CHAPTER 1

Nucleophilic Catalysts and Organocatalyzed Zwitterionic Ring-opening Polymerization of Heterocyclic Monomers

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1.1 Introduction

Organocatalysis refers to a form of catalysis whereby the rate of reaction is increased by an organic molecule preferably used in substoichiometric amounts. The use of organic molecules to perform chemical reactions is not a new concept and organocatalytic reactions look back on a respected history. Both cyanohydrin synthesis from quinine alkaloids[1] and proline-catalyzed Robinson annulation[2] belong to the most popular dated examples of organocatalytic reactions. Although organic molecules have been used at the beginning of the chemistry, their narrow scope of reactions has not really stirred scientific interest in the past. Nowadays, thanks to clever and sometimes serendipitous discoveries, the picture is changing and organocatalysis is becoming an indispensable part of organic chemistry, offering a wide diversity of reactions, catalysts and processes.[3–5]

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While most of the organo-based reactions concern the enantioselective preparation of small molecules, organocatalysis also offers number of prospects in the polymer community and proposes advantages over metal-based and bioorganic methods.[6] In this chapter, special attention is devoted to organocatalyzed ring-opening polymerization (ROP) of cyclic monomers and more especially the zwitterionic ROP (ZROP) from nucleophilic catalysts.

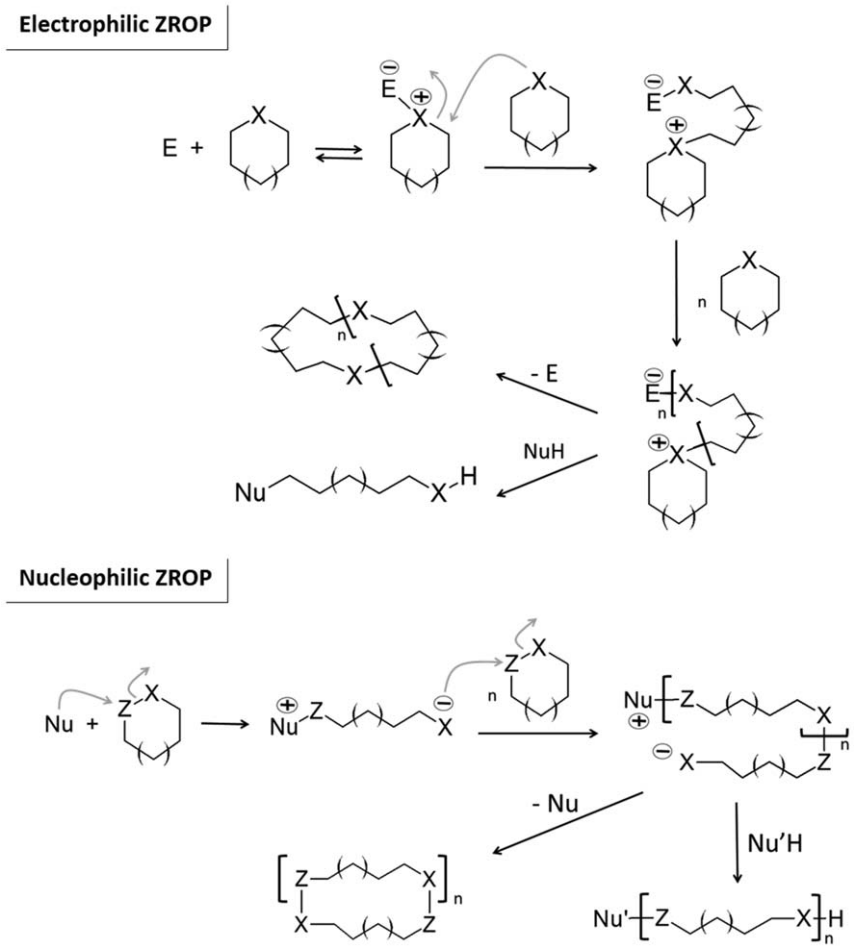
1.2 Definition of ZROP

ZROP is a chain polymerization in which a growing macromolecule bears two ionic chain carriers of opposite signs at its two ends and which usually grows from one of them.[7] The zwitterion propagating species—either obtained from a neutral nucleophilic initiator or a neutral electrophile—is initially poorly active since the electrostatic work needed for parting the opposite charged ions is the largest when they are close together. Stabilization of a zwitterionic species may involve the positive end of one zwitterion propagating chain acting as the counter-ion of the carbanion end of another zwitterion propagating chain.[8] Termination of the reaction may be caused by the presence of a protic nucleophile or by a charge cancellation step of the highly polar dimer leading to linear and cyclic structures, respectively.[9] While neutral electrophiles have already been used in ZROP,[10–12] zwitterionic polymerizations typically employ neutral nucleophiles that react with heterocyclic monomer to *in situ* produce the zwitterionic initiator (Scheme 1.1).

To date, several types of organic molecules have been employed as neutral nucleophiles to initiate ZROPs of cyclic monomers. Similarities with simple acylation reactions are unquestionable and allows pyridine-based molecules, imidazoles, amidines, tertiary amines, phosphines and N-heterocyclic carbenes (NHCs) to be used as initiating agents. Considering Scheme 1.1 (bottom of the scheme) as the general way of polymerization, the latent electrophile present on the cyclic monomer (Z) is most of time a carbonyl function. Strained lactones, thiolactones, *N*-caboxyanhydrides, carbosilanes and cyclic carbonates are then good candidates to undergo nucleophilic ZROP (see Chapter 11).

1.2.1 Pyridine-based Initiation

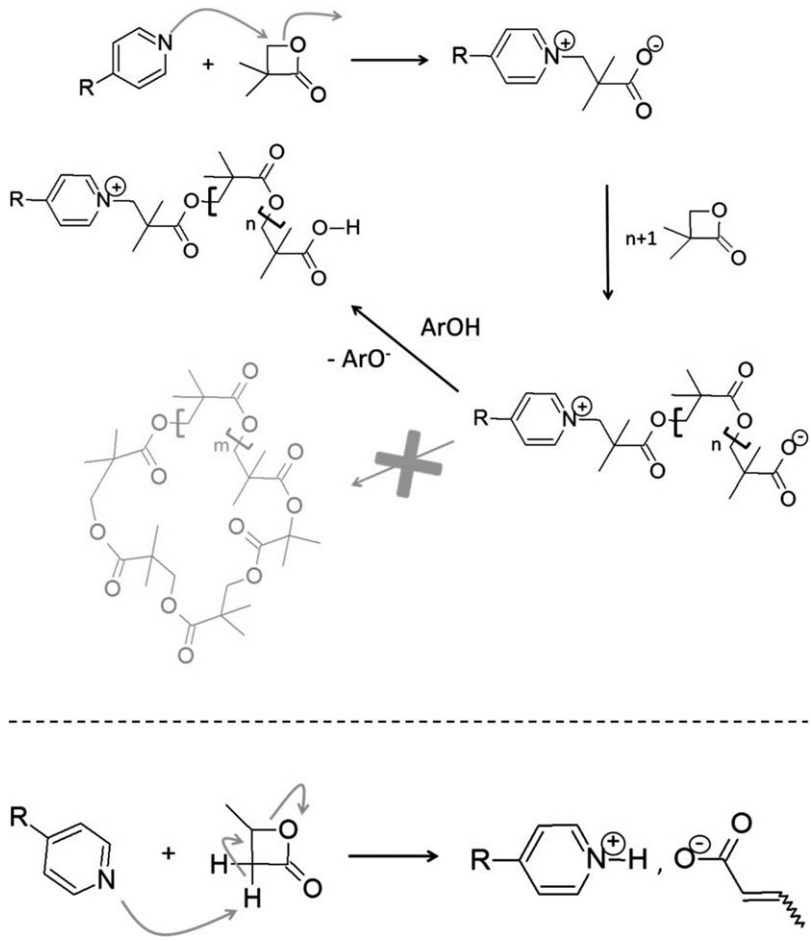
More than 50 years ago, β-lactones such as β-propiolactone and β-pivalolactone started to be polymerized by pyridine-based nucleophilic initiators.[13–16] For several reasons, the course of such ZROP was very complex, involving chain growth and step growth kinetics as well as elimination reactions regarding the type of initiator and monomer used. When moderate bases[17] such as pyridine, 4-methylpyridine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were used for the ZROP of pivalolactone,[16] linear chains having one pyridinium ion and a carboxylate ion as end groups were observed by ^{1}H NMR and MALDI-ToF analyses. The absence of cyclic structures



Scheme 1.1 General mechanism of electrophilic (top) and nucleophilic (bottom) zwitterionic ring-opening polymerizations (X and Z represent a heteroatom and an electrophilic site, respectively. Nu and E represent nucleophilic and electrophilic entities, respectively).

suggested that the ZROP proceeded exclusively from the CO_2^- anion (Scheme 1.2, top). In the case of β-propiolactone and β-butyrolactone (BL), complete elimination of the pyridinium ions and formation of acrylate and crotonate end groups, respectively, were observed (Scheme 1.2, bottom).[14,18]

