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Lewis Pair Polymerization: Perspective on a Ten-Year Journey

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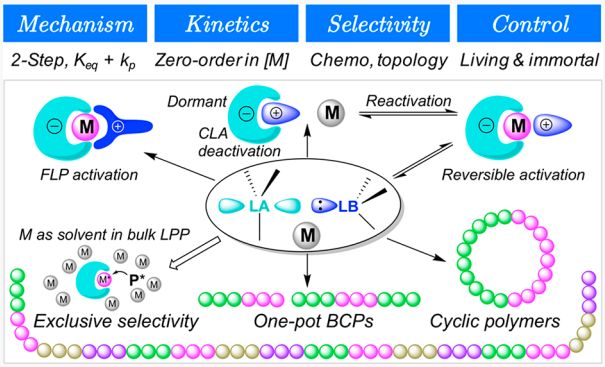
ABSTRACT: Ten years have passed since the conception of what was termed Lewis pair polymerization (LPP) that employs Lewis acid and base in pairs to not only activate monomers but also effect chain initiation, propagation, and transfer events. Compared to other polymerization methodologies, LPP's cooperative and synergistic two-component catalytic mechanism empowers several unique or advantageous features, including extraordinary tunability of catalyst/initiator systems, compounded thermodynamic and kinetic control over comonomer sequences in one-pot LPP of monomer mixtures for highly resolved block copolymers, complete chemoselectivity in LPP of multifunctional vinyl monomers, independent tuning of polymerization activity and target polymer molecular weight, controlled heat dissipation in bulk polymerization with unactivated monomers functioning as solvent molecules, and coupled selectivity and livingness with immortality of the active species to produce ultrahigh molecular weight polymers and block copolymers with record-number (53) blocks. Focusing on four fundamental attributes of any polymerization methodology—mechanism, kinetics, control, and selectivity—this Perspective narrates the growth and development of LPP, tracing each innovation back to fundamental principles so that each concept can be strategically applied, and describes new frontiers fertile for future research.



1. INTRODUCTION

Lewis pair polymerization (LPP),[1−3] a polymerization method introduced ten years ago,[4] uniquely utilizes both Lewis acid (LA) and Lewis base (LB) components to cooperatively and synergistically activate and polymerize a diverse scope of monomers. Through balancing the relative strength of LAs and LBs as well as steric interplays of Lewis pairs (LPs), chain initiation (k_i), propagation (k_p), termination (k_t), and transfer (k_{tr}) events can be significantly affected by Lewis pairing (during k_i) and ion-pairing (after k_i) dynamics, thus modulating activity, control (initiation efficiency, livingness, chain structure, topology, and sequence), and selectivity (regio-, chemo-, and stereoselectivity). The simple yet sophisticated chemistry of LPP has notably advanced synthetic polymer chemistry over the past ten years and continually inspired us and many other researchers to solve modern polymerization problems. By the time of the writing of this Perspective, LPP has been exploited to enable living polymerizations of many polar vinyl monomers[5−7] and controlled polymerizations of some of the most challenging vinyl monomers.[8−11] LPP has also been used to effect polymerizations of heterocyclic monomers, such as lactones,[2,12] epoxides,[13,14] cyclic carbonates,[15,16] and cyclic anhydrides.[17] The control of polymer topology,[14,18] architecture,[7] and sequence[19] has also been achieved by the LPP method.

Despite the significant advances already made over the past ten years, LPP is still a relatively young field as compared to other well-developed polymerization methods, and many features and opportunities for discovery are still unexplored. Just to highlight two frontiers at the outset, the chemoselectivity of LPP has been utilized to polymerize biorenewable monomers that are not polymerizable or polymerized effectively otherwise. As biomass conversion technology advances, many new bio-based monomers will become accessible and affordable. Utilization of such monomers represents not only a carbon-neutral strategy toward sustainable plastics but also an abundant, yet underexploited, source of carbon. However, biorenewable monomers are typically highly functionalized, as compared to petroleum-derived monomers before downstream functionalization, and therefore difficult to polymerize due to chemoselectivity challenges by conventional polymerization methods. In this context, LPP has successfully solved some notable challenges, polymerizing bio-based, multifunctional monomers such as

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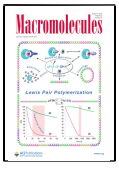

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sorbates,[18] crotonates,[9,20,21] cinnamates,[10] vinyl-functionalized α-methylene-γ-butyrolactones,[22] and β-angelica lactone,[8] effectively and chemoselectively by suitable LPs. On the second frontier in the synthesis of sequence-controlled polymers, most recently LPP enabled the rapid and scalable synthesis of a record 53-block copolymer (BCP) at room temperature (RT) through sequential additions of comonomers, demonstrating the remarkable robustness and living/immortal features of the LPs employed in that system.[23] Another powerful demonstration of the unique utility of LPP in the sequence-controlled polymer synthesis is direct polymerization of one-pot mixtures of highly reactive acrylates to well-defined and resolved di- or tri-BCPs through LPP's uniquely compounded thermodynamic and kinetic differentiation.[19]

For any polymerization method that could be made broadly useful, four major fundamental attributes, including mechanism, kinetics, control, and selectivity, must be thoroughly examined and understood. Accordingly, this Perspective examines the above four features of LPP, with an emphasis placed on the identification and strategic application of the key unique features characteristic of LPP and how they can be made useful among the broader picture of polymer chemistry.

2. MECHANISM

2.1. General Considerations: Lewis Paring, Initiation, and Propagation. All LPP systems employ both LA and LB components. The LA component is typically an electrophile with a single coordination site, so that when the terminal growing anions such as an enolate or alkoxide bind to the LA, the LA is saturated with electrons and cannot bind another free monomer. Thus, typically one LA is used to stabilize the active species while another activates the incoming monomer. The most frequently employed LAs are electron-deficient, coordinatively unsaturated compounds of group 13 elements (Al, B), which have smaller ionic radii compared to transition metals and complete an octet after coordination of a single monomer. Cationic silylium (R_3Si^+) species behave in a similar way. Transition metal LAs are rarely used, but complexes of some rare-earth elements[24−26] have been used. Many other common and readily available LAs have been used for ring-opening polymerization (ROP), including complexes or salts of Zn^{2+}, Li^+, Mg^{2+}, and Y^{3+} ions (Figure 1).

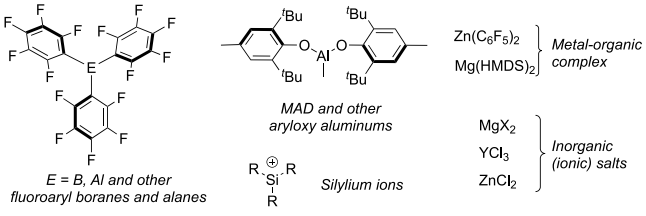

Figure 1. Classes of LAs discussed herein.

The LB component is typically a neutral base, predominately organic compounds, such as phosphines (PR_3), tertiary amines (R_3N), pyridines (Py), phosphazine superbases (PSB), *N*-heterocyclic carbenes (NHC), *N*-heterocyclic olefins (NHO), *N*-heterocyclic imines (NHI), hydrosilanes (R_3SiH), and silyl ketene acetals (SKA) (Figure 2). Most of them are strong neutral bases, and often also nucleophiles, which become cationic following attack on an electrophile.

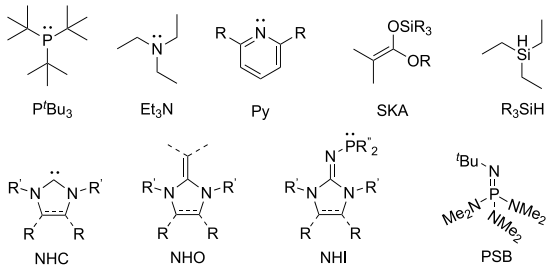

Figure 2. Classes of LBs discussed herein.

One factor always worth considering is the possibility of the LB attacking the LA to form a stable classical Lewis adduct (CLA). If this interaction is irreversible, a fraction of the LP will be poisoned, leading to low initiator efficiency, and this is the case for several reported LPP systems.[2−4] It is therefore advantageous if the LP interaction is weak and reversible (i.e., the case of interacting LPs) or, better yet, if the LP is sterically frustrated (Figure 3). In almost all non-frustrated Lewis pair

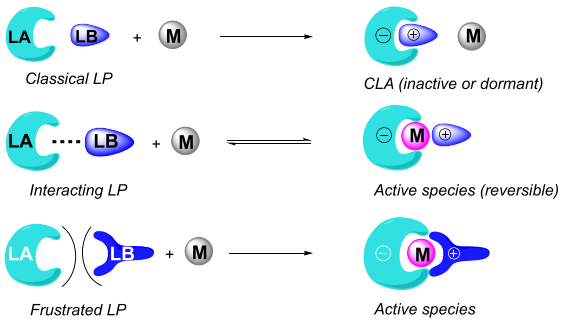

Figure 3. Effects of degree of the Lewis pairing on initiation.

