly stretchable with strain to failure greater than 1400%. Moreover, these triblock copolymers appeared to be cytocompatible, able to encapsulate proteins and to be readily printable at 60°C.

$\beta$ M $\delta$ VL was also copolymerized with cyclic carbonates to form elastomer networks.(123) 0.25 to 2 mol% bis(six-membered cyclic carbonate) (CC) was charged with  $\beta$ M $\delta$ VL, BDM and 0.1 mol% TBD with respect to  $\beta$ M $\delta$ VL, to target 100 kg/mol p( $\beta$ M $\delta$ VL) (assuming no cross-linker was added). After 20h curing, a cross-linked film was obtained with a glass transition of -48°C. Mechanical properties of cross-linked copolymers with the lower CC molar ratio showed higher tensile strength and elongation than vulcanized natural rubber. However, these materials exhibited higher energy loss and residual strain during hysteresis experiments than the ones containing higher molar ratio of CC. Radical cross-linking of p( $\beta$ M $\delta$ VL) was also experimented using benzoyl peroxide (BPO) as a cross-linker and extrusion process for the blending. With 2 to 3 wt.% of BPO, elastomers with higher tensile properties than the ones based on CC were obtained. Moreover, the addition of Fumed-Silica Aerosil, a hydrophobic filler, greatly improved the mechanical properties. Recyclability at 150°C of these two types of cross-linked materials achieved 91% and 93% recovery of  $\beta$ M $\delta$ VL monomer in the presence of Sn(Oct)<sub>2</sub> and pentaerythritol.

Within the family of  $\delta$ -substituted  $\delta$ -VL, Li and coll. described a sequential ROP of  $\delta$ -HL with L-LA using BDM as initiator and a *t*-Bu-P<sub>2</sub>/urea catalytic system.(33) Three triblock copolymers of high conversions were obtained and a clear shift of the unimodal molar masses in SEC confirmed the formation of triblock copolymers. Molar masses up to 121.7 kg/mol were obtained. Only the higher molar masses triblock copolymer with a L-LA volume fraction of 0.28 exhibited elastomeric properties with tensile strength of 13.4 MPa, 755% elongation at break and high elastic recovery in stress-strain test.

Triblock polyesters have been successfully synthesized using TBD or Sn(Oct)<sub>2</sub> as catalysts. Mechanical properties of these thermoplastic elastomers were sometimes close to those of commercial TPE. Table 4 lists the different monomers and catalysts used for the formation of triblock copolyesters.

#### 4.2.2. Block copolymers made of substituted $\delta$ -lactones and oligosaccharides

Recently, fully biobased and sustainable triblock copolymers were synthesized using p( $\delta$ -decalactone) as soft-block and oligosaccharides as hard-blocks (Figure 21).(124) The oligosaccharides (malto-oligosaccharide types: maltose, maltotriose, maltotetraose and maltohexaose) were composed of 12 monomer units per copolymers. ABA-, A<sub>2</sub>BA<sub>2</sub>-, A<sub>3</sub>BA<sub>3</sub>-, A(BA)<sub>2</sub>-, and A<sub>2</sub>(BA)<sub>2</sub>-type architectures were synthesized in three steps. First, a DPP-catalyzed ROP of  $\delta$ -DL at 40°C initiated by BDM yielded narrow distributed (1.1) p( $\delta$ -DL) of 11.3 kg/mol. This hydroxy-telechelic p( $\delta$ -DL) was then reacted with 6-azidohexanoic acid (mediated by EDC and DMAP) to obtain an azido-telechelic p( $\delta$ -DL). Other acids bearing 2 and 4 azido groups were also used in order to reach A<sub>2</sub>BA<sub>2</sub> and A<sub>3</sub>BA<sub>3</sub> architectures. To obtain A(BA)<sub>2</sub>- and A<sub>2</sub>(BA)<sub>2</sub>-type architectures,  $\delta$ -DL polymerization was initiated with 2-[(6-azidohexyloxy)methyl]-2-methylpropane-1,3-diol (N<sub>3</sub>-(OH)<sub>2</sub>) and 2,2-bis((6-azidohexyloxy)methyl)propane-1,3-diol ((N<sub>3</sub>)<sub>2</sub>-(OH)<sub>2</sub>). Triblock copolymers were finally obtained at 60°C in DMF by coupling reaction between azido-terminated p( $\delta$ -DL) arms and alkyne-functionalized malto-oligosaccharides of different sizes. At each step, <sup>1</sup>H NMR spectroscopy completed by FT-IR and SEC analyses proved the effectiveness of the functionalization. TGA analysis of these block copolymers showed a good stability over 240°C. Two T<sub>g</sub> were observed in DSC: -50°C for the soft block and between 84 and 143°C for the hard blocks, depending on the oligosaccharide chain lengths. Only amorphous triblocks were obtained. A phase-separation phenomenon was observed by AFM and SAXS, explained by the non-miscibility of the two blocks. Interestingly, the different architectures of triblock copolymers showed different morphologies in bulk: hexagonally close-packed cylinders for branched oligosaccharide systems and a body-centered cubic structure for the other ones. Remarkably, use of polydisperse but cheaper malto-oligosaccharide with pDL in a A<sub>2</sub>BA<sub>2</sub> architecture was also investigated. In terms of mechanical properties, they all exhibited elastomeric properties, but the latter, less well-defined block copolymer afforded the best performances, with Young modulus similar to styrenic-based TPE and elongation at break of around 700%.