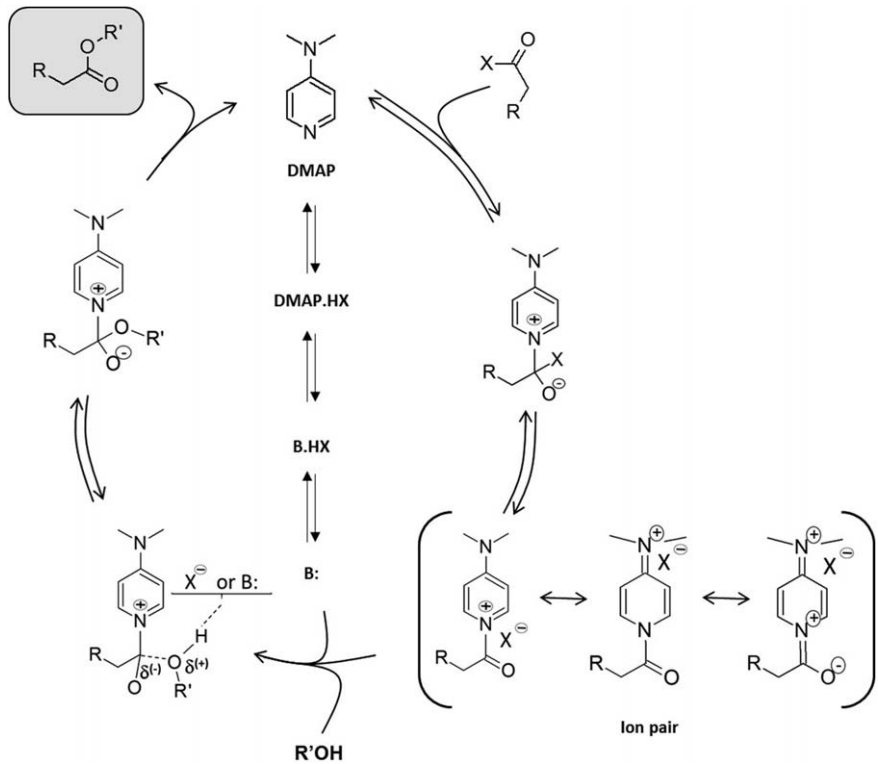
The catalytic potential of donor-substituted pyridines is well established since the report on DMAP by Litvinenko *et al.* in 1967 and by Steglich *et al.* two years later.[19,20] A catalytic improvement was reported in 1978 for 4-(pyrrolidinyl)pyridine (PPY),[21] and in 2003 with 9-azajulolidine.[22] Annelated pyridine derivative is a powerful organocatalyst not only suitable for acylation reactions, but also for other transformations such as the aza-Morita Baylis Hillman reaction.[23]



Scheme 1.2 Top: ZROP of pivalolactone by pyridine derivatives (R = H, pyridine; R = Me, 4-methylpyridine; R = $-N(CH_3)_2$, DMAP); bottom: crotonate formation from proton α-elimination of β-butyrolactone induced by pyridine.

The commercially available DMAP catalyst is often the common choice for acylation reactions proceeding by a nucleophilic mechanism involving an acyl pyridinium ion intermediate (Scheme 1.3). The amplified reactivity of aminopyridine derivatives—up to four orders of magnitude higher than pristine pyridine in representative acyl transfer[17,24]—may come from the greater equilibrium concentration of the acyl pyridinium intermediate and its increased electrophilicity because of looser ion pairing.[25–28]

In 2001, Hedrick *et al.* demonstrated that Lewis basic amines such as DMAP and PPY were highly effective for the ROP of lactide (LA) monomers.[29] Although other works on metal-free processes were published earlier,[30–32] his report is considered today as the nucleating agent in the field of the



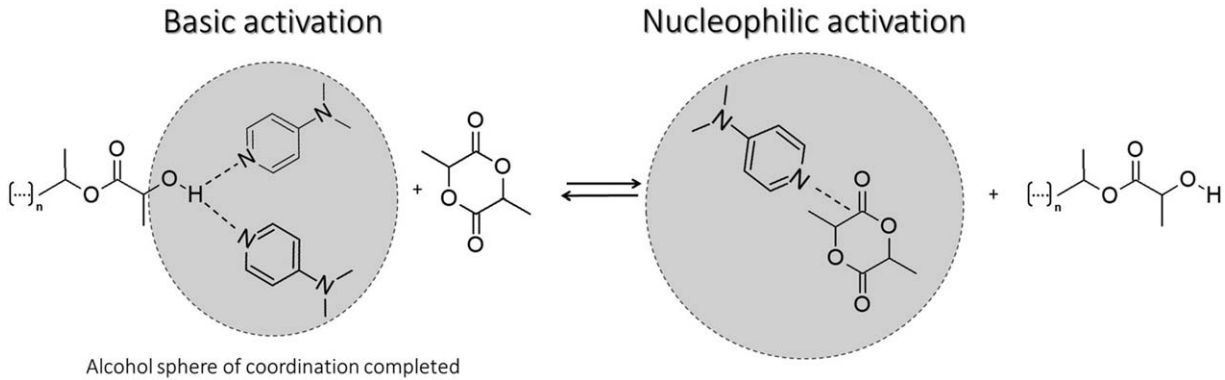
Scheme 1.3 Proposed mechanism for a DMAP-catalyzed acylation reaction. Simplification of the mechanism proposed by Spivey in [25].

organocatalytic approach to the living ROP of lactones. The motivations of such research came from the realization of the potentially dangerousness of the organometallic catalysts used so far in the preparation of polyesters produced for biomedical and electronic applications. The catalytic behavior of both DMAP and PPY in the ROP of LA was studied in dichloromethane at 35 °C using ethanol (EtOH) as initiator in the presence of 0.1 to 4 equivalents of amine as compared to EtOH. Under anhydrous conditions, no polymerizations were observed in the absence of initiating alcohol. Narrowed PLAs were produced for a degree of polymerization (DP) ranging from 30 to 120 in 20 to 96 h. By contrast to most organometallic-promoted polymerizations, the dispersity was kept extremely low well after complete conversion with no noticeable molecular weight modifications. The living character of the polymerization was deduced from the linear evolution of the molecular weight as a function of the conversion, the predictable molar masses and the low dispersities. This living character is the manifestation of the rapid initiation and the weakly nucleophilic propagating species (secondary alcohol) that is active only to the cyclic diester monomer, precluding undesirable transesterification reactions.[33]

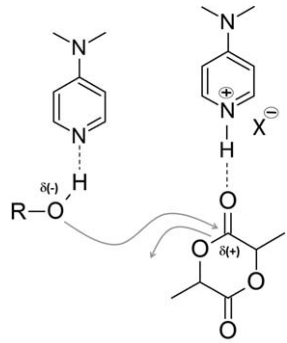
Polymerization was originally proposed to occur *via* a ''monomer-activated'' mechanism through nucleophilic activation of the LA (Scheme 1.4, route A). ^{1}H NMR analyses confirmed that the obtained PLA chains are end-capped in α position by an ester function generated from the initiating alcohol and in ω by a hydroxyl group. This suggests that for such mechanism the alkoxide/acyl pyridinium zwitterion generated by the nucleophilic attack of the DMAP on the LA is subjected to a proton transfer from the initiating/propagating alcohol and an acylation from the resultant alkoxide. However, subsequent computational studies realized by Bourissou *et al.* predicted that a base-catalyzed pathway would be of lower energy (Scheme 1.4, route B).[34] Those simulations were realized in gas phase, implying that in solution, and especially in the presence of alcohol initiators, the nucleophilic monomer activation could be predominant. In 2012, both Hedrick's and Bourissou's uncertain mechanistic concepts were conciliated.[35] Kinetic studies demonstrated that DMAP, generally used in excess as regard to the initiating alcohol, plays a double dealing and is involved in both nucleophilic activation of the LA and the basic activation of the initiating/propagating alcohol. It was demonstrated that ~2 DMAP molecules complete the coordination sphere of the initiating/propagating alcohol and that any excess of DMAP is involved in the nucleophilic activation of the monomer (Scheme 1.5). Interestingly, in the same study, the equimolar ratio of DMAP and *N,N′*-dicyclohexylcarbodiimide (DCC) was demonstrated to better control the ROP of L-LA. As compared to the DMAP alone, a DMAP/DCC mixture was proved to be the only catalytic system totally responding to a livingness criterion.

Ironically, if DMAP represents a very effective catalyst for the metal-free ROP of LA, it is also one of the less active. To circumvent that problem, Péruch *et al.* applied in 2010 the concept of ''dual catalysis'' to enhance the polymerization activity.[36] That notion, where a Lewis acid supports a nucleophile to gain an increased catalytic effect, broadly falls in the categories of cooperative (synergistic)[37] or cascade catalysis,[38] depending on the proposed polymerization mechanism and is related to the chemistry of frustrated Lewis pairs.[39] In their study, Péruch *et al.* developed an organocatalytic system containing both basic and acidic sites activating cooperatively the alcohol chain end and the LA monomer. To this end, equivalent amounts of DMAP and its protonated form (DMAP.HX) were used as a dual catalytic system for L-LA polymerization initiated by different alcohols (Scheme 1.6). It was shown that the corresponding DMAP/DMAP.HX systems are significantly more active than DMAP alone, and yield well-controlled poly(L-lactide) up to 15 000 $g\,mol^{-1}$ in DCM at 40 °C after 48 h. While enhancement of the reaction was demonstrated highly dependent on the nature of the counter-anion ($CF_3SO_3^- > CH_3SO_3^- > Cl^-$), transesterification reactions were prevented by fine-tuning the experimental conditions. Note also that this synergetic concept was later applied by Kakushi *et al.* by protonating DMAP with diphenyl phosphate.[40]

Scheme 1.4 Proposed mechanism for the ROP of LA using DMAP catalyst. Route A: nucleophilic activation; route B: basic activation.



Scheme 1.5 Representation of both basic and nucleophilic activations of the (propagating) alcohol and the LA monomer, respectively. The nucleophilic activation of the LA monomer is here envisioned if free DMAP is present in the reactive medium. (The number of DMAP implied into the coordination of the OH may vary from 1 to 3.)



Scheme 1.6 Possible activation mechanism of LA during its polymerization from a DMAP/DMAP.HX mixture.