(FLP) cases, the best way to avoid initiation inhibition due to strong Lewis paring is to first premix the LA (employed in a catalytic amount relative to monomer) and the monomer, so that the LA is coordinated to a monomer before exposure to the LB. It should be noted here that weakly interacting LPs can be used to generate orthogonal reactivity wherein the LP is rendered dormant at low temperatures but active at high temperatures. This technique is useful for storing and employing highly reactive and air-sensitive LPs while synergistically feeding the entropic advantage of macrolactones at high temperatures.[27]

One key advantage of LPP is the extraordinary degree of tunability inherent to it. Individual aspects of a polymerization, such as events involving k_i, k_p, k_t, and k_{tr}, can be targeted and manipulated with an unprecedented level of selectivity. The tunability of this system is a consequence of many factors. (1) The ability to manipulate both the LA and LB components *independently* grants a higher level of control to LPP in comparison to other methods. Both the LA and LB structures render significant impact on the polymerization characteristics. Thus, being able to manipulate one but not the other in any particular scenario is extremely useful. (2) The very nature of LA and LB structures is a very sensitive and delicate relationship between structure and reactivity. As a consequence, a great variety in reactivity can be obtained by simple structural changes. (3) The rapid growth of independent fields of organocatalysis[28−35] and main-group FLP chemistry[36−40] has provided the LPP field with a massive library of LP structures available for synthesis or commercial availability. (4)

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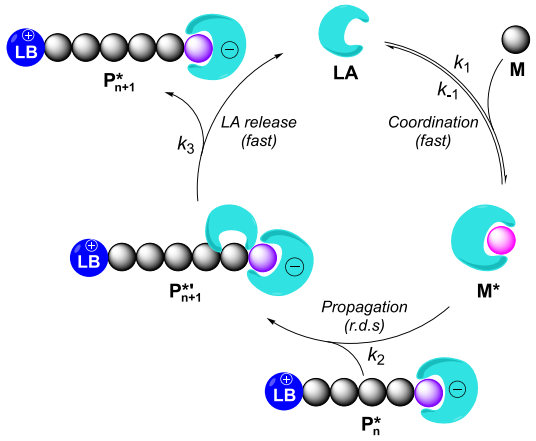
The LA and LB components commonly have simple structures, accessible either commercially or in only a few synthetic steps, making a great variety of structures and therefore reactivities accessible with little investment.

Although many variations on the mechanism of LPP exist, there is a common thread that unites and defines all LPPs: the LA propagation cycle, generally involving first activation of a free monomer (M) by a free LA, followed by addition of active growing chain (P_n*) to the activated monomer (M*) as the rate-determining step (rds), and finally release of the LA (Scheme 1). The LA cycle is critical to the way we think about

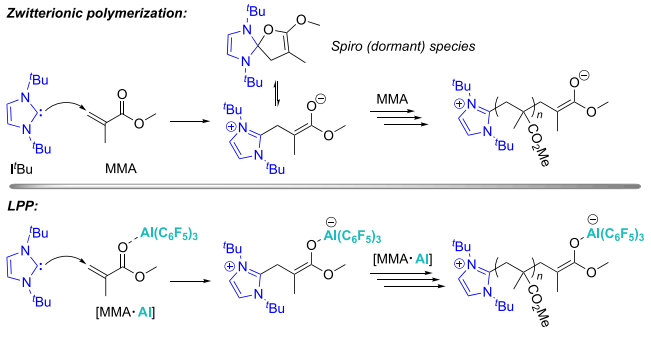
Scheme 1. Propagation Cycle Defining LPP



these polymerizations. In particular, the two-step activation process (activation followed by chain addition) fundamentally changes the kinetics and the selectivity of polymerization. Consequently, much of our work is related to ways upon which one can exploit the kinetic and selective advantages associated with this two-step activation. Because there are some reactions that technically fit into the category of LPP while not following the strict mechanism outlined here (such as coordination–insertion LPP, *vide infra*), we will only lightly discuss those reactions and maintain a focus on zero-order reactions to emphasize our key arguments.

To illustrate the contrast between LPP and typical chain-growth polymerization, here we first consider two analogous polymerization reactions (Scheme 2), one being the organocatalytic conjugate addition polymerization of methyl methacrylate (MMA; note that for simplicity and consistency we use MMA to represent common polar vinyl monomers throughout this Perspective) by an NHC[41,42] and the other

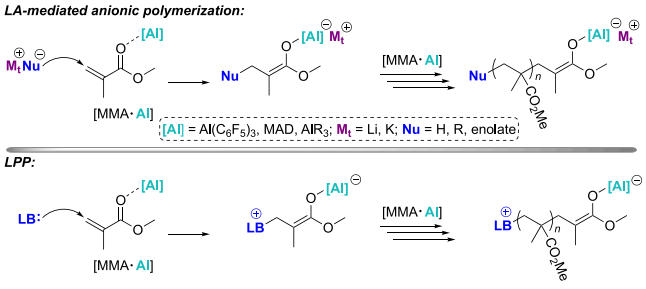
Scheme 2. Mechanistic Comparisons of Zwitterionic Polymerization and LPP



being LPP of MMA by an NHC/$Al(C_6F_5)_3$ LP.[2] The former has been commonly termed *zwitterionic polymerization*, as both positive and negative charges are covalently tethered on the active species. Such zwitterionic species can adopt both the open chain form (active for further monomer additions) and the cyclic spiro form (dormant state), the relative stability of which depends on the NHC and monomer structures as well as the solvent polarity. Although both of these examples do contain zwitterionic active species, the latter must be distinguished as LPP because of the contrast in reactivity provided by the LA. In the LPP case, the zwitterionic active species do not react with free monomer, but only an activated equivalent of monomer, *making the free monomer essentially solvent molecules* to dissipate heat in a bulk LPP. This scenario gives the polymerization zero-order rate dependence on $[MMA]_t$ and first order in $[LA]_t$ (typically this is understood as $[LA]_0$). As a consequence, the conversion vs time profile of the LPP reaction would be a linear curve from start to finish. In contrast, the zwitterionic polymerization propagates with any free monomer in solution. Thus, the rate has first-order dependence on $[MMA]_t$ and therefore experiences a first-order decay as MMA is consumed. This first-order decay is present in almost any other chain-growth polymerization method, including typical anionic, coordination, and radical methods. Thus, it is an important distinction which has led to several innovations (*vide infra*). Likewise, the stabilization of the zwitterionic intermediate is key for selectivity and control in that it is generally very stable and not prone to unwanted side reactions such as chain termination and chain transfer. As a general rule, the LA-stabilized nucleophilic chain end does not react with any carbonyl other than a carbonyl activated by a second equivalent of LA, the implications of which will be discussed later.

Next, we should compare LA-mediated anionic polymerization[43,44] and LPP (Scheme 3) to point out some important

Scheme 3. Mechanistic Comparisons of LA-Mediated Anionic Polymerization and LPP



distinctions as well. (1) The anionic active species is composed of an anionic enolate and a metal (M_t) cation derived from initiation by a charged anionic nucleophile. This results in a very tight ion-pairing with little spatial separation between ions, thus lowering the energy of the active species through electrostatic stabilization. In comparison, the zwitterionic active species typically found in LPP is composed of a highly separated ion pair, with anion and cation found on opposite ends of the growing polymer chain; thus, the looser ion-pairing (Figure 3) results in a more reactive enolate. (2) The cationic initiating group attached to the α-terminus during LPP can potentially act as a leaving group, opening up the possibility of cyclic polymer formation and chain transfer (*vide infra*), while

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the inert Nu (e.g., alkyl) initiating end group found in anionic polymerization will not react and can be therefore forgotten. In other words, the Nu in LA-mediated anionic polymerization plays a role only in chain initiation, while the LB in LPP can play a role in not only chain initiation but also propagation and transfer. (3) The LA-mediated anionic polymerization can be tuned by the choice of LA and has perhaps a few metal ions to choose from while the LPP has an enormous library of LBs to choose from which not only change the character of chain initiation and propagation but also provide access to different mechanisms.