Malto-oligosaccharides being edible and thus potentially in competition with the food industry, the same group investigated the use of cellulose-based block copolymer (BCP).(125) Similarly, telechelic pDL blocks of 6, 10 and

Table 4 : Substituted  $\delta$ -lactones and catalysts used for the obtention of triblock polyesters with benzenedimethanol diol.

Ref.	Block A	Block B	Catalyst	Temp. (°C)
101	$\delta$ -DL	D,L-LA	TBD	RT
55	$\beta$ M $\delta$ VL	L-LA or D,L-LA	TBD	RT
17/120		D,L-LA	Sn(Oct) <sub>2</sub>	140°C
121		$\epsilon$ -CL	Sn(Oct) <sub>2</sub>	130°C
122		CC	TBD	RT
31	$\delta$ -HL	L-LA	<i>t</i> -BuP <sub>2</sub> /Urea	RT

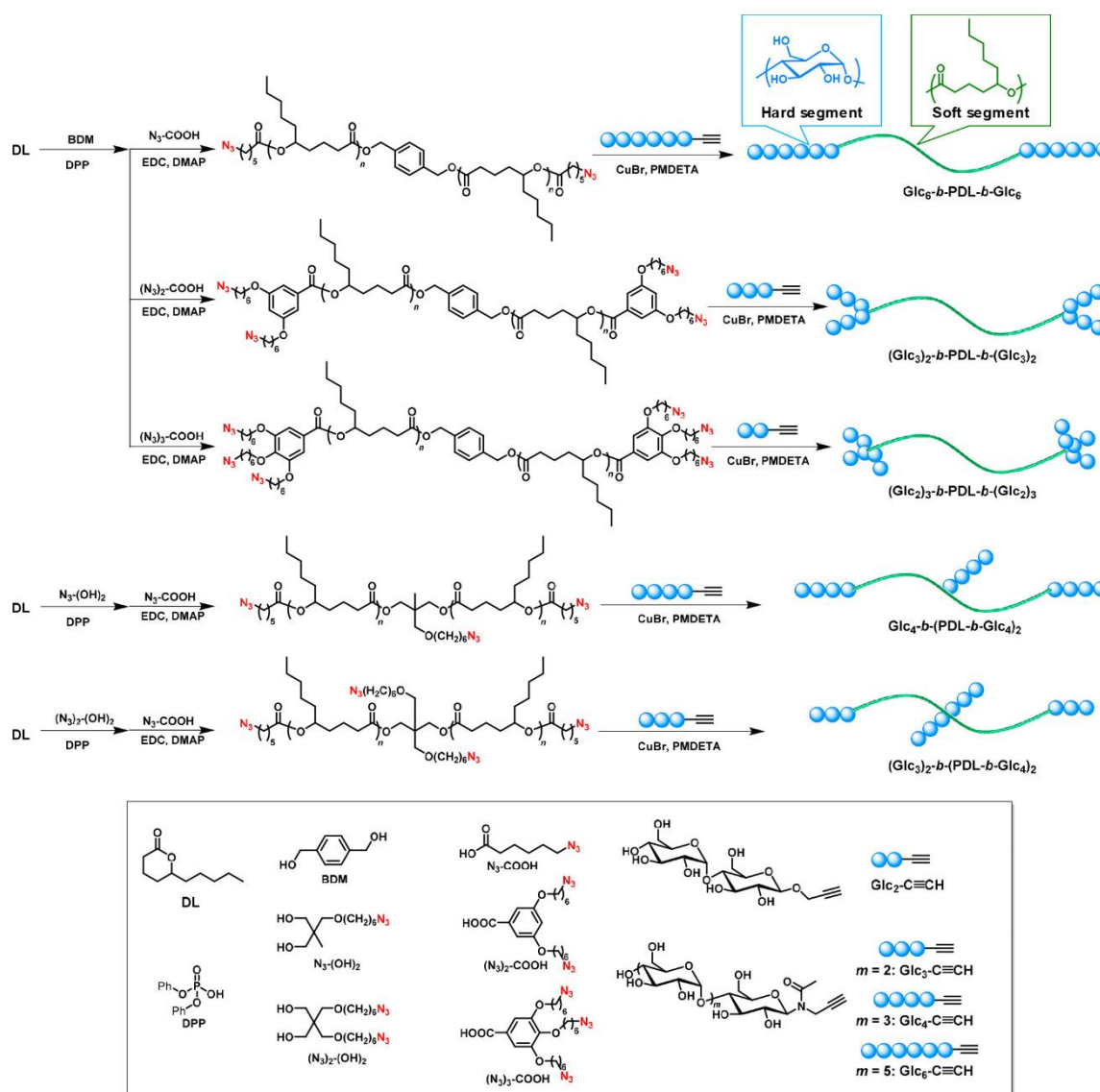


Figure 21 : Schematic illustration of triblock copolymer syntheses from  $\delta$ -DL polymerization to functionalization with azido group and click-reaction with alkyne-functionalized maltooligosaccharide of different sizes.(124)

22kg/mol were functionalized with azido groups prior to click reactions with a propargyl-functionalized cello-oligosaccharide triacetate of 4 kg/mol. The same reaction was performed for a maltooligosaccharide triacetate for comparison. Globally, linear triblock copolymers of around 10, 15 and 26 kg/mol and a dispersity of 1.05 were obtained. Typical TPE thermal properties were obtained and SAXS experiments showed a phase structuration only for cello-oligosaccharide-based BCP. Concerning mechanical properties, cellulose-based BCP have shown high level of elastic recovery for the higher length of pDL and better tensile properties than amylose-based BCP (malto-oligosaccharide). By increasing the pDL chain length, lower Young modulus (decreasing from 69 to 1.3 MPa) and