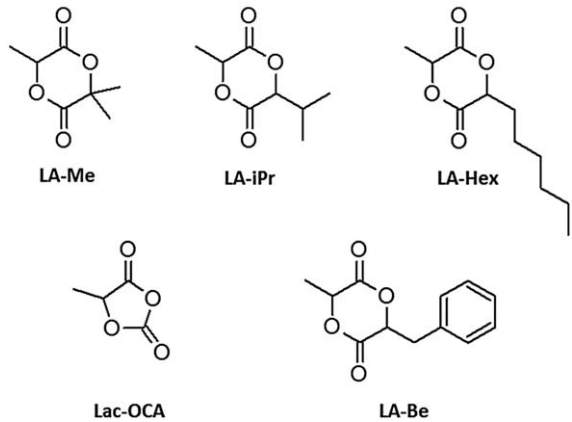
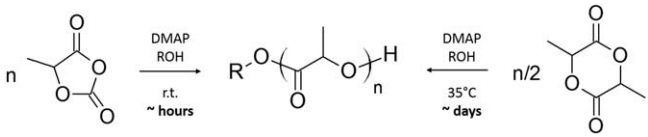


Figure 1.1 Structures of functionalized lactides (LA-Me, LA-*i*Pr, LA-Hex, LA-Be) and lactic *O*-carboxyanhydride (Lac-OCA) polymerized by DMAP catalyst.

Next to lactide, a series of other monomers have also been polymerized with pristine DMAP (Figure 1.1). Alkyl-substituted LA were studied by Moeller and coworkers starting in 2004.[41,42] In their study, authors did compare the catalytic efficiency of DMAP to the well-known tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) catalyst. Used in the same concentration (1.5 mol% *vs.* monomer, $[ROH]_0/[DMAP]_0 = 2$), DMAP was demonstrated more active than its metallic homologue. After 24 h in bulk at 110 °C, a 65% conversion was recorded for LA-Me showing good control in terms of molecular weight and dispersity values. By using an excess of DMAP ($[ROH]_0/[DMAP]_0 = 0.5$), polymerizations of LA-Me, LA-*i*Pr, LA-Be and LA-Hex reached 35, 80, 95 and 97% conversion, respectively, in only one hour. Interestingly, this result indicates that DMAP is more efficient in polymerizing steric-hindered lactides (with good control in both M_n and $Đ_M$) than $Sn(Oct)_2$ catalyst.



Scheme 1.7 DMAP catalyzed ROP of LA and lac-OCA.

In 2006, Bourissou *et al.* employed DMAP to catalyze the polymerization of the lactic *O*-carboxyanhydride (Lac-OCA, Figure 1.1).[43] This α-lactone equivalent exhibited remarkable reactivity compared to LA in DMAP catalyzed ROP (Scheme 1.7). Depending on the targeted DP (10–600), complete monomer conversions were obtained in minutes to hours (in CH_2Cl_2, 0.75 M, $[ROH]_0/[DMAP]_0 = 1$) while four days were necessary for DMAP to catalyze a DP 10 in LA at 35 °C. Such differences in terms of activity between the two monomers is due to the liberation of carbon dioxide when Lac-OCA is ring-opened and not to the mechanism strictly speaking, which, based on computational investigations, is ascribed to a base-catalyzed route.[44] The optimized intermediates and transition states substantiate the role of multiple hydrogen bonding, evidencing the possibility of the DMAP acting as a bifunctional catalyst. Remarkably, if a basic-catalyzed mechanism may lead to the deprotonation of the α-methine hydrogen of OCA during a ROP process,[45,46] no detectable amount of epimerization of the stereogenic carbon atom of Lac-OCA was observed by homonuclear decoupled ^{1}H NMR spectroscopy.

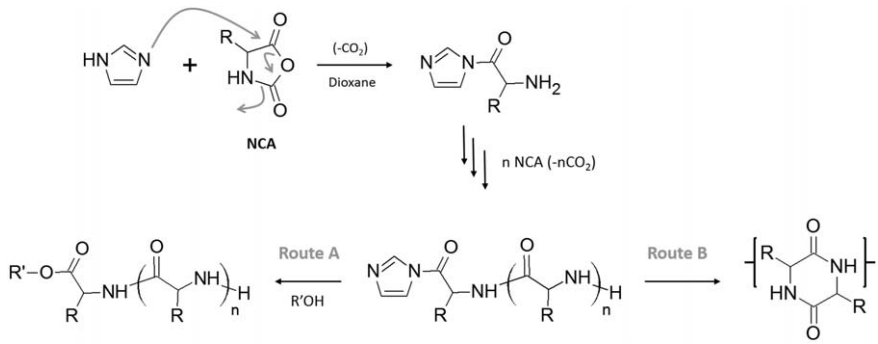
To face the low propensity of DMAP to polymerize other lactones than LA, *e.g.* ε-caprolactone (CL) and ω-pentadecalactone (PDL),[47–49] Dove *et al.* explored the cooperative effects between Lewis acids and the DMAP organobase (beyond others).[50] While a cocatalysis with YCl_3 and $AlCl_3$ delivered intermediate and no activity, respectively, the combination of DMAP with MgI_2 was revealed to be a very active catalytic duo for both PDL and CL polymerizations. In only two hours, PPDL and PCL samples of 70 000 g mol^{-1} ($Đ_M \approx 1.8$) and 29 000 g mol^{-1} ($Đ_M \approx 1.3$), were prepared in toluene at 110 °C and in THF at 70 °C, respectively.

1.2.2 Imidazole-based Initiation

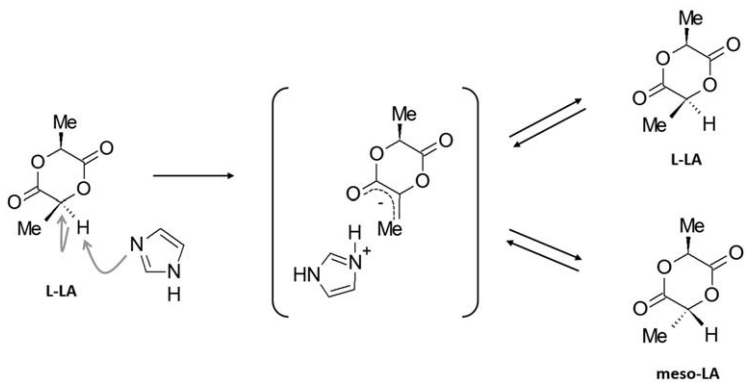
Next to DMAP, the less toxic imidazole has also been proved to be an efficient catalytic system for transesterification reactions between aliphatic acid esters and alkyl alcohols.[51] In 2003, imidazole was demonstrated as being as efficient as DMAP for a series of reactions between anhydrides and various alcohols under microwave treatment.[52] At the beginning of the 21st century, Kricheldorf and coworkers highlighted the ability of imidazole to promote and lead polymerizations of α-amino acid *N*-carboxyanhydrides (NCA) and L-LA.[53,54] A series of NCAs from sacrosine (Sar), D,L-leucine (Leu), D,L-phenylalanine (Phe) and L-alanine (Ala) was prepared and polymerized in dioxane at 60 °C for two days and various NCA-to-imidazole ratios. As attested by

^{1}H-NMR spectroscopy and MALDI-ToF spectrometry, the authors concluded that polymerizations of Sar, Leu and Phe led majorly to the formation of cyclic oligopeptides obtained from the combination of chain-growth, step-growth and cyclization processes (Scheme 1.8, route B). Comparatively, in the case of poly(Ala), the solubility of the secondary polymer structure induced the rapid precipitation of the growing macromolecule preventing the cyclization step and leading to linear poly(Ala) (Scheme 1.8, route A).

The rare combination of both chain- and step-growth processes has also been observed during the L-LA polymerization initiated/catalyzed by imidazole-based molecules.[54] Bulk polymerization of L-LA (~100 °C) results in complete polymerization within two days. After four hours of reaction, even-numbered PLA cycles were observed and obtained from end-to-end cyclizations. Authors demonstrated that all prepared cycles were amorphous, suggesting a base-catalyzed racemization from reversible deprotonation of the LA α-CH group by the imidazole molecule (Scheme 1.9). Longer reaction times favored the equilibration with odd-numbered PLA cycles and has been observed total after eight hours at 150 °C. If several protic heterocycles are



Scheme 1.8 Imidazole initiated ROP of NCAs.



Scheme 1.9 Reversible α-deprotonation of L-LA by imidazole.

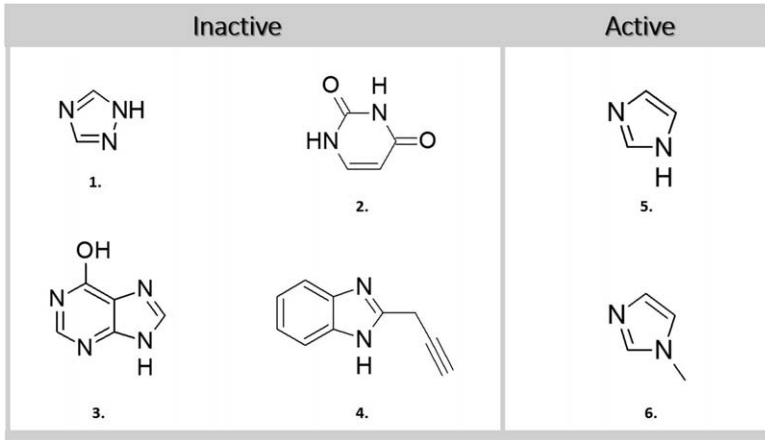
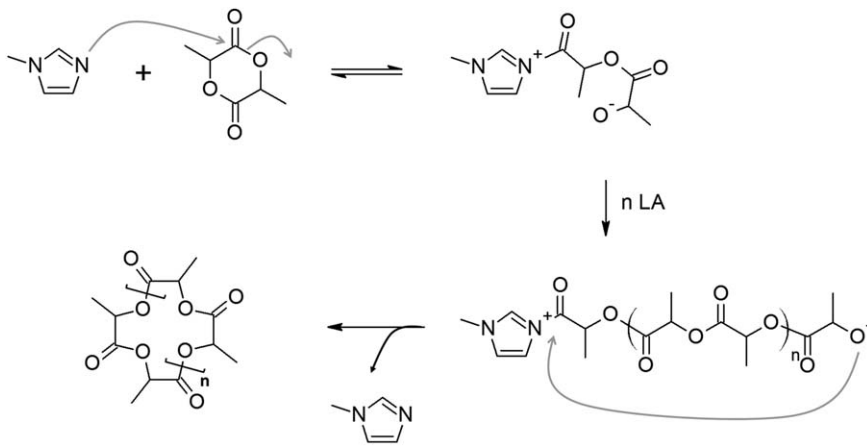


Figure 1.2 Heterocycles tested for the bulk ZROP of L-LA: 1. 1,2,4-triazole; 2. uracil; 3. hypoxanthum; 4. benzylimidazolyl acetonitrile; 5. imidazole and 6. *N*-methyl imidazole.