One might be tempted to think the LB is important during the initiation step but negligible thereafter. However, this would be a mistake as the *LB plays a critical role not only in initiation but also in propagation and chain transfer*. For example, in our recent study of the LPP of methyl crotonate (MC),[9] we performed a direct comparison between several LBs while keeping the LA constant throughout. In particular, two LBs, an NHO, 1,3-dimethyl-4,5-diphenyl-2-(propan-2-ylidene)-2,3-dihydro-1*H*-imidazole), and an NHC, 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene (TPT), both operated by the same zwitterionic LPP mechanism, and the cationic end groups generated by them were similar in structure, containing five-membered heterocycles with phenyl substitutions. The only differences, apart from the exact phenyl substitution, were that the NHO contained an imidazolium frame while TPT a triazolium. This seemingly subtle change imparted notable changes on both the activity of polymerization and propensity for chain transfer. For example, the TPT cation promoted a slower, but a more controlled, polymerization with low dispersity ($Đ$ = 1.18), presumably due to formation of a tighter ion pair with the enolaluminate anion and therefore being less prone to transfer. Similarly, Rieger[45] found in LPP of *tert*-butyl methacrylate (^{t}BMA) that the sterics associated with the phosphine LB employed had an effect on the chain-end selectivity of the LPP, with PCy_3 providing noticeably higher syndioselectivity than PEt_3, presumably due to the proximity of the bulky cyclohexanyl ligands to the transition state of propagation. In general, it should be assumed that ion-pairing exists between the cationic LB end group and the anionic enolate or alkoxide end group, whether inter- or intramolecular (Figure 4), or solvent-separated states, depending on the nature of solvent and added additives if any (such as salts),[1] and has a significant effect on the transition state of propagation.

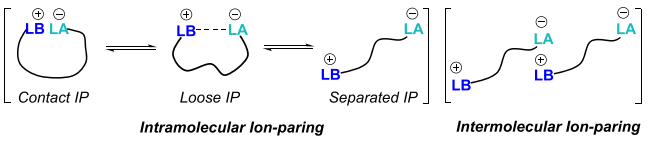
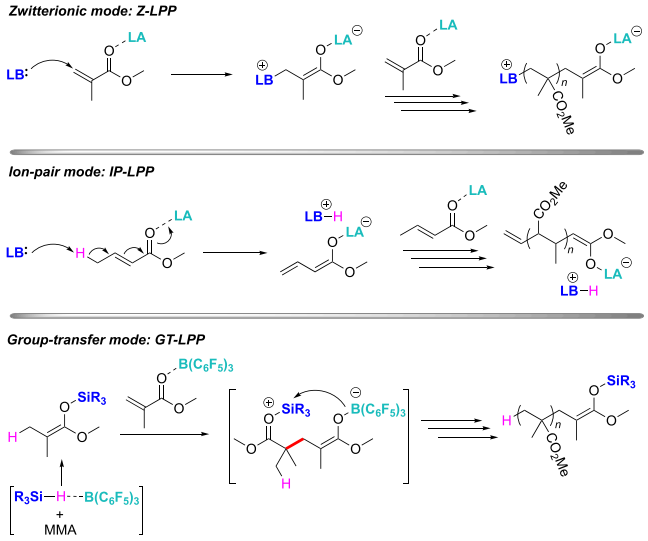


Figure 4. Zwitterionic ion-pairing modes during chain propagation in LPP (IP = ion pair).

Variations on LPP have been disclosed through the years, which will be termed LP modes. Discussions on these modes will be broken into sections as vinyl addition and ROP LPP systems.

2.2. Vinyl-Addition LPP. The aforementioned case, *zwitterionic* mode (Scheme 4), was not only the first mode discovered but also the most common.[2−6,9,11,18,19,45−60] In the zwitterionic mode (Z-LPP), a neutral LB undergoes a

Scheme 4. Mechanism of Vinyl-Addition LPP Operating in Three Different Modes



nucleophilic attack on an activated monomer to generate a zwitterionic active species. The active species containing an enolate goes on to propagate with an activated monomer. Z-LPP is typically highly active and chemoselective, making it a robust option. For example, several extended polar vinyl monomer families including acrylamides,[3,6,45,61] vinyl phosphonates,[45,61] vinylpyridines,[45,46,61] and vinyl oxazolines[45,46] have been effectively polymerized by the zwitterionic mode. It is most common because typical polar vinyl monomers have an electrophilic site most prone to nucleophilic addition by the LB. The LB cation found at the α-terminus is inert in most cases but can sometimes act as a leaving group, allowing the formation of cyclic polymers (*vide infra*).

The second case, *ion-pair* mode—IP-LPP (Scheme 4),[8,9,45] can occur if there is an acidic proton on the activated monomer. In this event, the LB deprotonates the activated monomer, generating an enolate stabilized by the protonated LB cation. In the case of MC, IP-LPP reactions are notably more reactive than their zwitterionic analogues and are also prone to chain transfer via deprotonation of the protonated LB by the LA-stabilized enolate and subsequent reinitiation by the released free LB. This unique reaction sequence allows polymers to be synthesized in a catalytic fashion.

In the third case, LPP can operate in *group transfer* mode, GT-LPP (Scheme 4), which can be considered a special case (LA-mediated) group transfer polymerization (GTP).[62−66] Although there are several GTP mechanisms,[1] the LA-catalyzed variant, or GT-LPP, is unique in that it relies on a rds being the conjugate addition to LA-activated monomer. Therefore, the selectivity and kinetic themes discussed herein are only relevant to this particular group transfer variant. GT-LPP can be executed either by an SKA coupled with an auxiliary LA,[20,67−73] such as $B(C_6F_5)_3$, or through an SKA/SiR_3^+ pair. In the former case, an SKA at the ω-terminus acts as a nucleophile and does a conjugate addition on an LA-activated monomer. The result is a zwitterionic intermediate containing a cationic silylium and an anionic auxiliary LA-stabilized enolate. The enolate oxygen then quickly recaptures the silylium moiety and releases a free LA. GT-LPP can be initiated by FLP-type hydrosilylation of a polar vinyl monomer or by using a monomeric SKA directly. These reactions are

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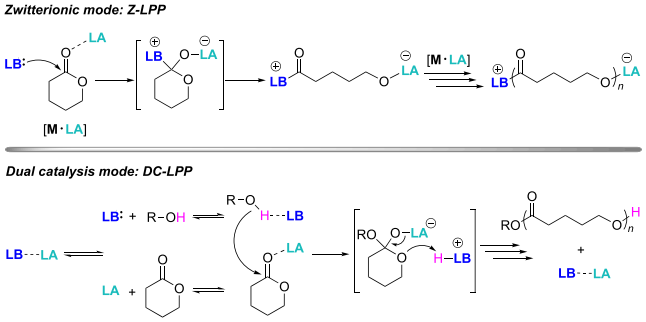
typically less active than their zwitterionic counterparts and are the most selective of any mode due to the stability of the neutral SKA. On the other hand, an SKA/SiR_3^+ pair can be generated through hydride abstraction or from deprotonation[74−77] of a strong Brønsted organic acid by an SKA. The activity of these reactions can be tuned by the degree of interaction with the charge compensating anion. For example, silylium $[SiR_3]^+[B(C_6F_5)_4]^-$ can be generated by hydride abstraction[78−81] of an SKA or a hydrosilane. The formal cation will render a highly reactive system. In contrast, $(Tf)_2NH$ can be deprotonated by an SKA to render $[SiR_3]^+[(Tf)_2N]^-$, which exists as a weakly bonded (and thus much more stable) $(Tf)_2N-SiR_3$.[7,10,21,82]

2.3. Ring-Opening LPP. Similar to vinyl monomers, lactones can also be ring-open-polymerized by LPs via a zwitterionic mode (Scheme 5). Z-LPP of lactones initiates by

Scheme 5. Mechanism of LPP of Cyclic Esters Operating in Different Modes[a]



[a]δ-Valerolactone (δ-VL) is used as a demonstrative example.

attack on an activated lactone monomer by a LB, followed by ring-opening of the lactone to an LA-stabilized alkoxide. Z-LPP has been utilized to effect polymerization of lactides,[83−86] lactones,[2,3,12,87−89] epoxides,[13,14,90−92] and cyclic carbonates.[93] This method is highly selective, especially where maintenance of stereocenters is of concern (such as lactides and ring-fused bicyclic lactones) and when cyclic topologies are desired. Perhaps the most useful application of this strategy is in the *inhibition of chain-to-chain transesterification*, which causes dispersity broadening and prevents the synthesis of well-defined BCPs. Much of the work done in this area has concerned the LA $Zn(C_6F_5)_2$, which, unlike the more typical LAs such as $B(C_6F_5)_3$, is bifunctional and relies on a coordination−insertion mechanism.