higher elongation at break (increasing from 209 to 385%) were obtained.

Fully sustainable graft block copolymer thermoplastics were also synthesized using a poly(hydroxypropyl methylcellulose) (HPMC) backbone grafted with p( $\beta$ M $\delta$ VL) and p(L-LA) (Figure 22).(126) A two-step sequential addition approach was used, starting with the synthesis of HPMC-*g*-p( $\beta$ M $\delta$ VL) at 80°C and catalyzed by DPP in bulk. A copolymer with a  $M_n$  of 650 kg/mol and a dispersity of 1.86 was obtained at a conversion of 80%. Different ratios of L-LA were then added to the so-formed macroinitiator to obtain several HPMC-*g*-(p( $\beta$ M $\delta$ VL)-*b*-p(L-LA)) of  $M_n$  up to 5140 kg/mol through Sn(Oct)<sub>2</sub> catalysis at 105°C in toluene.

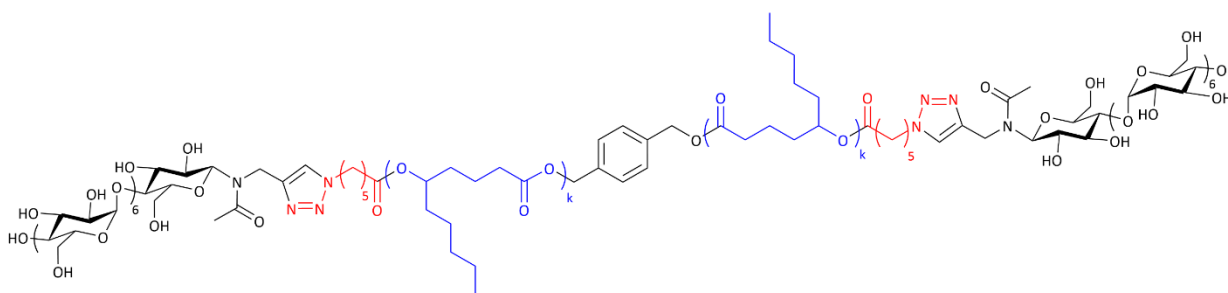


Figure 23 : Schematic representation of maltoheptaose-*block*-p( $\delta$ -decalactone)-*block*-maltoheptaose triblock copolymer.

This type of architecture was shown to increase the strain at break of the material but lowered its ultimate tensile strength compared to a linear triblock of p(L-LA)-*b*-p( $\beta$ M $\delta$ VL)-p(L-LA) of the same L-LA volume fraction. At similar HMPC-*g*-p( $\beta$ M $\delta$ VL) backbone length, the increase of p(L-LA) volume fraction in the copolymer has appeared to transform the copolymer from an elastomer to a ductile material.