Scheme 1.10 *N*-methylimidazole-catalyzed ZROP of LA.

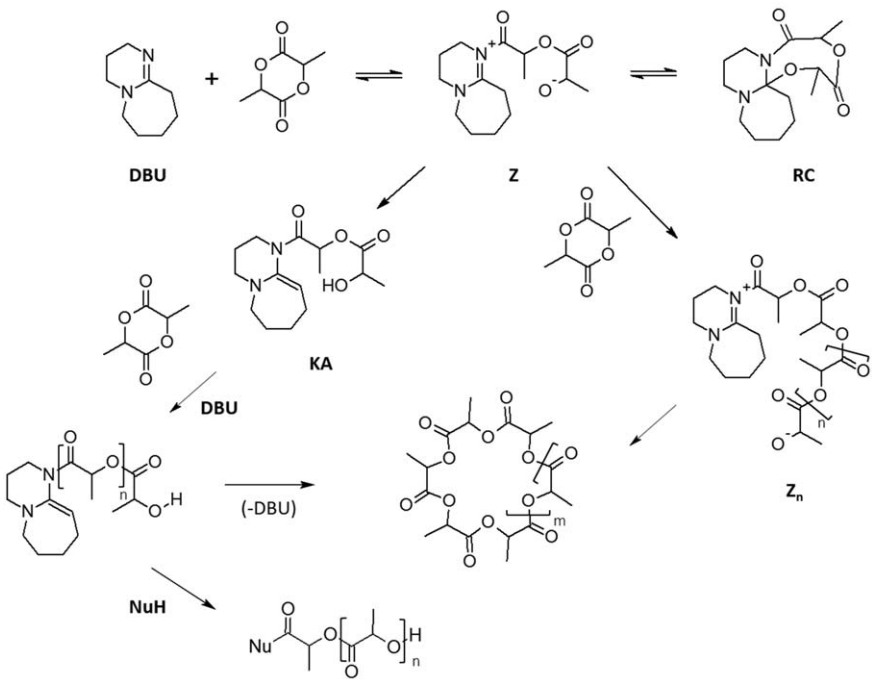
also tested (Figure 1.2), the *N*-methyl imidazole is the only one active in bulk, leading to cyclic PLA (with several by-products). The formation of PLA macrocycles is explained by a zwitterionic mechanism as outlined in Scheme 1.10.

1.2.3 Amidine/Guanidine-based Initiation

Lewis bases such as DMAP and imidazole-based molecules present the ability to promote acylation processes due to their adequate nucleophilicities.[55] Among potential other candidates, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) have also been

demonstrated highly active in representative reactions[56–60] despite the fact they have also been termed as ''non-nucleophilic'' bases.[61–64] Mayr and coworkers clarified the situation by determining quantitatively their nucleophilicities and their Lewis basic characters.[65,66] As compared to DMAP, both nucleophilicities and Lewis basicities gradually increase in the series DMAP < DBU < DBN.

In 2012, Waymouth *et al.* studied the possibility of using both DBU and DBN to promote the ZROP of lactide in the absence of an exogenous protic initiator (Scheme 1.11).[67] While no reactions were observed in THF at r.t., polymerizations proceeded readily in DCM and THF/DCM mixtures affording PLAs with M_n up to 53 000 g mol^{-1} and $Đ_M < 1.6$. Discordance between theoretical and experimental molar masses is observed, hampering the control of the polymerization process ($M_{n,\mathrm{exp}} > M_{n,\mathrm{th}}$). The rate of polymerization is first order in lactide and demonstrated to be approximately three times higher with DBU than with DBN. MALDI-ToF mass spectrometry and dilute solution viscosity studies revealed that resulting polymers were predominantly cyclic polylactides, along with minor amounts of linear PLA. Theoretical studies suggested that both DBU and DBN may act as nucleophilic initiators leading to the *in situ* generation of a zwitterionic species (Z) in equilibrium with its ring-closed homologue (RC). Addition of lactide to the alkoxide of the zwitterion Z results in chain growth to larger structures (Z_n). Cyclization by attack of the alkoxide end-group to the electrophilic acyl

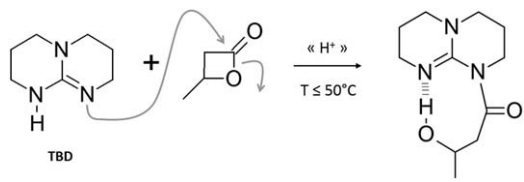


Scheme 1.11 Proposed mechanism for the DBU-mediated ZROP of LA.

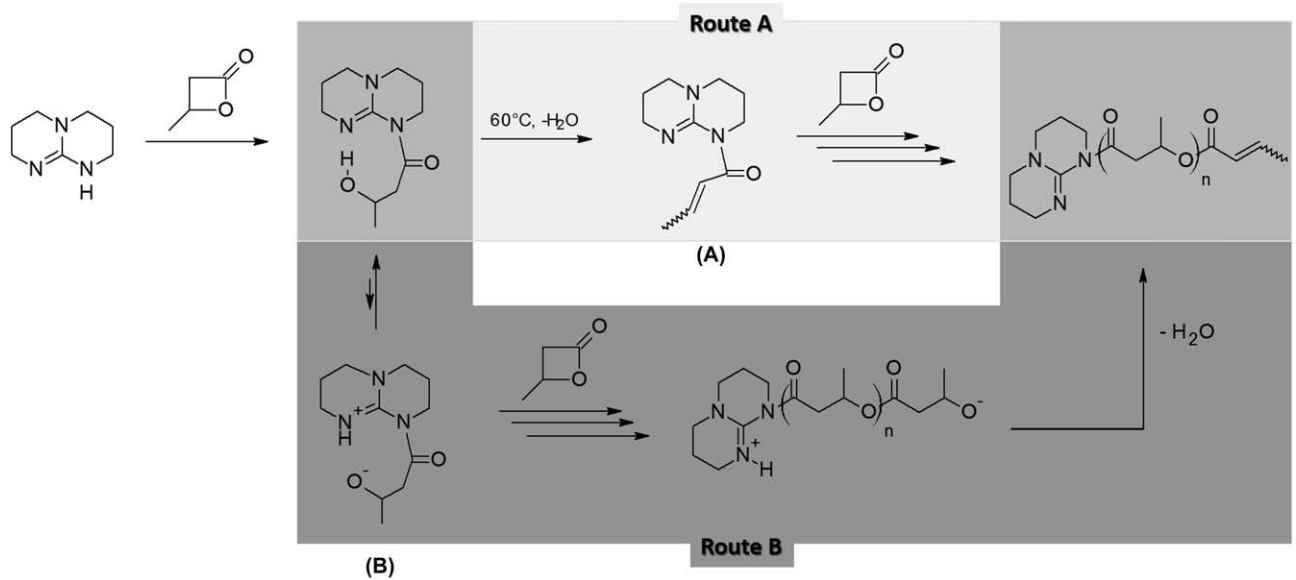
amidinium liberates the cyclic PLA and the pristine amidine. Contamination of those cyclic structures by linear species was explained by the energetically accessible ketene-aminal intermediate (KA) obtained by deprotonation of Z. In the presence of excess DBU, KA could undergo a chain growth process generating linear PLA. Under the workup procedure, substitution of the amidine by exogenous nucleophile (NuH) would lead to NuH end-capped chains.

The ability of both amidine and guanidine to initiate the nucleophilic ZROP of β-lactones has also been assessed.[68] Guillaume *et al.* demonstrated the efficiency of both DBU and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) to act as neat initiators in the ROP of the recalcitrant BL in bulk at 60 °C. Interestingly, the inability of that lactone to be polymerized by using TBD was claimed by Hedrick *et al.* in 2006 when performing the reaction in solution at r.t. (in the presence of an alcohol).[69] The authors demonstrated by ^{1}H and HMBC 2D-NMR that a 1 : 1 mixture of TBD and BL induces the formation of an acyl intermediate stabilized by strong hydrogen bonding of the acidic proton of the ring-opened BL to the adjacent TBD nitrogen atom (Scheme 1.12). Attempts to disrupt this H-bonding at 50 °C led to the generation of oligomers and crotonate byproducts. Theoretical calculations have also proved that this amide-like intermediate is too highly stabilized, presenting an ''insurmountable'' energy barrier to propagate.[70]

The effective ROP of BL was however demonstrated by Guillaume *et al.* when performing the polymerization reaction in bulk at 60 °C, highlighting the importance of both monomer concentration and temperature. For various monomer-to-catalyst ratios ($[BL]_0/[TBD \text{ or } DBU]_0 = 100–500$), TBD proved to be better than DBU at promoting polymerizations. PBL samples presented experimental molar masses in accord to the theoretical ones (up to 20 000 g mol^{-1}) and proportional to the conversion evolution. All attempts to improve the kinetics by increasing the temperature (up to 90 °C) led to an uncontrolled process characterized by PBL of relatively low molar masses. Interestingly, the introduction of an excess of exogenous alcohol (1 to 10 eq. *vs.* the catalyst) did not affect significantly the polymerization in terms of kinetics and microstructure. Multinuclear NMR spectroscopies and MALDI-ToF spectrometry allowed the authors to speculate on the nature of the PBL end-groups corresponding likely to an amidine (or guanidine) α-chain end and ω-crotonate moieties. The origin of those end-groups was postulated from two possible mechanistic routes (Scheme 1.13) involving either the



Scheme 1.12 Formation of a stable adduct between TBD and BL (in presence of a protic alcohol, H^+).