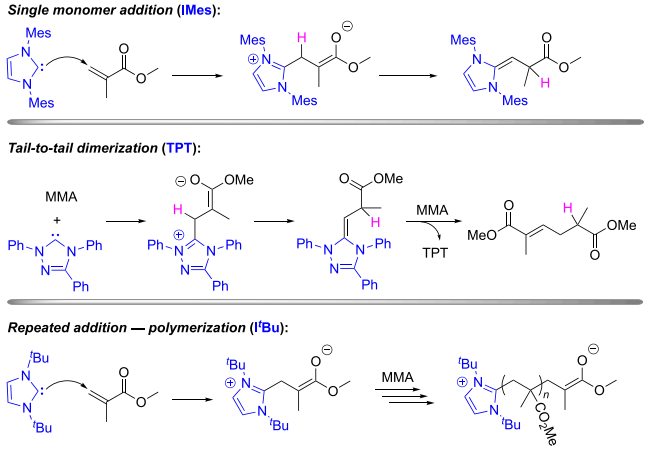
Proton-mediated dual catalysis (or DC-LPP, Scheme 5)[15,16,86,87,94−99] is a diverse and robust methodology, wherein a LA activates a lactone through carbonyl coordination while a LB activates an alcohol by electron donation to the hydroxyl proton. The activated alcohol can then attack the LA-activated carbonyl (thereby transferring the proton to the LB) and effect ring-opening of the lactone. Following ring-opening, the acyl oxygen recaptures the proton from the LB to re-form a terminal alcohol. Interestingly, this system employs three different components to effect activation (alcohol, LA, and LB). Consequently, this relieves any one component of necessity to be highly reactive. *Thus, mildly strong LAs and LBs can be employed for optimal results*. This feature leads to unexpected reactivity of some of the mild LAs, such as metal halides (LiCl, MgX_2, ZnX_2, and YX_3), and mild LBs, such as TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), although NHOs seem to be superior in many cases. The moderate catalyst reactivity allowed for by this methodology can be particularly useful for achieving desired selectivity and control in ROP of cyclic esters. The specific mechanism, however, often becomes very complicated, and unexpected kinetic factors such as LP activation/deactivation as well as the reliance on (not one but) two prior equilibria must be considered (section 3.2).

3. SELECTIVITY AND CONTROL

3.1. Vinyl-Addition LPP. As previously mentioned, the selectivity of LPP is a major advantage as compared to other methods. The most important fundamental principle of the LPP selectivity is the simple assumption that the LA-capped anionic active chain-end species will not interact with any unactivated carbonyls in the case of LPP of conjugated Michael acceptors. Gratifyingly, most side reactions that would normally terminate a polymerization can be eliminated by this simple nuance. Many examples will be given below to show the meaningful implications of this understanding. Additionally, the tunability of LPP makes a sizable contribution to selectivity as often it has been shown that some optimization is involved to find the ideal LP for a given scenario. Herein we will give a few examples to demonstrate the strategic implementation of this concept.

During the development of organocatalytic polymerization mechanisms, especially LPP, LB-mediated GTP,[100−104] and zwitterionic polymerizations,[41,42] many groups were exploring the effectiveness of several NHCs for zwitterionic polymerization on the benchmark monomer MMA. Here we summarize in Scheme 6 three different pathways by which three different NHCs interact with MMA.

Scheme 6. Diverse Reactivity of MMA with Different NHC Structures



IMes (1,3-dimesitylimidazolin-2-ylidene) attacks a monomer by conjugate addition to form a zwitterionic active species but quickly thereafter undergoes an intermolecular 1,2-proton transfer (involving two zwitterions) based on the acidity of the β-proton adjacent to the IMes group to form an inert neutral enamine single-addition product (Scheme 6).[41,42] TPT, a weaker nucleophile but a better leaving group, also undergoes 1,2-proton transfer to generate the enamine; however, this enamine is a strong enough nucleophile to attack a second monomer, at which point the molecule undergoes a convoluted sequence of proton transfers to yield a neutral

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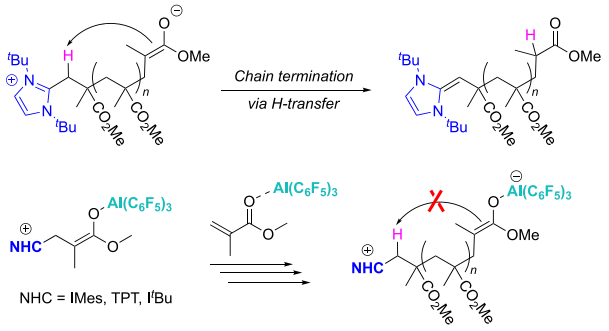
tail-to-tail dimer.[105−107] I^{t}Bu (1,3-di-*tert*-butylimidazolin-2-ylidene), the strongest nucleophile of this NHC series, is not reactive with MMA in THF or toluene, with enamine formation being inhibited by the steric hindrance of the *tert*-butyl substituents. However, in the polar solvent DMF, I^{t}Bu allows facile conjugate addition polymerization.[41,42] The diverse reactivity by just these three discussed, NHC-based LBs illustrates the delicate structure/reactivity relationship associated with these molecules and how often problems can be solved by the manipulation of their structures.

The I^{t}Bu-mediated zwitterionic polymerization, which occurs rapidly in DMF without a LA, is not controlled and unable to reach a high degree of polymerization (DP) due to a termination reaction caused by deprotonation of the carbon directly bonded to the cationic I^{t}Bu$^+$ initiating group by the enolate chain end (Scheme 7).[41,42] As a result, polymerizations

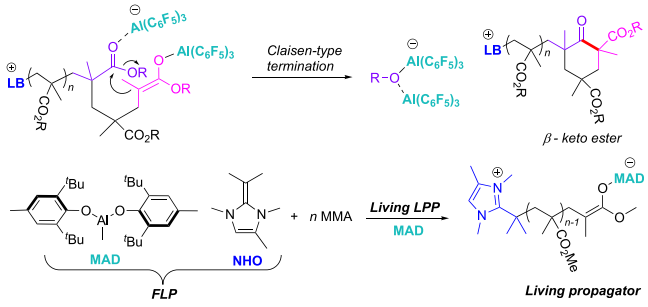
Scheme 7. Chain Termination in Zwitterionic Polymerization and Inhibition of Termination in LPP



do not reach full conversion at high [MMA]/[I^{t}Bu] ratios. In contrast, LPP can inhibit this termination reaction by stabilizing the enolate with a LA so that the enolate is not basic enough to effect such deprotonation. Thus, by using the strong LA Al(C$_6$F$_5$)$_3$, polymerization of MMA was achieved with all three of the aforementioned NHC-based LBs (Scheme 7).[3−5] Now, the enamine pathway observed between IMes/MMA and TPT/MMA can be shut down in LPP, wherein the zwitterionic enolate is now capped by a LA. The LA lowers the energy of the enolate by sharing the negative charge with the enolate oxygen and thus raises the barrier of the intra- or intermolecular proton transfers to such an extent that it is completely inhibited.

The performance of LPP of MMA and other acrylic monomers by these NHC/Al(C$_6$F$_5$)$_3$ LPs, although greatly improved relative to their purely organocatalytic counterparts, still suffered from two major problems. First, the strong Lewis acidity of Al(C$_6$F$_5$)$_3$ coupled with the high basicity and nucleophilicity of NHCs (especially I^{t}Bu) results in a large fraction of the LP catalyst being lost by CLA formation before the polymerization even begins (Figure 3), causing poor initiator efficiencies and therefore formation of polymers with much higher than expected molecular weight (MW) values.[3,5] Second, a termination reaction still exists with strong LAs wherein the LA-capped enolate attacks an in-chain carbonyl to effect a Claisen-type cyclization to form either a lactone or a β-ketoester (Scheme 8) and eliminate an alkoxide that poisons the LA.[47] This termination reaction results in higher than expected MW values, broadened dispersity, and the inability for chain extension in block copolymerization, thus an uncontrolled nonliving system. It should be noted that the

Scheme 8. Claisen-Type Termination by LPs Based on Al(C$_6$F$_5$)$_3$ and Living Polymerization by NHO/MAD LPs



Claisen-type backbiting termination is a ubiquitous problem throughout the vinyl ester polymerization literature,[10,21,47,57,103] especially concerning anionic polymerization,[108−111] and is consistently a limiting factor in terms of achieving living polymerization and producing well-defined BCPs. Compared to anionic polymerization, LPP is better equipped to deal with this problem since the LA-stabilized enolate will not react with an in-chain carbonyl unless it is activated by a second equivalent of LA. Typically, it is unfavorable for a LA to coordinate to an in-chain carbonyl when there is excess free monomer present, whereas a metal cation (in anionic polymerization) can simply chelate with an in-chain carbonyl, activating it for the Claisen cyclization.