Finally, a three-step strategy enabled the obtention of an ABA-type triblock copolymers composed of maltoheptaose (MH) hard blocks and poly( $\delta$ -decalactone) soft block (Figure 23).<sup>(127)</sup> At first, a dihydroxytelechelic p( $\delta$ -DL) was synthesized in bulk at 40°C through DPP catalysis. The so-formed polymer was then functionalized with 6-azidohexanoic acid in the presence of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide and DMAP to obtain azido groups at the chain-ends of the copolymer. Finally, MH was attached to the latter through the click reaction of propargyl and azido groups mediated by CuBr/PMDETA in DMF. Interestingly, this block copolymer was successfully self-assembled into highly ordered hexagonal cylindrical structures, switching from horizontal to vertical orientation with thermal annealing for some of the synthesized copolymers in a thin film state.

These new triblock copolymers which are biobased, biocompatible and potentially biodegradable seem promising alternatives to petroleum-based thermoplastic elastomers or for nanolithographic applications.

#### 4.2.3. Polyurethane elastomers based on poly(substituted $\delta$ -lactones)

The ring-opening of lactones produces polyesters with hydroxyl chain-ends that can serve as polyols in the course of polyurethanes. By using poly(substituted  $\delta$ -lactone)s as soft blocks, thermoplastic polyurethanes (TPU) were obtained.

A first report of TPU was made using a dihydroxytelechelic p( $\beta$ M $\delta$ VL) of 2000 g/mol, 2,4-tolylene diisocyanate (TDI) and butanediol.<sup>(128)</sup> The presence of the methyl substituents appeared to lower the water uptake and increase the hydrolytic stability in comparison to PCL-based PU. 24 months outdoor stability was performed, and the properties of the PU were compared over time. It resulted that such TPU had excellent thermal stability and weatherability.

An extended library of TPU were synthesized through the creation of p( $\beta$ M $\delta$ VL) polyols.<sup>(129)</sup> Diol, triol

(trimethylolpropane ethoxylate) and tetraol (pentaerythritol ethoxylate) were used as initiators for the DPP-catalyzed ROP of  $\beta$ M $\delta$ VL. To obtain TPU, methylenebis(phenyl isocyanate) (MDI) and Sn(Oct)<sub>2</sub> were mixed with the polyols and allowed to react before the introduction of a chain-extender. Molar masses up to 100 kg/mol were obtained with dispersity around 2. Interestingly, foams were also prepared from this system.

TPU with high content of p( $\beta$ M $\delta$ VL) exhibited similar properties than majorly used TPU, alike foams. Moreover, an interesting pathway for the recyclability of these PU was presented. Based on the reversibility of urethane bonds and the depolymerization of p( $\beta$ M $\delta$ VL) at high temperature, pyrolytic degradation mediated by Sn(Oct)<sub>2</sub> in a distillation apparatus enabled the almost full recovery of high purity  $\beta$ M $\delta$ VL.

Alternative chain-extenders allowed for the formation of new  $\beta$ M $\delta$ VL-based TPU with lower amount of isocyanate.<sup>(130)</sup> In order to decrease the amount of isocyanate used in the PU, the idea was to synthesize a chain extender from  $\beta$ M $\delta$ VL with a diamine or ethanolamine, thus bearing amide groups.

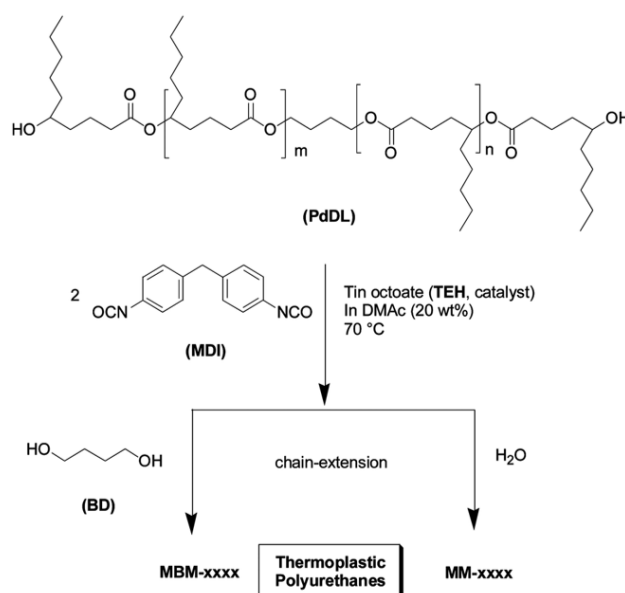


Figure 24 : Synthesis of thermoplastic polyurethane based on dihydroxytelechelic p( $\delta$ -decalactone), methylenebis(phenyl isocyanate) and 1,4-butanediol or water.<sup>(131)</sup>

Change in chain-extender allowed for the formation of TPU with better mechanical properties than mentioned above (around 800-900% strain at break, 14 to 33 MPa stress at break and Young moduli around 9-38 MPa). Moreover, the overall TPU contained a maximum of 75 wt% of  $\beta$ M $\delta$ VL thus diminishing the amount of isocyanate compared to the previously mentioned study.