Scheme 1.13 Proposed nucleophilic mechanisms for the BL ROP from TBD in bulk at 60 °C.

in situ generation of an *N*-acyl-α,β-unsaturated species (**A**) (Scheme 1.13, route A) or the generation of a zwitterionic intermediate (**B**) able to ring-open BL monomers (route B).

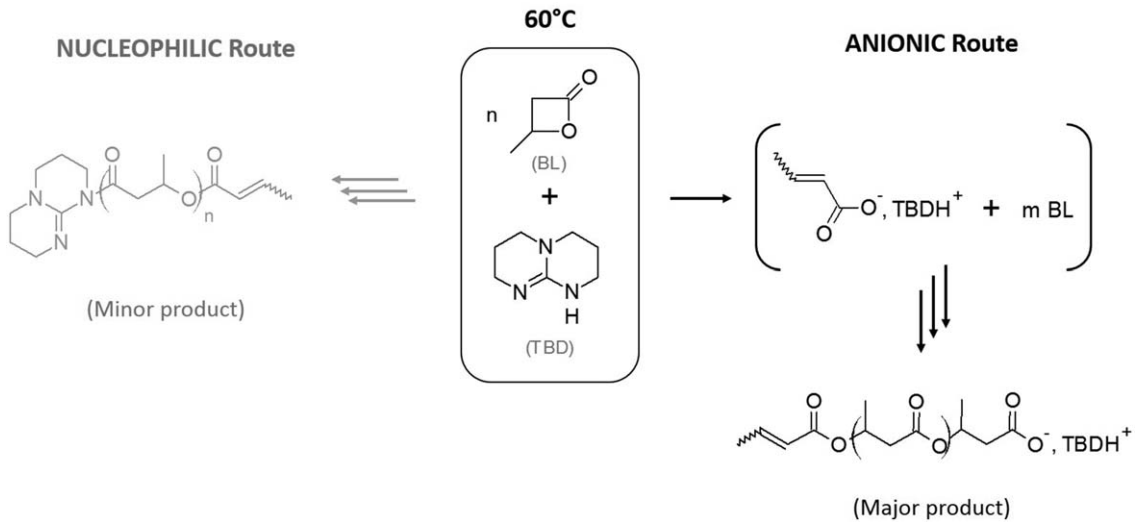
Quite recently, the bulk ROP of BL from TBD (only) at 60 °C has been reinvestigated.[71] On the contrary to the Guillaume's report, results proved that the process is majorly due to an initial deprotonation of the monomer from the guanidine base generating *in situ* crotonate initiators for which the carboxylate ($-C(O)O^-$) is compensated by the protonated TBD ($TBDH^+$). The association of experimental technics allowed attesting that the previously established nucleophilic mechanism is marginal while the anionic one is dominant. Thanks to ^1H/DOSY NMR and MALDI/ESI-MS, TBD was also demonstrated not covalently linked to the PBL chain mainly playing the role of counter-ion in the $-C(O)O^-$, $TBDH^+$ active site (Scheme 1.14).

1.2.4 Tertiary Amine-based Initiation

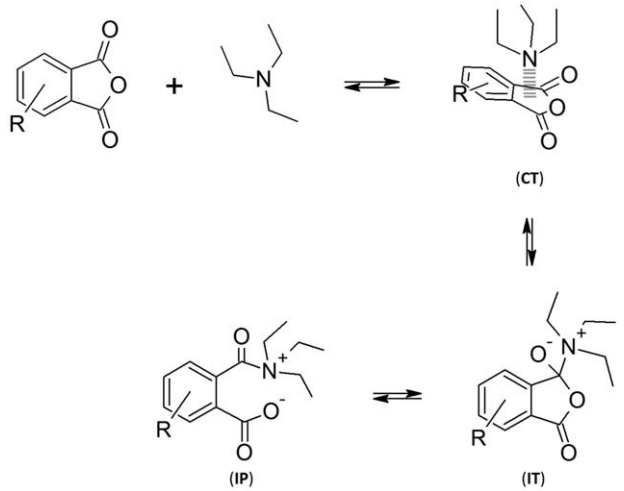
In the early 1970s, the ability of tertiary amines, such as triethylamine (TEA), to react with carbonyl groups by a nucleophilic attack *via* a "charge transfer" (CT) complex formation was discussed.[72] The Authors demonstrated that a CT complex intermediate, either formed in the steady state concentration or in pre-equilibrium with the reactant, induced the generation of an ionic tetrahedral (IT) structure leading to an ion pair (IP) product. This typical nucleophilic catalysis was peculiarly studied for the reaction of phthalic anhydrides with TEA (Scheme 1.15).[73]

Just like with pyridine (*cf.* Section 1.2.1), Kricheldorf put the nucleophilic behavior of tertiary alkylamines to good use by realizing the ZROP of pivalolactone (PL).[16] To that end, three aliphatic tertiary amines, namely TEA, diazabicyclooctane (DABCO) and 2-ethyloxazolidine (2-EOX) were selected. Polymerizations were realized in NMP at 20 and 100 °C for 48 and 24 h, respectively. No information on molecular masses and dispersities were provided by the authors. Quantitative polymerizations from DABCO were obtained whatever the temperature used. MALDI-ToF mass spectrometry of the as-obtained PVL exclusively displayed mass peaks of linear chains obtained from a chain growth process from both nitrogens. In the case of TEA and 2-EOX, a 100 °C temperature was required to reach, respectively, 98 and 50% conversions. In both cases, the ZROP of PL was the prevailing process but was hampered by side reactions such as initiation from water when TEA was used and formation of cyclic oligolactones from a 2-EOX initiation. The authors concluded that the cyclization process issued from an end-to-end reaction between the nucleophilic carboxylate end-group and the electrophilic methylene group of the oxazolidine moieties (Scheme 1.16).

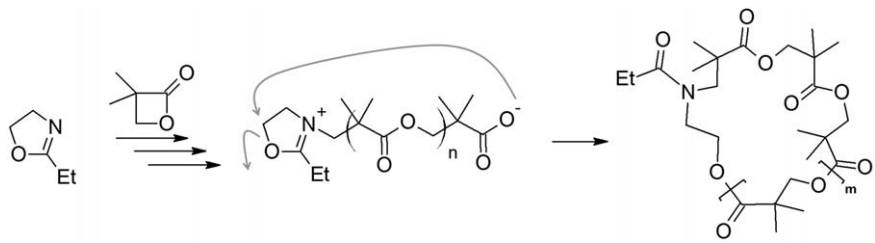
The polymerization of dithiolane-2,4-dione (DTD) was described by Kricheldorf and coworkers about 45 years ago.[74,75] It was found that tertiary amines were the only useful catalysts to generate high molar mass poly(thioglycolide)s. Due to a lack in characterization technics at that time, the mechanism of the reaction was only elucidated in 2007.[76]



Scheme 1.14 Comparison between nucleophilic and anionic routes leading to PBL chains as obtained from bulk ROP of BL at 60 °C and initiated from TBD.



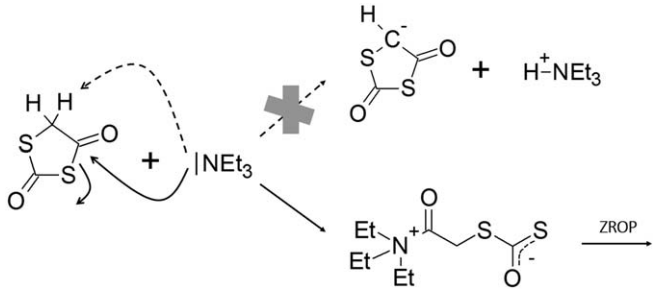
Scheme 1.15 Postulated mechanism of the reaction between phthalic anhydride molecules and triethylamine.



Scheme 1.16 Polymerization of PL from 2-EOX and backbiting cyclization reaction.

Polymerizations were performed in dioxane at 20 °C using TEA as catalyst at a monomer–catalyst ratio of 20. After two days of reaction, polymerizations were worked up with three different NuH non-solvents including water, methanol and ethanol. MALDI-ToF mass spectrometry allowed them to conclude that TEA reacted by formation of an initiating zwitterion leading after precipitation in the NuH non-solvent to a mixture of cyclic and linear chains end-capped by the used NuH. This result contradicted the speculated mechanism of 1973 where the authors assumed that TEA was deprotonating DTD, resulting in a carbanion initiating the ROP process (Scheme 1.17).