The first issue, CLA formation, can be addressed by using an FLP. The second issue, Claisen-type termination, can be solved by using a LA that sterically inhibits the attack on an in-chain carbonyl (this typically consists of a six-membered transition state). In 2018, Zhang and Chen[5] reported a suite of dimethyl-substituted NHOs (at the α-terminal carbon) that formed FLPs with a sterically hindered aluminum LA, methyl aluminum di(2,6-di-*tert*-butyl-4-methylphenoxy) (MAD) (Scheme 8). The combined sterics and electronics of MAD were sufficient to facilitate the LPP of methacrylates including MMA, while sterically inhibiting the Claisen termination. The livingness of this LPP by the MAD-based FLP at RT was unequivocally verified by five lines of evidence, including (1) predictable polymer MW (M_n up to 351 kg mol^{-1}), coupled with low dispersity ($Đ$ = 1.05); (2) high to quantitative initiation efficiencies, implying that while CLA formation was avoided initiation can still occur rapidly and cleanly; (3) linear increase of polymer M_n vs monomer conversion and monomer-to-LB ratio; (4) precision in multiple chain extensions; and (5) formation of well-defined AB di-BCPs and ABA tri-BCPs with low dispersity ($Đ$ = 1.09−1.13). This result was a major improvement over the first-generation FLP ^{t}BuP$_3$/Al(C$_6$F$_5$)$_3$,[3] which, due to the steric hindrance of the phosphine, was not nearly as nucleophilic and resulted in slow/incomplete initiation (thus high dispersity).

While there are already plenty of living polymerizations for MMA, many fundamental insights were learned over the course of this narrative. First, highly reactive zwitterionic active species generated by organocatalysts can be harnessed in such a way that unwanted side reactions can be avoided, while simultaneously preserving and focusing its reactivity toward only the activated monomer. Second, there is an intense structure/reactivity relationship associated with these LPs, and it is important to utilize the vast library of LPs available to find the optimal match for any particular monomer. In more recent years, these fundamentals have been implemented to find right

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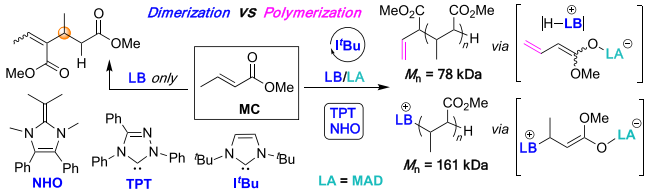
polymerization conditions for several challenging monomers, especially biorenewable monomers which are typically more highly functionalized relative to petroleum-derived monomers.

One of these biorenewable monomers, MC, a constitutional isomer of MMA and a much more challenging monomer to polymerize, due to not only a more sterically hindered (substitution at the electrophilic β-carbon) and thermodynamically stable alkene but also acidic γ-protons, was successfully polymerized by LPP (Scheme 9).[9] Waymouth[112]

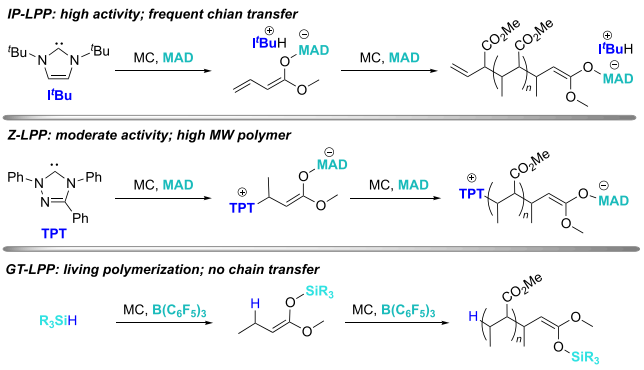
Scheme 9. Selectivity Comparisons between Using LB Alone and LA/LB Pairs toward Crotonates



reported earlier several fundamental reactions involving MC and several NHC organocatalysts. In the presence of a strongly basic NHC (*N*-^{i}Pr-substituted NHC, I^{i}Pr), an acidic γ-proton of MC gets deprotonated to form an enolate/NHC$^+$ ion pair that undergoes conjugate addition to another monomer. However, the newly formed dimeric enolate deprotonates another free monomer before any further propagation, resulting in selective head-to-tail dimerization. Alternatively, the LB can attack the β-carbon to form the zwitterionic enolate, propagate once, and then undergo a 1,3-elimination, also forming the head-to-tail dimer. Other less basic NHCs such as TPT and IMes attack the β-carbon, followed by 1,2-proton transfer to form the enamine single-addition product. Thus, knowing that LPP is capable of stabilizing reactive enolate intermediates, we hypothesized that these dimerization reactions could be avoided so that polymerization can occur selectively. Indeed, the use of a LA was able to stabilize the structure to such an extent that polymerization occurred readily. IMes and TPT both formed the LA-stabilized zwitterionic active species but were not permitted to isomerize to the enamine and instead proceeded to propagate via Z-LPP. Although high MW poly(methyl crotonate) (PMC) can be synthesized by this method, the rare occurrence of chain transfer was also observed due to deprotonation of an activated monomer by the enolate active species. Interestingly, I^{t}Bu initiated the polymerization by deprotonating a γ-proton and forming an enolate ion pair (Scheme 9). However, with LA stabilization, the decreased basicity of the enolate was sufficient to prevent deprotonation of other monomers until substantial chain growth via IP-LPP had already occurred. In fact, it was determined kinetically that growing chains were deprotonating activated monomers as well as the protonated I^{t}Bu$^+$, both resulting in the same chain transfer product. Thus, polymers can be produced catalytically and indefinitely without need for an external chain transfer agent (Scheme 10). The same strategy was later used for the LPP of another challenging biorenewable monomer β-angelica lactone (β-AL).[8]

We sought for ways to stabilize the enolate even further to completely inhibit chain transfer so that well-defined PMC with predictable MW values could be synthesized. To this end, we employed the GT-LPP method, which uses a silylium group to stabilize the propagating chain end instead of a neutral LA. Unlike a neutral LA, the silylium-capped enolate, a SKA, is

Scheme 10. Comparison of MC Polymerization Selectivity and Control by Different LPP Modes



neutral and thus much lower in energy and reactivity. By using the SKA LB in conjunction with the common borane LA, $B(C_6F_5)_3$, we were able to completely inhibit chain transfer altogether and obtain well-defined PMC with narrow dispersity values (Scheme 10).[20]

The GT-LPP mode is perhaps the most selective and controlled variant of LPP due to the neutral enolate stability. Kakuchi et al. have reported several examples[67−70] of living polymerizations utilizing the LA $B(C_6F_5)_3$ which has allowed for the living polymerization of most notably the challenging acrylate class of monomers, known for their extremely high reactivity and propensity for termination. Additionally, the group transfer mechanism, which continuously transfers the silylium moiety (originating from the LB) to the enolate, is extremely useful because it enables manipulation of the silylium-LA capping the enolate and the auxiliary-LA activating the incoming monomer individually. Thus, in theory, one can reduce the reactivity of the enolate by manipulation of the SKA initiating species (increasing selectivity) while simultaneously increasing the reactivity of the activated monomer by increasing the acidity of the LA catalyst (increasing polymerization activity). In practice, however, this concept has been challenging to realize because GT-LPP becomes problematic when highly oxyphilic LAs are used, such as $Al(C_6F_5)_3$[72] or MAD,[11] of which only a few examples have been reported. The development of GT-LPP systems that obtain high degrees of stabilization for the enolate and high degrees of activation for the incoming monomer is therefore an area of great opportunity.

GT-LPP also works well with employment of discrete silylium (SiR_3^+) LAs generated by hydride abstraction[78−81] or ligand dissociation.[7,10,21,82] This strategy has found great success in the polymerization of several monomers, most notably MC and methyl cinnamate (MCin). MCin, which contains a β-substituted phenyl group that both stabilizes the alkene electronically and protects the β-carbon sterically, and is thus not polymerizable by any other known methods, would require the strong and sterically unhindered LA $SiMe_3^+$ for polymerization by GT-LPP.[10] However, although silylium cations (SiR_3^+) are some of the strongest known LAs, they tend to be less selective than neutral LAs such as $B(C_6F_5)_3$. One explanation is that for propagation, as well as unwanted side reactions (such as Claisen-type termination), the neutral LAs must proceed through a transient high-energy zwitterionic intermediate before group transfer to the stable propagation or termination product. Conversely, silylium LAs can get to a neutral propagation or termination product in a single

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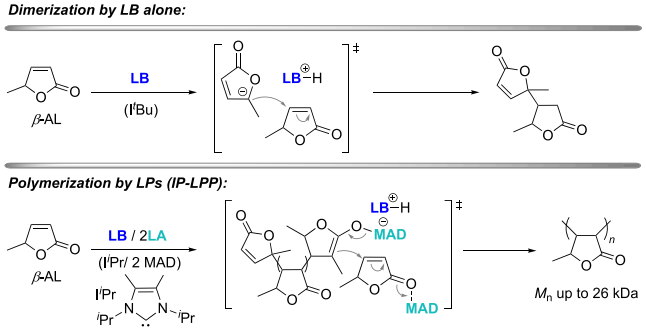
concerted step. This termination activity was reported by Abe et al. for GT-LPP of both crotonates[21] and cinnamates.[10]

Considered a cyclic analogue of MC, bio-derived β-AL or unsaturated γ-valerolactone (GVL) is also β-substituted. Additionally, β-AL carries an internal double bond, thus being a challenging monomer to polymerize. An earlier study of treating β-AL with a LB (I^tBu) alone led to dimerization via a base-catalyzed pathway[113] (Scheme 11). Most recently,