Dihydroxytelechelic p( $\delta$ -DL)s were also used for the formation of TPU (Figure 24).<sup>(131)</sup> Mid-blocks of 1300, 1800 and 2700 g/mol of 1,4-butanediol initiated pDLs were first synthesized using the same conditions reported by Martello *et al.*<sup>(103)</sup> In this case, the obtained crude polymers needed to be purified before further chain-extension to remove the catalyst and remaining monomers. Interestingly, a new way to purify the crude pDL was proposed, using basic extraction with potassium hydroxide solution to remove remaining reagents, giving a similar result than precipitation in methanol, usually performed for polyesters. Reaction of these dihydroxytelechelic p( $\delta$ -DL) with MDI in presence of Sn(Oct)<sub>2</sub> in 20 wt% of dimethylacetamide (DMAc) at 70°C were then carried out to give a series of TPU with hard segment contents from 16 to 31%. Butanediol and water were used as chain-extenders to obtain respectively urethane and urethane/urea functions. The latter gave TPU with higher modulus, higher stress at break and lower hysteresis due to higher hydrogen bonding between urea and ester functions. As a further consequence, for a same soft block length, a higher initial degradation temperature was observed for water-base TPU with 308°C vs. 273°C for butanediol chain-extender.

The impact of the soft block size was characterized by calorimetric analyses. It was observed that the smaller the pDL chain length, the higher the difference of  $T_g$  with the one of pDL homopolymer. Indeed, a  $T_g$  difference of 44°C was obtained for a pDL with  $M_n$  of 1300 g/mol ( $T_g = -16^\circ\text{C}$ ), while a difference of 20°C was obtained for  $M_n = 2700$  g/mol ( $T_g = -36^\circ\text{C}$ ). This was explained by a restricted motion of small soft segments induced by the presence of hard blocks (increasing the  $T_g$  of soft blocks) and an enhanced microphase separation for longer soft block (bringing the  $T_g$  closer to that of pDL homopolymer).

The successful synthesis of TPUs with substituted  $\delta$ -lactones demonstrates the feasibility to introduce renewable and biodegradable polyester polyols. In addition, the mechanical properties of these TPUs revealed competitive with those of conventional TPU.

#### 4.2.4. Substituted $\delta$ -lactones based copolymers for self-assembly and drug delivery

Inherent degradability, combined with biocompatibility have allowed polyesters to be majorly used in medical and drug delivery applications. Furthermore, substituted  $\delta$ -lactones, in addition of being renewable, have a high potential for encapsulation of specific drugs thanks to their alkyl pendant chain. The latter increases the hydrophobicity of the polymer, disrupts condensed packing and forms consequently an amorphous polymer also promoting degradability. In addition, organocatalysis could bring the low toxicity missing in

organo-metallic ROP polyesters. All these interesting properties of substituted lactones promoted their incorporation in plenty of copolymers of various structures.

The first work reporting substituted  $\delta$ -lactone was handled by Bansal *et al.*, using  $\delta$ -decalactone initiated by OH-PEG-OH and MeO-PEG-OH to respectively form amphiphilic triblock and diblock copolymers (Figure 25 A and B).<sup>(39)</sup> TBD was used for each reaction to reach conversions close to 90% at 40 and 50°C.  $M_{n,NMR}$  of around 10kg/mol and narrow dispersity in SEC were obtained. Knowing that PEG is around 5000 g/mol, a 50/50 wt.% diblock copolymer was prepared. The removal of an homopolymer fraction due to residual initiation was required prior to investigate the self-assembly of these copolymers.

The enhancement of encapsulation properties compared to pCL-based copolymers was shown through a nanoprecipitation in water. This technique has indeed proven to be the only one to provide particle formation without aggregates. After filtration with good recoveries, CMC calculations by fluorescence spectroscopy using pyrene as sensor, showed a 2.5 times lower CMC of pDL copolymers particles compared to pCL ones (1.33 mg/L vs. 3.34 mg/L). The formation of micelles was demonstrated by means of DLS and TEM characterizations, giving 163 nm and 34 nm unimodal spherical micelles for the triblock and diblock copolymers, respectively. The encapsulation capacity of these copolymers was confirmed by UV-Vis spectroscopy using Nile Red as a dye. Amphotericin B, a hydrophobic anti-fungal compound, was loaded in the diblock micelles and studied in an *in vitro* release and degradation study. It appeared that AmpB content was 7 times higher in pDL based micelles than pCL ones and released quite linearly in 8 days. Complete cleavage of ester fragments from mPEG block only occurred at pH 4 after 53 days while a slow and linear  $M_n$  drop of 16% was observed after 4 months in physiological pH. It was however reported that a faster degradation occurred for this diblock copolymer compared to pCL-*b*-PEG (9% degradation in physiological pH after 4 months) that might have been due to a difference of crystallinity.