As DBU, low and mild basic sparteine and sparteine surrogates have also proven to be highly effective for the ROP of LA monomers by activating the alcohol initiator.[77,78] Inspired by the pioneering works of Kricheldorf on the use of alkali tertiary amines to promote ZROP of various heterocyclic monomers, some of us decided to investigate whether (+)-sparteine (SP) can act as an efficient initiator for the ROP of L-LA without the use of an exogenous protic source.[79] Polymerizations were realized in DCM ($[LA]_0 = 2M$)



Scheme 1.17 Hypothetical initiation mechanisms and reaction product of TEA-initiated ZROP of dithiolane-2,4-dione.

at r.t. for $[LA]_0/[SP]_0$ ranging from 20 to 300. SEC analyses, ^{1}H-NMR spectroscopy and MALDI-ToF mass spectrometry allowed us to make conclusions on the effective ZROP of L-LA from both nitrogens of the SP initiator. Highly pure (>95%) *cyclo*-PLAs were obtained with dispersities ranging from 1.13 to 1.47. The molecular mass evolution joined to a kinetic study allowed us to make conclusions on a polymerization characterized by a rate of propagation (k_p) much higher than the initiating one (k_i). Therefore, controlled molar masses were only obtained for high LA-to-SP ratios rending possible the generation of controlled *cyclo*-PLAs with M_n up to 13 500 g mol^{-1}. The controlled formation of cyclic polyesters was ascribed to a backbiting process from an *in situ* generated tertiary amine-containing symmetrical binary zwitterion.

1.2.5 Phosphine-based Initiation

In 1993, Vedejs and coworkers reported tributylphosphine (Bu_3P) as a potent catalyst for the acylation of alcohols by acetic acids and anhydrides.[80,81] As compared to DMAP, which is a more versatile catalyst due to its double role as nucleophile and base, the authors brought in evidence that Bu_3P is less sensitive and not deactivated by carboxylic acid, does not require basic additives and is appropriate to be used in neutral conditions for acylation reactions proceeding through a nucleophilic activation mechanism. Consequently, Hedrick *et al.* surmised that tertiary phosphines could be another general class of ROP catalyst and studied a series of phosphines as transesterification agents for the LA polymerization.[82] Reactions were realized both in bulk (135 and 180 °C) and in solution (THF, toluene and DCM). When performed in bulk, the catalyst concentration proved to be an important variable and excess of tertiary phosphines as compared to the initiating alcohol must be precluded to limit adverse transesterification reactions. In that condition ($[\text{phosphines}]_0/[\text{initiator}]_0 = 1$), narrowly dispersed PLA ($M_w/M_n = 1.1$–1.4) with predicted molecular weights (target DPs 30–100) have been produced (in minutes to hours regarding the catalyst). Kinetical studies revealed that phosphine activity is dependent on the nature of their

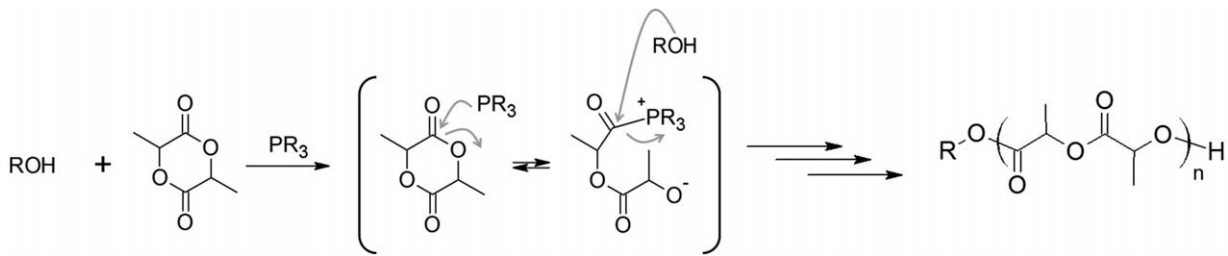
substituents and on the general steric hindrance according the following order: P(*n*-Bu)$_3$ > P(*tert*-Bu)$_3$ > PhPMe$_2$ > Ph$_2$PMe > Ph$_3$P > P(MeO)$_3$ ≈ 0. Alkyl-substituted phosphines are more basic/nucleophilic than phosphines containing aryl ligands promoting then a faster reaction while P(*tert*-Bu)$_3$ is less active than P(*n*-Bu)$_3$ due to the steric constraints. Even by using the most active Bu$_3$P, polymerizations realized in solution were slower and less selective than those catalyzed by DMAP with, for example, a conversion of 60% achieved in one week at 50 °C in THF (target DP 60). ^{1}H-NMR and SEC analyses of the as-obtained PLA, joined to the reactivity order of the various studied phosphines, support a nucleophilic-based LA ROP process (Scheme 1.18).

1.2.6 N-heterocyclic Carbene-based Initiation

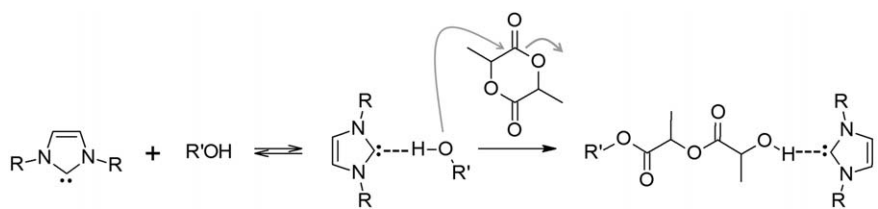
The demonstration by Breslow that stabilized singlet carbenes derived from thiamine cofactors are nucleophilic catalysts[83] and the pioneering works of Wanzlick and coworkers[84–88] on the deprotonation of thiazolium and imidazolium salts are to date considered as the initiating steps on the use of NHCs as nucleophilic catalysts.[89] In 2002, independent works of Nolan,[90] and Hedrick and Waymouth[91] on the use of NHCs as performing catalysts for transesterification reactions led to their investigation as catalysts for ROP of lactones.[92]

Initially, NHCs were used in presence of alcohol initiators.[93–96] The first reported example was dealing with the ROP (in THF at 25 °C) of a series of (di)lactones in the presence of the 1,3-bis-(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes) NHC and various alcohol initiators.[97] Whatever the monomer used, the obtained molecular weights closely tracked the monomer-to-initiator ratios, dispersities were narrow and the process exhibited features of a ''living'' polymerization. At that time, Hedrick and Waymouth proposed two possible mechanisms: (a) an anionic/basic ''chain-end'' mechanism where the carbene activates the initiating/propagating alcohol by H-bonding (Scheme 1.19), and (b) a monomer-activated ''nucleophilic'' mechanism involving a zwitterionic intermediate (Scheme 1.20).

While both mechanisms were conceivable, experimental results suggested that the carbene acts as a nucleophile and not a base. For transesterifications of esters with ethyl alcohol catalyzed by *N*-alkyl-substituted carbenes, the pK_a of the alcohol[98] is higher than that of the conjugate acid of the carbene (30 *vs.* 22–24 in DMSO).[99,100] Thus, it is unlikely that the carbene catalyzes the ROP process by deprotonating the less acidic alcohol. Additionally, a steric effect observed by Waymouth and Hedrick indicated that the reaction occurs *via* nucleophilic catalysis and not base catalysis.[91] Contradictory results were however postulated in 2005 where DFT calculations suggested that the zwitterionic intermediate (Scheme 1.20) was higher in energy than the H-bonded adduct (Scheme 1.19), implying a more probable ''chain-end activation'' mechanism when an exogenous alcohol is used.[101] Finally, Arnold *et al.* demonstrated that NHCs in the presence of alcohol can



Scheme 1.18 Plausible nucleophilic polymerization of LA from tertiary phosphines.



Scheme 1.19 Anionic/basic ''chain-end'' mechanism for the NHC-mediated ROP of LA in the presence of alcohol.

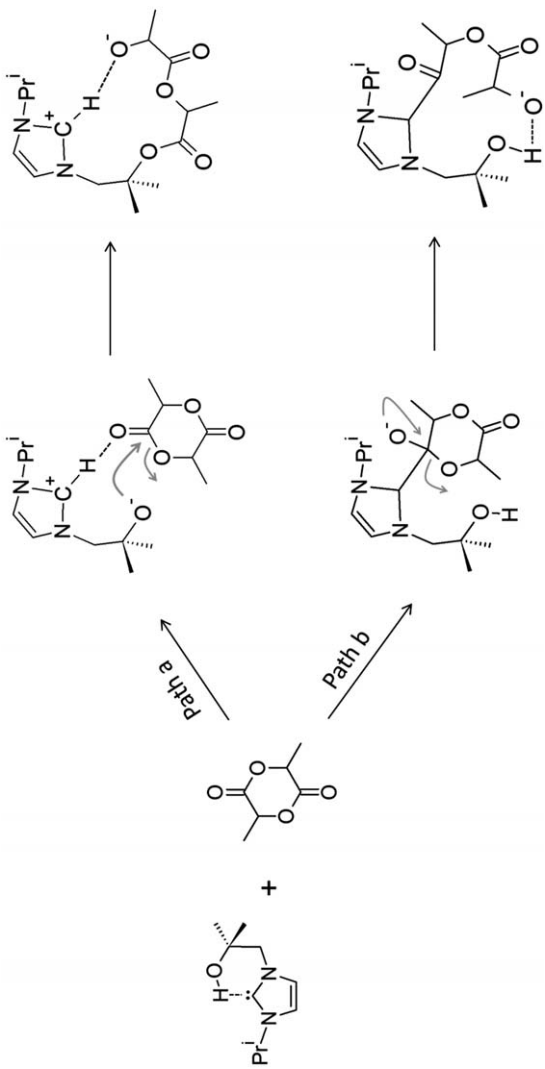
Scheme 1.20 Monomer-activated ''nucleophilic'' mechanism for the NHC-mediated ROP of LA in the presence of alcohol.

act as bifunctional catalysts, suggesting that both mechanisms may compete.[102] To that end, a reaction between a hydroxylated NHC with one equivalent of D,L-LA in THF, pyridine or toluene afforded two compounds (Scheme 1.21). Those products were identified as being issued from either an alkoxide initiator (path a, Scheme 1.21) or a nucleophilic one (path b, Scheme 1.21).