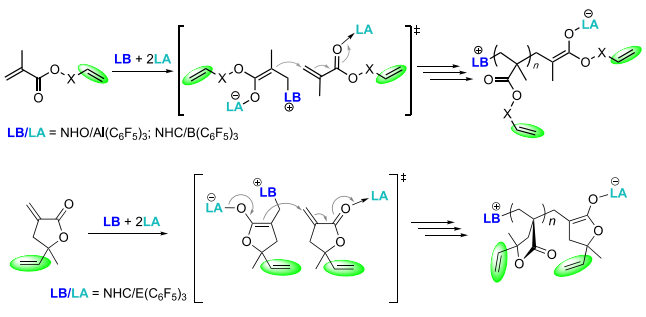
Scheme 11. Selectivity Comparisons between Using LB Alone and LA/LB Pairs toward an Unsaturated γ-Butyrolactone



Hong found that LPs consisting of a strong NHC base (I^iPr) and a bulky aluminum LA (MAD) brought about an effective LPP, affording a vinyl-addition polymer with M_n up to 26 kDa.[8] As in other LPP systems, the LA employed here, namely MAD with balanced sterics and acidity, both stabilizes the propagating enolate and activates the monomer for selective chain growth, thus suppressing side reactions (e.g., chain transfer to monomer). In this particular LPP, chain initiation occurs with deprotonation of β-AL by the LB, operating in the IP-LPP mode (Scheme 4); thus, the use of a strong NHC base (I^iPr) prevents back proton transfer.

The selectivity of LPP toward multifunctional acrylic monomers has been shown to be *perfectly chemoselective*,[49,52] polymerizing only the vinyl group activated by the conjugated carbonyl that is coordinated to the LA (Scheme 12). This

Scheme 12. Selected Examples of Perfectly Chemoselective LPP of Multifunctional Linear and Cyclic Acrylics Monomers



perfect chemoselectivity over the entire conversion range at RT is noteworthy as other polymerization methods, such as radical, anionic, or group-transfer polymerizations, all encounter various issues to achieve or maintain precise chemoselectivity, especially at later stages of polymerization.[1] Such precision in controlling the chemoselectivity has also been achieved in the LPP of multivinyl-functionalized γ-butyrolactones derived from biorenewable feedstocks,[22] indicating a general chemoselective feature of LPP.

3.2. Ring-Opening LPP. While there are several methodologies that can produce well-defined polyesters from classic monomers such as ε-, δ-, and β-lactones, it is of great interest to understand the most selective and controlled ROP strategies since biorenewable molecules often come with hydroxy or carboxylic acid groups that can be ring-closed into cyclic monomers for ROP. Furthermore, the ROP of γ-lactones[114−116] is one of the most promising strategies for a sustainable polymer economy with several examples of full chemical recyclability reported, while the ROP of other derivatives such as GVL is still not reported.

Unlike vinyl-addition polymerization, ROP contains a propagation step (transesterification) that is more thermoneutral. The main driving force in ROP of small- and medium-ring lactones is alleviation of ring strain of the monomer, which is miniscule compared to the driving force of olefin polymerization (C−C bond formation). Thus, these polymerizations are often less active for less strained monomers, and it is not uncommon to see these reactions happening over the course of hours or even days. Hence, the active species is exposed for long periods of time, where it has plenty of time to participate in unwanted side reactions. For example, chain-to-chain transesterification is a common side reaction known to cause dispersity broadening and scrambling of block copolymers.[117−123] Chain-to-chain transesterification is thermoneutral and very similar in character to propagation. To prevent transesterification and produce well-defined polymers or BCPs, the active species must be designed to *select between two very similar reactions (propagation and chain-to-chain transesterification)* and not only discourage but also completely inhibit transesterification.

In 2017, a LPP approach was employed to address the above-described selectivity issue in the ROP using examples of the two most common lactones: ε-caprolactone (ε-CL) and δ-VL.[12] Here, $Al(C_6F_5)_3$/NHO LPs were employed, wherein NHOs with and without the dimethyl-substituted exocyclic carbon were compared. NHOs with an exocyclic methylene underwent an unexpected initiation process wherein, during the initial ring-opening, a proton is transferred from the NHO methylene carbon to the terminal alkoxy to form a neutral enamine. This molecule is still nucleophilic enough to attack the next monomer through the carbonyl conjugated to the enamine, which transpires a living polymerization. Interestingly, this initiation sequence achieves a near-ideal efficiency (106%) and effects a living polymerization, where transesterification is completely avoided. On the other hand, the dimethyl-substituted NHO, which cannot undergo proton transfer, results in broad dispersity. The ability to shut down the transesterification side reaction in this LPP enabled the synthesis of well-defined homo-, di-, and tri-BCPs with M_n as high as 855 kg mol^{-1} and $Đ$ as low as 1.02 (Figure 5).[12] The mechanism by which transesterification is interesting and twofold. First, the LA-stabilized alkoxide is not a strong enough nucleophile to attack in-chain carbonyls, unless in-chain carbonyls are activated by a LA. It may be reasonably assumed that in this LPP system the LA $Al(C_6F_5)_3$ has a higher affinity for free monomer carbonyls rather than in-chain carbonyls. However, if this were the only relevant argument, one would suspect that after complete conversion the free LA would then be permitted to begin activating the in-chain carbonyls. This does not seem to be the case based on the absence of

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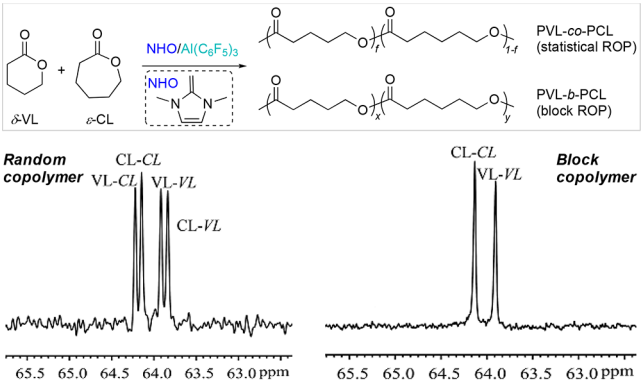
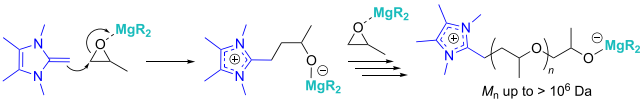


Figure 5. Zwitterionic ring-opening copolymerizations by the NHO/$Al(C_6F_5)_3$ LP to well-defined random and block copolymers with ^{13}C NMR spectra showing a mixture of homo- and heterodyad sequences (OCH_2) in random copolymer but only homodyads in BCP.

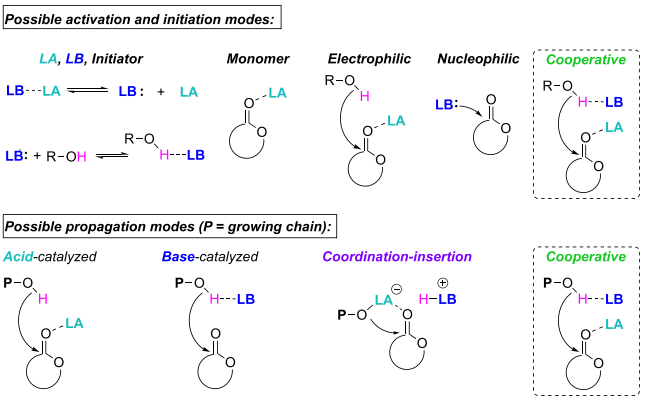
transesterification following the chain extension and copolymerization experiments. Thus, it seems likely that there is a steric factor that excludes the development of inter- and intrachain-to-chain transition states. This work—although employing the sensitive $Al(C_6F_5)_3$—is one of the only examples of true living Z-LPP of lactones through the zwitterionic mode as defined in Scheme 5. Similar reactions have been examined earlier with $B(C_6F_5)_3$/amine[124] and $B(C_6F_5)_3$/phosphine[2] systems, and the initial ring-opening was observed. However, polymerization thereafter was sluggish or nonexistent. Therefore, this is also a fertile area of opportunity for the development of LP structures that can improve on Z-LPP. For example, most recently Naumann developed rapid and selective Z-LPP of epoxides such as propylene oxide (PO) with NHO/$Mg(N(SiMe_3)_2)_2$ LPs, which circumvented the common side reactions (e.g., chain transfer to monomer) encountered in the zwitterionic polymerization employing an NHO alone and thus enabled the synthesis of high MW PPO with M_n up to 1.4 MDa (Scheme 13).[13]

Scheme 13. LPP of PO to High MW PPO in Zwitterionic Mode



The dual catalysis methodology shown in Scheme 5 only precariously fits our aforementioned definition of LPP, where propagation occurs through the attack on a LA-activated monomer. Note that only a reaction between the LA-activated monomer and the active species does one get the zero-order monomer rate dependence, and only then do our kinetic and selective arguments apply. Thus, only if propagation occurs strictly through the mechanism outlined in Scheme 1 would it be called a LPP according to that definition. The complexity of the three-component system (LA, LB, and ROH) opens up a number of different elementary steps (Scheme 14), especially propagation steps which if working simultaneously lead to a less predictable and less manipulatable system. The mounting literature on this topic deserves a more comprehensive analysis, but for the purposes of this paper, we will briefly summarize the key conceptual points and compare the system against our perspectives on LPP.