Later, the same author reported the use of the same diblock copolymer for the effective encapsulation of curcumin.<sup>(35)</sup> The copolymers showed to form non-haemolytic particles up to a concentration of 40 mg/mL and low toxicity for rats at a 400 mg/kg dose.

Liposomes were also created using these diblocks, by mean of their incorporation into phospholipid bilayers.<sup>(132)</sup> Copolymers of lower ratios of mPEG compared to pDL were used with molar ratio of up to 2:98 mPEG: $\delta$ -DL. The presence of mPEG-*b*-pDL copolymers showed to enhance the stability and morphologies of these liposomes.

In addition, a MDS-based computational method was employed to predict miscibility of drugs in those particles in order to save time and use the right drug for the corresponding micelles.<sup>(133)</sup>

Copolymerization of  $\delta$ -HL or  $\delta$ -DL with  $\epsilon$ -CL has also been initiated by PEG for the obtention of small triblock copolymers (Figure 25 C).<sup>(134)</sup> As reported by Song *et al.*, DPP-ROP of these two monomers should afford random structure but

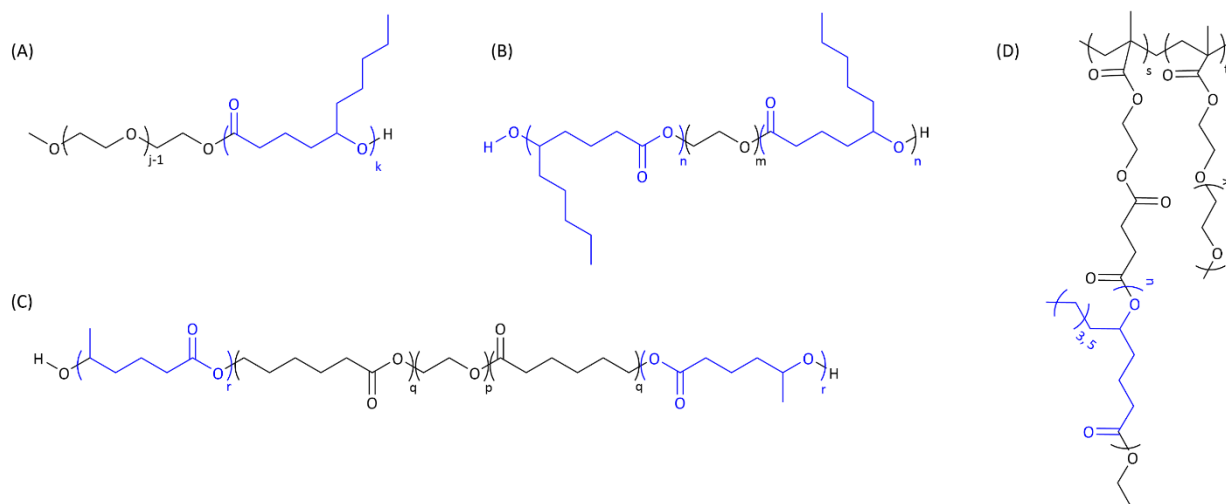


Figure 25 : Schematic representation of some of the block copolymers containing substituted  $\delta$ -lactones and used for drug delivery applications. (A) mPEG-*b*-p( $\delta$ -DL), (B) p( $\delta$ -DL)-*b*-PEG-*b*-p( $\delta$ -DL), (C) p( $\epsilon$ -CL-co- $\delta$ -HL)-*b*-PEG-*b*-p( $\epsilon$ -CL-co- $\delta$ -HL), (D) Grafted copolymer containing  $\delta$ -DL, HEMA succinate and EGMA.

crystallinity for high content of  $\epsilon$ -CL. Indeed, pCL domains were observed with a ratio of CL/DL = 3.4 by XRD. Triblock copolymers of 5 kg/mol and a dispersity of 1.3 were dissolved in water and showed thermo-induced gelation for  $\delta$ -HL triblock and normal hydrogel for  $\delta$ -DL. CMCs of around 0.15 mg/mL were also reported, which are approximately 10 times lower than values for PEG-*b*-pDL diblock copolymers reported by Bansal et coll.

More recently, diblock copolymer formed from PEG and pDL *via* click chemistry was reported.(40) By using azide-PEG and pDL initiated by propargyl alcohol, copper-catalyzed click reactions could produce well-defined diblock copolymers. Furthermore, functionalization of PEG with targeting ligands or tracking molecules has shown to form diblock copolymers with tunable number of functions, allowing formation of nanoprecipitated micelles with higher cellular uptake.