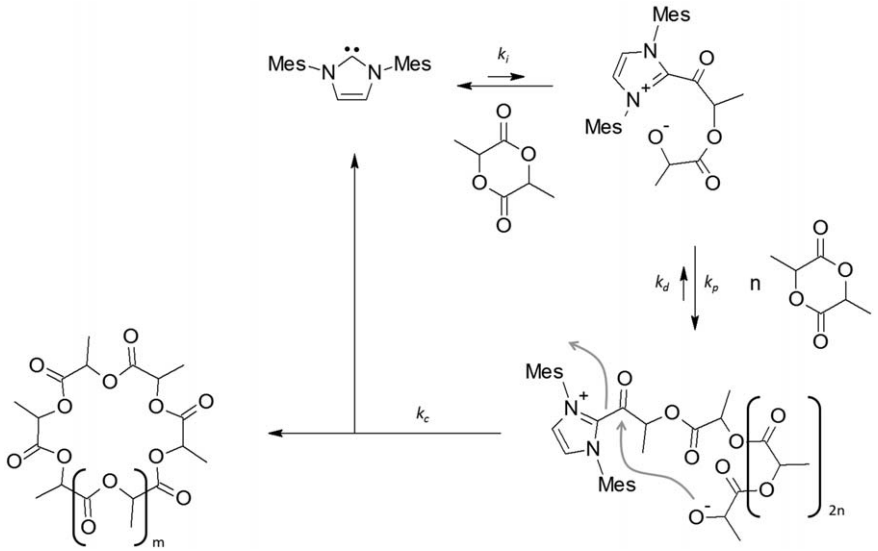
The zwitterionic intermediate generated *in situ* by the nucleophilic attack of NHC on LA has been indirectly evidenced by Waymouth *et al.* by performing polymerization in the absence of an alcohol initiator.[103,104] Remarkably, the polymerization of *rac*-LA with 1,3-dimesitylimidazol-2-ylidene (IMes) in THF ($[LA]_0 = 0.6–1.0$ M) occurs rapidly (5–900 s) at 25 °C to yield PLAs with molecular weights from 7 to 26 kg mol^{-1}. The combination of SEC, ^{1}H-NMR spectroscopy and MALDI-ToF analysis indicated that the resulting PLAs were of cyclic nature. As attested by DSC, cyclic PLAs obtained from either L- or D-LA are isotactic. As compared to their linear homologues,[105] the as-obtained semi-crystalline cyclic PLAs present both lower melting point and optical rotation (linear: $T_m = 181$ °C, $\Delta H_f = 85$ J g^{-1}, $[\alpha]_D = -156°$; cyclic: $T_m = 133$ and 143 °C, $\Delta H_f = 22.7$ J g^{-1}, $[\alpha]_D = -118°$).[104,106,107] This suggests possible epimerization reactions of either the LA monomer or the polymer by the basic IMes.[103,108] Kinetic investigations revealed a slow initiation step that is second order in monomer rationalizing the reversible formation of the zwitterionic intermediate and a first order propagation, much faster than the initiation step ($k_p \gg k_i$).[109] The observed molecular weight distributions *vs.* monomer conversion are explained by the fast propagation relative to the macrocyclization and the slow initiation at high monomer conversion due to its second-order dependence on lactide. Finally, the cyclization, although slow relative to the propagation ($k_p > k_c$), places limits on the molecular weights that can be achieved liberating the carbene and generating cyclic PLAs (Scheme 1.22).

Cleverly, the possibility of acyl imidazolium being attacked by the alkoxide end group, *i.e.* evidencing the viability of the cyclization step, has been assessed by reaction between sodium methoxide and an IMes benzoyl chloride derivative (Scheme 1.23).[103] To that end, an acyl imidazolium was generated from the reaction of IMes and benzoyl chloride. The as-obtained product was quickly reacted with sodium methoxide yielding the pristine IMes and the expected methyl benzoate.

Stochastic kinetic simulations suggest that the ZROP of lactide from IMes NHC is not a living polymerization, that the initiator efficiency is less than 75% (even at high monomer concentration) and that the carbenes that did not form zwitterions (or those liberated after cyclization) do not initiate chains later in the process. The amount of active zwitterion is not predictable and does not allow the control of PLA molecular weights from the initial $[LA]_0$-to-$[IMes]_0$ ratio.[109] If the kinetic control of the LA ZROP from pristine IMes is certain, however, its feasibility is delicate for a reaction completed in few seconds and a slightly slower process may be of interest. Because the quantity of initiating zwitterion is function of both monomer and NHC



Scheme 1.21 NHC bifunctionality demonstrated on LA; path a: anionic/basic mechanism; path b: nucleophilic mechanism.

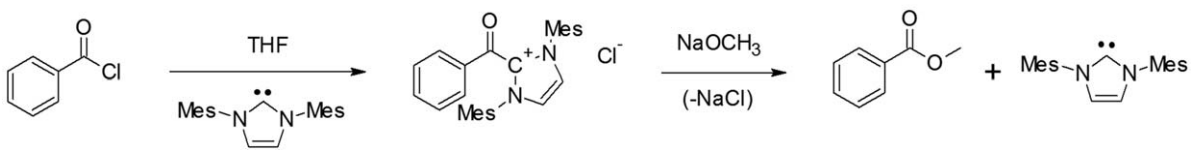


Scheme 1.22 Proposed mechanism for the synthesis of cyclic PLA from 1,3-dimesitylimidazol-2-ylidene (IMes) NHC (with k_i, k_p, k_d and k_c corresponding to rate constants of initiation, propagation, depolymerization and cyclization, respectively).

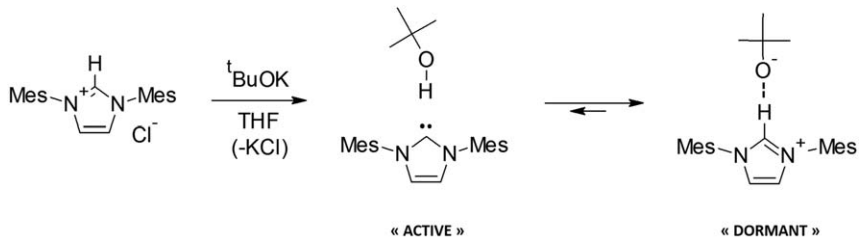
concentrations, diluting the medium of polymerization would not be of help. To slow down the overall kinetics (while maintaining the same initial $[LA]_0$), the ability that allows the IMes carbene to reversibly form a ''dormant'' adduct was exploited in 2010.[110] Rather than using an isolated carbene, the authors took advantage of the reversible hydrogen-bonded adduct formed between IMes and *t*-BuOH.[111] The ZROP of LA was then initiated in THF (at r.t.) by using the non-isolated IMes carbene produced *in situ* by reacting its corresponding chloride salt and potassium *tert*-butoxide (*t*-BuOK). As outlined by Scheme 1.24, the generated ''dormant'' alcohol adduct is in equilibrium with the ''active'' IMes carbene and free *t*-BuOH unable to initiate the ROP of lactones.[91,112] This allows diminishing the carbene activity by a factor of *ca.* 15 (all other experimental conditions unchanged). Such modification of kinetics allows preparation of ''jellyfish'' structures based on a PLA macrocyclic inner-core grafted by poly(methyl methacrylate) chains.[110]

Because the aryl substituted IMes carbene is inactive towards larger lactones, such as ε-caprolactone (CL) and δ-valerolactone (VL),[113,114] Waymouth *et al.* used more nucleophilic *N*-alkyl-substituted carbenes[115] such as 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene (**1**), 1,3-diethyl-4,5-dimethylimidazol-2-ylidene (**2**) and 1,3,4,5-tetramethylimidazol-2-ylidene (**3**) to investigate the ZROP of CL in absence of alcohol (Scheme 1.25).[116]

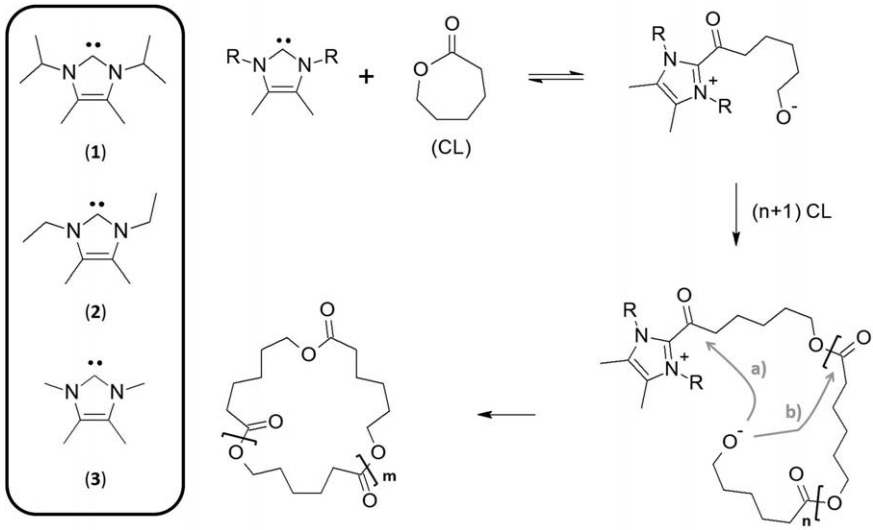
As compared to the LA ZROP from IMes, the polymerization of CL from carbenes (**1**)–(**3**) generates polymers of ultrahigh molecular weights



Scheme 1.23 Indirect proof of the cyclization step presented in Scheme 1.21: reaction of NHC acyl-imidazolium with sodium methoxide.



Scheme 1.24 Equilibrium between ''active'' IMes and its corresponding ''dormant'' hydrogen-bonded tertiary alcohol adduct.