Scheme 14. Possible Elementary Reactions and Modes of Initiation and Propagation in a Three-Component System (LA, LB, and ROH)



The cooperative propagation mechanism, shown in Scheme 5, is the superior mechanism and highly desired for selectivity and kinetic advantages (*vide infra*). The challenge, however, is elucidation of conditions that allow strictly the cooperative mechanism and exclude the base- and acid-catalyzed propagation mechanisms. The reason that these must be excluded is because if base-catalyzed propagation (Scheme 14) is possible, it is therefore reasonable to assume base-catalyzed transesterification—although not as thermodynamically favored—has a similar activation barrier and is thus possible. If the reactivity of the LP is too high, it is conceivable that full deprotonation of the alcohol is possible to give a LA-stabilized alkoxide, and if the LA-stabilized alkoxide is bifunctional—which most of the LAs used in this type of polymerization are (MgX_2, YX_3, and ZnX_2)—propagation could occur through a coordination−insertion mechanism. If propagation can occur through coordination−insertion, then it is reasonable to assume that transesterification can also occur through a coordination−insertion mechanism (not shown). If the LB is nucleophilic enough to ring-open a monomer on its own, it is reasonable to assume that a free LB might at some point during the reaction effect chain scission (effectively a transesterification). If, however, only the combined efforts of both electrophilic and basic activation are sufficient to effect propagation, it then logically follows that only cooperative transesterification (not shown) could possibly effect transesterification. This type of transesterification would require the consecutive LA activation of an in-chain carbonyl, which would likely be a rare event if monomer is present, as well as a collision between the LB-activated hydroxy and the LA-activated in-chain carbonyl, also a rare event. As previously noted, we assume the LA has a considerable preference for monomer carbonyl coordination over in-chain carbonyl coordination. Therefore, when monomer is still present, it will sequester most of the LA and not allow it to coordinate polymer. But even when monomer is depleted, a sizable fraction of the LA population will be sequestered as a CLA. To our knowledge, only a few systems strictly follow the cooperative mechanism.[15,16] In addition to the selectivity advantages of this type of reactivity, kinetic advantages, which are discussed in the next section, also become available. Compounded sequence control, for example, which we recently reported for vinyl-addition polymerization, now becomes available because only LA-activated monomers can enter the propagation cycle.[19] If two comonomers are present,

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there will arise an inherent preference for which comonomer the LA will coordinate and thus which monomer is permitted to enter the propagation cycle.

Note that the ROP operating strictly through acid-catalyzed propagation[97] (Scheme 14) nicely fits our LPP definition in that the growing alcohol cannot react with any carbonyls except those activated by LA. Thus, our selectivity and kinetic arguments (*vide infra*) apply. However, only a few examples are reported, most notably, the ROP of lactide and ε-CL by $Al(C_6F_5)_3$ alone in the presence of alcohol initiator. Likewise, the decarboxylative ROP of *N*-carboxyanhydrides (NCAs) proceeds through electrophilic activation of the NCA by a borane[125] or Zn[126] LA followed by attack on anhydride carbonyl by the aniline initiator. Subsequent ring-opening of the anhydride is accompanied by facile decarboxylation and re-formation of the propagating amine end group.

Dove and Naumann's method of dual catalysis,[94−96,98] which employs organic LBs and simple metal halide LAs, does efficiently control the polymerization and suppress transesterification,[94] as evidenced by low dispersity, but often the mechanism of suppression is based on deactivation of the LB by temporary CLA formation. For example, the unsaturated, highly basic NHO (1,3,4,5-tetramethyl-2-(propan-2-ylidene)-2,3-dihydro-1*H*-imidazole), which by itself produces PCL with bimodal MW distributions due to multiple initiation pathways and extensive transesterification, produces PCL in a controlled fashion when YCl_3 is present, as indicated by a dispersity of 1.07. This is likely due to the NHO existing in a dormant state (CLA) for the majority of the reaction, similar to atom-transfer radical polymerization, where it is not participating in unwanted transesterifications, enolizations, and chain scissions. Notably, the polymerization of unstrained ω-pentadecalactone (PDL) was realized by this mechanism in a controlled fashion as well as the controlled polymerization of CL and VL at RT. However, when one-pot block copolymerization of VL/CL was attempted,[94] only marginal differentiation was accomplished. It is evident that LA-based differentiation was somewhat involved since reactivity ratios reverse based on choice of LA (ZnI_2 or YCl_3). The result, however, was still an effectively random copolymerization, with the resulting product being a liquid at RT (PCL and PVL and their BCPs are crystalline solids at RT). Notably, YCl_3 and 1,3-dimethyl-2-(propan-2-ylidene)-imidazolidine (five-membered saturated NHO) was capable of achieving a perfectly random CL/VL copolymer, which shows that the mechanism suppresses the natural thermodynamic gradient copolymer preference. Thus, it is likely that multiple propagation mechanisms are operating, including cooperative activation. It is well-known that LBs can effect ROP of lactones[127−129] and lactides in the presence of alcohols. It is not unlikely that much of the propagation in this case operates through a purely base-catalyzed mechanism and is therefore outside of the influence of the LA. In a related work,[87] Naumann adapted this strategy for the thermodynamically challenging γ-butyrolactone (GBL) using LiCl/NHO LPs in the presence of an alcohol initiator. However, in the same study, it was shown that GBL could be polymerized by a wide variety of BnOH/NHOs in the absence of a LA. Therefore, when the LA is present, cooperative activation possibly makes only a small contribution to the overall propagation. Recently, Wu et al.[130] reported a sterically encumbered aminobisphenolate zinc LA paired with a weak LB (3-fluoropyridine) to effect the decarboxylative ROP of the O-carboxy anhydride of mandelic acid (manOCA) to form crystalline poly(mandelic acid) from *rac*-manOCA. Notably, the steric contribution of the LA affords high chain-end isoselectivity, making it possible to gain stereocontrol over the racemic monomer with P_m = 0.92 and a melting transition temperature of 116 °C. Furthermore, the stereocenter of manOCA is prone to epimerization among highly activating catalysts and thus required precise tuning of the moderately weak Zn LA and weak pyridine LB components to avoid racemization of the isotactic-rich polymer.

LPs have also been used to carry out the alternating copolymerization of epoxides/CO_2,[90,131] epoxides/COS,[91] and epoxides/anhydrides.[17,132] Most notably, Et_3B paired with the ^{t}Bu-P_2 PSB in the presence of alcohol initiator can make one-pot sequence-controlled di- and tri-BCPs by mixing anhydride monomers with excess epoxide comonomer.[133] At the start of the reaction, anhydrides and epoxides selectively copolymerize alternatively until the anhydride is depleted (giving the first block). Then, chain extension by homopolymerization of the remaining epoxide gives the second block. Similarly, BCPs of lactones and epoxides can be made by the same Et_3B/^{t}Bu-P_2 pair by sequential addition.[134] Here, ^{t}Bu-P_2 alone in the presence of alcohol initiator polymerizes CL. Then Et_3B is added, which shuts down polymerization of CL (*and all transesterification*), with epoxide which affords chain extension by LPP of the epoxide. Another important principle here is that in LPP the LA or LB components can be added midway through the reaction to change the mechanism, affording another degree of control.

3.3. Topological Control. It is well-known that zwitterionic ROP by organocatalysts, especially NHCs, produces cyclic polymers.[129,135] The nucleophilic organic initiating group at the α-terminus of a growing chain, which becomes cationic after addition, can act as a leaving group for S_N2 substitution by the alkoxide active species at the ω-terminus (aided by macrocyclic ion-pairing which puts the termini in proximity). The result is a macrocyclic polymer, and re-formation of the original initiating NHC which can then proceed to reinitiate more chains if free monomer still exists in solution. Although this methodology is well studied, simple, and useful, there are limitations to the degree of control one can obtain over this reaction with respect to dispersity of the target polymer. In simple zwitterionic ROP, MW of the resulting polymer can hypothetically be represented by the ratio of the rate of propagation (k_p[P*][M]) to the rate of ring-closing (k_{tr}[P*]):

$$\mathrm{MW} \propto \frac{k_p[\mathrm{P}^*][\mathrm{M}]_t}{k_{tr}[\mathrm{P}^*]} \tag{1}$$

Thus, MW can be estimated if the rate constants are known and likewise can be manipulated by changing $[M]_0$. However, there are no control factors for when the ring-closing event actually happens. Thus, ring-closing is a probability evenly distributed across a broad range of molecular weights. Furthermore, the $[M]_t$ changes throughout the course of the reaction which, if eq 1 is true, implies that the statistically derived MW also changes throughout the reaction. These matters get even more complicated if one considers the reopening of a macrocycle by a free LB and subsequent interactions with monomers or even other macrocycles. As a result, dispersity cannot be controlled.