Other strategies to obtain lower CMC and drug loading particles included the synthesis of a grafted copolymer through ROP and RAFT polymerization.(135)  $\delta$ -decalactone and  $\delta$ -dodecalactone oligomers of 1 kg/mol initiated by ethanol were obtained *via* TBD catalyzed ROP at 0°C. Coupling of these oligomers with HEMA succinate allowed for the RAFT polymerization of the formed methacrylate-oligomers with those of EGMA to form a graft copolymer (Figure 25 D). Particles below 50 nm were formed and gave CMC of 0.09 mg/mL, a lower value than the linear amphiphilic diblock performed by Bansal and coll. However, release of the hydrophobic drug PTX showed a plateau at 30% within 24h.

ROP and ATRP were also combined to obtain an amphiphilic triblock of  $\delta$ -DL and oligoEGMA (Figure 26 A).(136) ROP of  $\delta$ -DL using TBD and a red-fluorescent dye diol (DPTBT) as initiator was first performed. Functionalization of hydroxyl group with bromoisobutyryl bromide was then performed, prior to ATRP of OEGMA with this macroinitiator. The thus formed polymer showed a dispersity of 3.3 and a  $M_n = 23$  kg/mol. After water nanoprecipitation, blank particles and DOX-loaded micelles were characterized. As reported earlier,

pDL triblock copolymer showed the highest drug-loading capacity (7 wt%) and largest extent of drug release in acidic media. These particles have also shown to be internalized into HeLa cells after 2h incubation and showed sustainable release of DOX and cytotoxicity. This interesting work shows the possibility to form drug delivery fluorescent polyester-based particles, suitable for imaging-guided therapy.

Bernaerts and coll. explored another way to perform grafted copolymers with p( $\delta$ -UDL) and poly(ethylene imine) (PEI) in a 3-step reactions (Figure 26 B).(137) BnOH initiated TBD-ROP of  $\delta$ -UDL at -10°C was first achieved with  $M_{n,SEC} = 1$  kg/mol and  $\bar{D} = 1.06$ . Hydrogenolysis of the latter with Pd/C under hydrogen atmosphere allowed for the formation of a COOH-pDL-OH. At 150°C and during 5h, the polymer was allowed to react with PEI, affording increased molar masses but also unreacted PEI and pDL.

Here again, Bansal *et al.* proposed the use of a novel lactone called jasmine lactone ( $\delta$ -JL) containing an unsaturation on the alkyl pendant chain (Figure 26 C).(65) Functionalizations by thiol-ene chemistry of the resulting polymer with hydroxyl, carboxyl and amine end-group and conjugation of drugs were undertaken to afford nanoparticles with high drug loadings and targeted delivery *via* disulfide bond cleavage. Comparison with commercially available drug carrier (Soluplus®) showed a 334-fold increment in aqueous solubility of clotrimazole using particles of carboxyl terminated p( $\delta$ -JL) copolymer.(36)

Nanoemulsion in PBS using Pluronic F-68 as surfactant and pDL as the oil phase has shown to greatly increase the aqueous solubility of various hydrophobic drugs from 3 to 10 times compared to surfactant micelles alone.(34) Moreover, a good stability and a similar toxicity were induced by the use of pDL instead of classical oils.

Another mean to create emulsion but without adding surfactant has also been reported.(138) TBD-ROP of  $\delta$ -DL initiated by 2-dimethylaminoethanol enabled to form water surfactant with an ionizable amino end group (Figure 26 D).