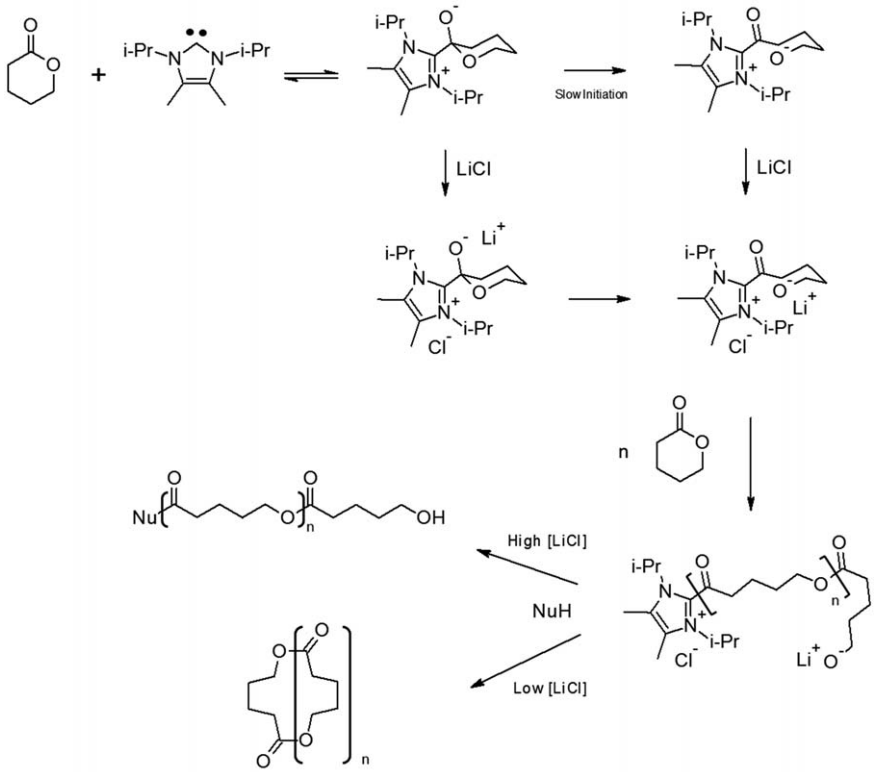


Scheme 1.25 1,3-Diisopropyl-4,5-dimethylimidazol-2-ylidene (**1**), 1,3-diethyl-4,5-dimethylimidazol-2-ylidene (**2**) and 1,3,4,5-tetramethylimidazol-2-ylidene (**3**) alkyl-substituted carbenes used for the ZROP of CL.

($M_n \leq 114.00$ g mol^{-1}) in a few hours. ^{1}H-NMR spectroscopy, MALDI-ToF spectrometry and SEC analyses confirm the cyclic nature of the PCL samples while doubts subsist on the purity of those by linear contaminants. The polymerization, performed in toluene or THF ($[CL]_0 = 1$M), is not controlled, the relatively low efficiency of initiation is dependent on the polarity of the medium and the synthetic strategy is suspected to yield entangled macrocyclic structures. Finally, the high dispersity values ($1.36 \leq Đ_M \leq 2.16$) support the hypothesis of a competition of cyclization between the alkoxide end-group on the acyl imidazolium extremity (path a, Scheme 1.25) and on internal ester group of the macrozwitterion (path b, Scheme 1.25). The ability presented by those alkyl-substituted carbenes to polymerize large lactones has also been taken into account for preparing cyclic gradient polymers by batch copolymerization of CL and VL.[117] To that end, Waymouth *et al.* utilized the unsaturated carbene (**2**) to produce a range of copolymer compositions. Polymerizations were realized in toluene ($[M_{tot}]_0 = 1$ M) at r.t. for reaction times ranging from 7 min to 2 h. The wide difference in reactivity between VL and CL ($r_{VL} = 26.4$; $r_{CL} = 0.38$) with carbene (**2**) gave access to gradient cyclic copolymers presenting melting points that are similar to the ones of homopolymers.

Kinetic studies[109,118] and theoretical simulations[119] brought some light on the complicated sequence of steps involved during the ZROP of lactones by NHCs. The *in situ* generated NHC-monomer complex presents a high energy barrier that account for a slow initiation leading to molecular weight polyesters significantly higher than expected. This is particularly true for the ZROP of VL from NHC;[120] SEC traces of polymer samples revealed the

presence of a high molecular weight shoulder all along the conversion evolution suggesting the presence of independent propagating species. Those include ion pairs, solvent-separated ion pairs, free ions and aggregates, all presenting an independent rate of propagation.[121] Because the situation in which the rate exchange between different ion pairs and/or aggregates is slow relative to the rate of propagation favors the appearance of bimodal molecular weight distributions, Waymouth *et al.* proposed a ZROP where the propagating alkoxide anion undergoes ion pairing with the acylimidazolium chain end to explain the as-observed broad and multimodal SEC traces. To evaluate the consequences of ion-pairing, the influence of LiCl to the ZROP of VL from the 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene carbene (**1**) has been investigated in THF at r.t. (Scheme 1.26). As expected, the addition of LiCl resulted in a more controlled polymerization with a good correlation between experimental and theoretical molar masses. While low distribution samples were obtained from a very efficient initiation, MALDI-ToF analysis revealed the presence of both linear and cyclic products whose proportions depend on the lithium salt initial content.



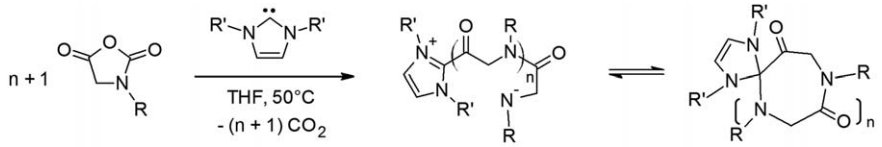
Scheme 1.26 Influence of the LiCl content on the ZROP of VL from 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene carbene.

The ZROP of β-lactones, such as β-propiolactone and β-butyrolactone (BL), with saturated IMes (SIMes) carbene also leads to polymers of cyclic nature further evidencing the intermediacy of zwitterions in that kind of process.[122] The authors discovered that reacting the SIMes with one equivalent of BL generates a zwitterion, which collapses to an isolable spiro imidazolidine compound (**SpI**) (Scheme 1.27). DFT calculations indicate that this compound is generated due to the release of ring strain from the four-membered lactone to the benefit of a five-membered ring. As compared to the ZROP of LA, CL and VL, the initiation of the polymerization from the spiro (**SpI**) occurs much more rapidly and is quantitative. That difference is due to the slightly higher nucleophilicity of the SIMes carbene relative to IMes[115] and the higher ring strain of the four-membered lactone[123] relative to that of larger lactones. Polymerizations present characteristics of a ''living'' process with a linear semilog plot evolution and molecular weights tracking the initial $[M]_0/[SIMes]_0$ molar ratios. As compared to the ZROP of LA, CL and VL, the authors proposed a novel mechanism involving a reversible collapse of the zwitterionic species to macrocyclic spirocycles all along the propagation. This mechanism responds to the definition of a ring-expansion polymerization on the same title as the ring-expansion of spirocyclic tin initiators[124] or cyclic Ru carbenes.[125]

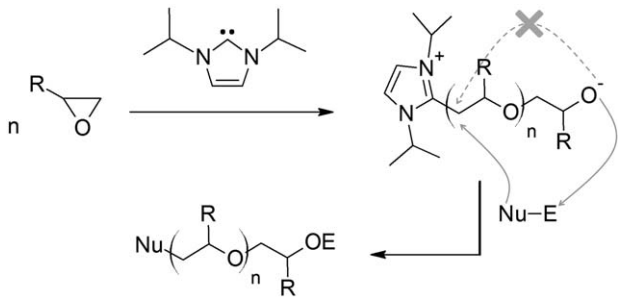
If unsaturated carbenes give access to cyclic polyesters, Zhang and coworkers also demonstrated their ability to (co)polymerize *N*-carboxyanhydride monomers (NCA).[126–129] The carbene-initiated ZROP of NCAs provides an elegant strategy for preparing cyclic poly(α-peptoid)s of controlled molecular weight (up to 30 000 $g\,mol^{-1}$) and characterized by narrow dispersities.[126] When realized in THF or toluene, the loss of CO_2 from the *in situ* formed zwitterion favors the efficiency of the initiation and explains the perfect agreement between the evolution of molecular weight with both NCA conversion and the initial $[NCA]_0$-to-$[NHC]_0$ ratio. Polymerizations performed in DMF or DMSO result in low oligomers whatever the starting $[NCA]_0/[NHC]_0$.[126] Top-down multidimensional mass spectrometry methods allowed Wesdemiotis *et al.* to demonstrated that NHC-mediated ZROP in THF at 50 °C yields spirocyclic poly(α-peptoid)s, *i.e.* carrying the NHC initiator on the *cyclo* poly(α-peptoid) (Scheme 1.28).[130]

Very interestingly, Gnanou and coworkers also reported that NHCs could trigger the ZROP of oxirane-based monomers, such as ethylene oxide (EO) and propylene oxide (PO).[131–133] By contrast to the ZROP processes applied on (di)lactones or on NCAs, no competitive intra- or intermolecular transfer reactions were observed during the ZROPs of those monomers leading exclusively to linear polyether chains. Cleverly, this strategy allowed the authors to use NuE moieties as terminating agents, leading quantitatively to α-Nu, ω-OE polymers through nucleophilic substitution of the imidazolium moiety by $Nu^{(-)}$ and concomitant reaction of the ω-growing alkoxide chain with $H^{(+)}$ (Scheme 1.29).

Scheme 1.27 ZROP of β-lactones using SIMes carbene.



Scheme 1.28 Spirocyclic poly(α-peptoid) generated by NHC-mediated ZROP of NCA.



Scheme 1.29 Linear end-functionalized polyether chains as obtained by ZROP of oxirane-based monomers (R = H or CH_3) followed by a NuE quenching step.

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