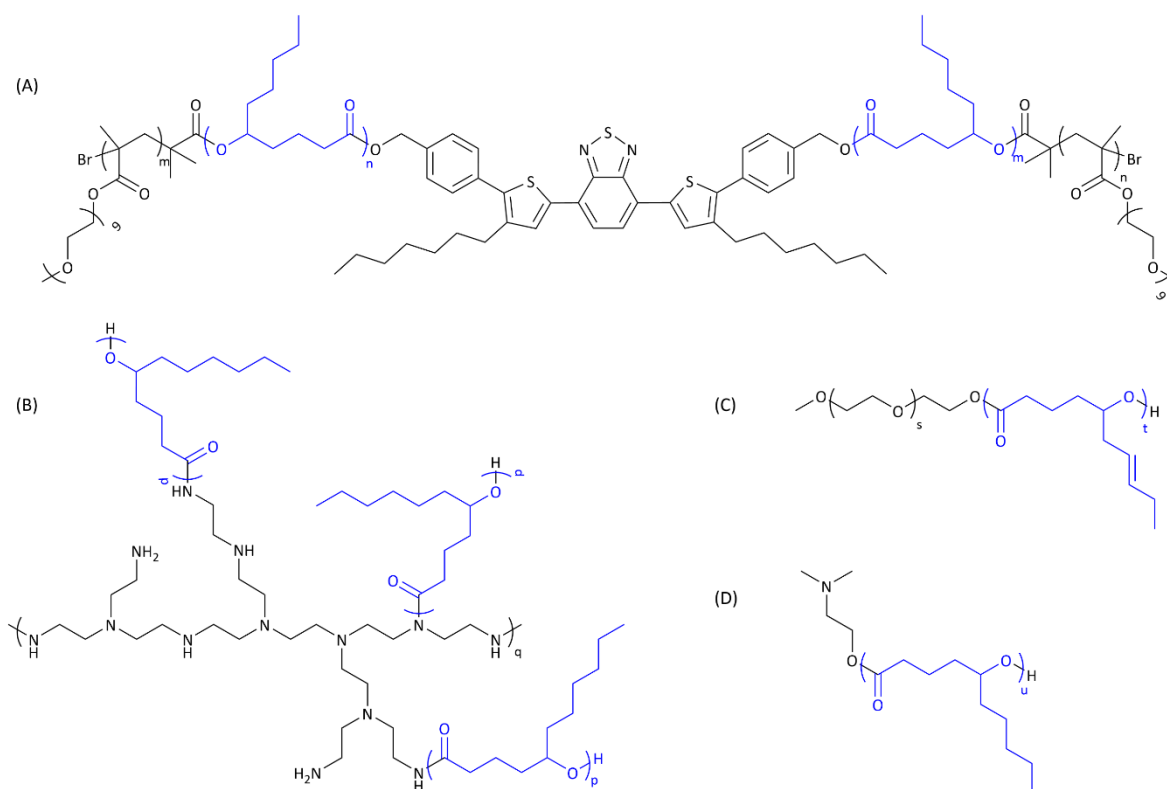


Figure 26 : Schematic representation of some of the block copolymers containing substituted  $\delta$ -lactones and used for drug delivery applications or particle formation. (A) Block copolymer containing DPTBT,  $\delta$ -DL and EGMA, (B) PEI-*g*-p( $\delta$ -UDL), (C) PEG-*b*-pJL, (D) Deanol initiated p( $\delta$ -DL).

85% w/w of perfume loading into nanoprecipitated particles was achieved, as well as high adsorption on negatively charged surfaces like hair or clothes and long-lasting fragrance perception.

Drug delivery issues have pushed scientists to find ways to enhance encapsulation and targeted delivery of highly toxic drugs to avoid severe side-effect for human beings. Reported works showed the synthesis of innovative architectures and the formation of well-defined non-toxic particles with good encapsulation and release of hydrophobic drugs, based on block copolymers of substituted  $\delta$ -lactones. The latter features were enhanced compared to PCL-based block copolymers for example, thanks to the amorphous nature and hydrophobicity of poly(substituted  $\delta$ -lactone)s. These polyester particles are thus interesting substitutes to non-biodegradable/non-renewable-based particles.

## Conclusion

This state of the art has provided an overview of substituted  $\delta$ -lactone monomers including their production, the thermodynamic restrictions and their (co)polymerization using different catalysts.

Many of these lactones have appeared to be produced from renewable sources such as  $\beta$ -methyl  $\delta$ -valerolactone and  $\delta$ -decalactone. However, thermodynamic parameters of substituted  $\delta$ -lactones have been described as “unfavorable” or “intermediate” for their ring-opening polymerization, meaning that high monomer concentrations and low

temperatures are needed to favor polymerization over depolymerization and achieve high monomer conversions.

Organocatalysts, alkali metal alkoxides and dual catalytic systems have appeared to give the highest conversions, molar masses and control for the ring-opening polymerization of substituted  $\delta$ -lactones. Indeed, these catalysts such as TBD, DPP or NaOMe, have allowed the ROP of these lactones at low temperature, favoring their ability to polymerize. Moreover, dual catalytic systems such as *t*-Bu-P<sub>2</sub>/Urea or KOMe/Urea have shown to greatly decrease the reaction time while offering an excellent control of the reaction and high conversions.

Even though the harsh thermodynamic parameters of these lactones have restricted the use of high activation temperature catalysts, they enabled the easy chemical recycling of the corresponding polymers to retrieve monomers or valuable chemicals at high yield and at temperature below 120°C.

Copolymerization of substituted  $\delta$ -lactones with other monomers have successfully afforded copolyesters of reduced crystallinity, thermoplastic elastomers and amphiphilic diblock copolymers for drug delivery. It allowed for the increase of the biosourced moieties in former petroleum-based polymers without loss of performances for the latter mentioned applications. Besides renewability and chemical recyclability, the use of these monomers for the design of copolymers has enhanced the degradation rate in aqueous medium, making them an overall alternative for more sustainable polymers.



## Conflicts of interest

The authors of this publication received research funding from L'OREAL Advanced Research which is developing products related to research described in this review.

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