In contrast, LPP can be used to gain such control over macrocycle synthesis. The most thoroughly studied LP

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structures in this domain are phosphine/$Zn(C_6F_5)_2$, amine/$Zn(C_6F_5)_2$, and pyridine/$Zn(C_6F_5)_2$ pairs which operate in the zwitterionic mode and thus form a natural macrocycle by zwitterionic ion-pairing and undergo the same ring-closing substitution as previously mentioned.[83] Propagation facilitated by $Zn(C_6F_5)_2$ goes through a coordination−insertion mechanism as opposed to bimetallic addition, distinguishing it from typical LPP. Nonetheless, polymerization of cyclic esters can be performed with LB/$Zn(C_6F_5)_2$ pairs in a controlled fashion, with some reports describing cyclic poly(lactide) (PLA) with dispersity as low as 1.1 with optimized conditions.[84,85] The exact mechanism that affords such control is not entirely understood. However, it may be that coordination of the carbonyl at the α-terminus to the Zn center may be necessary for ring closure and saturation of the Zn center by monomer during the course of polymerization is preferred until monomer depletion (Figure 6). Alternatively, it may be that

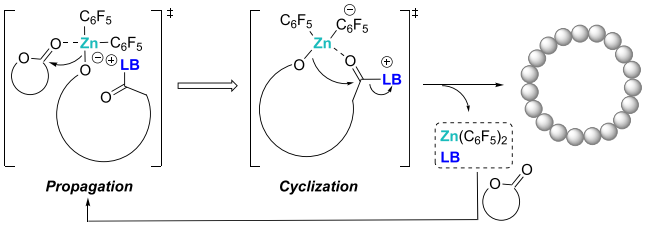
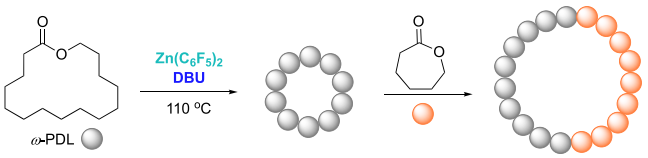


Figure 6. Postulated propagation and cyclization (ring-closing) transition state structures for cyclic polymer synthesis by LPP.[84,85,88]

the rate of cyclization is slowed down to such an extent that it does not compete with propagation, and only long after the monomer is depleted does the ring close. Regardless, it is now possible to synthesize cyclic PLA with low dispersity and other cyclic polymers from even more challenging lactones such as PDL.[85,88]

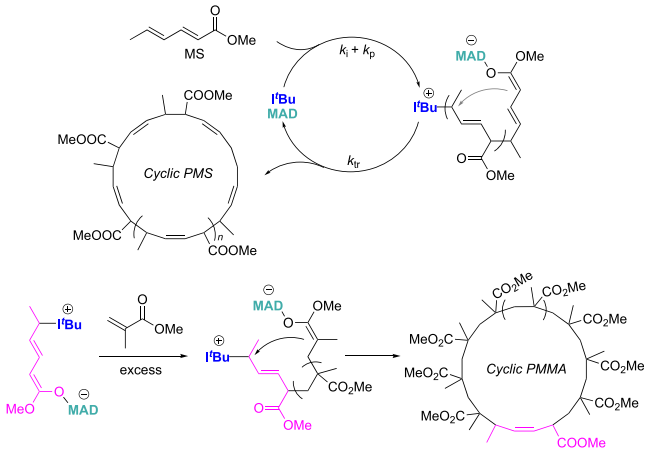
Intriguingly, this system completely inhibits transesterification, as indicated by low dispersity even at prolonged reaction times which allows for sequential addition of a second comonomer for the formation of cyclic di-BCP.[88] If it can be assumed that ring closure occurs before comonomer addition, the observed chain extension implies reopening and chain extension to existing macrocycles (Scheme 15) as opposed to reinitiation of the new comonomer.

Scheme 15. Synthesis of Cyclic BCP by Sequential Addition LPP



Sorbates, a biorenewable monomer containing two alkenes conjugated to an ester, have been included into the scope of LPP and are interesting because of the unique ditactic polymer structure obtained (two chiral centers per repeat unit). Sorbates were studied extensively by Hirabayashi[136−138] using LA-mediated anionic polymerization which outlined principles for controlling chain-end stereoselectivity of ditactic monomers using typical LAs common in LPP. More recently, the LPP of sorbates[139] has revealed important insights such as the 1,4-addition regioselectivity promoted by MAD as well as the topological control afforded by the unique I^{t}Bu/MAD combination used in conjunction with sorbates, which results in S_N2-type macrocyclization to form cyclic polymers (Scheme 16). This method was recently expanded by Takasu[140] to

Scheme 16. LPP of MS to Cyclic PMS and the Use of MS-Based Zwitterionic Species for LPP of MMA to Cyclic PMMA



formulate a more general methodology for synthesizing cyclic polymers from any vinyl ester by initiating polymerization on only 1 equiv of methyl sorbate (MS) and subsequently adding to the reaction many more equivalents of MMA which proceeded to polymerize until depletion, at which point the PMMA−enolate performs the same S_N2 macrocyclization to form well-defined cyclic PMMA (Scheme 16). We proposed earlier the possible formation of cyclic PMMA via zwitterionic polymerization initiated by I^{t}Bu, but proton transfer from the methylene carbon directly bonded to the positively charged NHC (α-carbon) to the anionic enolate chain end that forms a umpolung (enamine) intermediate (Scheme 7) complicated the cyclization chain transfer process via direct nucleophilic attack of the enolate chain end to the electrophilic α-carbon.[42]

4. KINETICS

4.1. General Considerations. The unique LPP mechanism which disposes itself to several exploitable features (Scheme 1) follows

$$\text{rate} = k_2[\text{LA}]_0[\text{LB}]_0 \approx k_2[\text{M}^*]_t[\text{P}^*]_t \quad (2)$$

where $[\text{LB}]_0 \sim [\text{P}^*]_t$, the concentration of zwitterionic active species, and $[\text{LA}]_0 \propto [\text{M}^*]_t$, the concentration of activated monomers), and subsequently gives linear conversion vs time plots. It should be noted that 1 equiv of LA is consumed at the start of the reaction to generate the active species. Thus, in an experimental scenario, a 2/1 LA/LB ratio actually yields a 1/1 $[\text{M}^*]/[\text{P}^*]$ ratio, but for the purposes of this discussion, that will be neglected. Equation 2 differs from typical (nearly inescapable) chain-growth kinetics which follow the rate = $k_p[\text{P}^*]_t[\text{M}]_t$, where $[\text{P}^*]_t$ (active growing chains). Several interesting conceptual advancements follow. First, the kinetics of LPP allow the targeted MW ($[\text{M}]_0/[\text{LB}]_0$) and the targeted polymerization activity ($[\text{LA}]_0$) to be split between two different handles. For example, should there be a desire to increase the MW of any given LPP, one could simply decrease the $[\text{LB}]_0$, while compensating the $[\text{LA}]_0$ to maintain the

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reasonable reaction times and full monomer conversion. In theory, *ultrahigh MW can be achieved by this strategy without compromise in activity and conversion*, simply by independent manipulation of the [LA]/[LB] ratio.

To illustrate this point, Figure 7 shows four different simulated LPP reactions, all making DP = 1000 polymers with

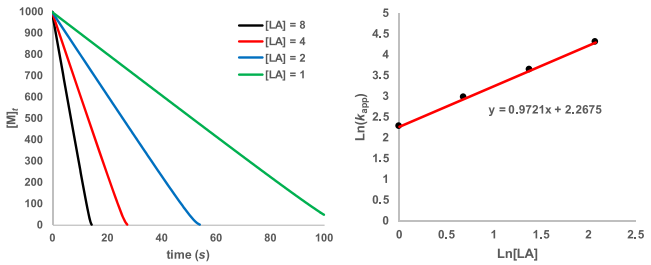

Figure 7. (left) COPASI (Complex Pathway Simulator) simulation of generalized LPP according to Scheme 1, with differing $[LA]_0$. Conditions: $K_{eq}(k_1/k_{-1}) = 1$; $k_2 = 10$; $k_3 = 100$; $[M]_0 = 1000$; $[LB]_0 = 1$; $[LA]_0 = \{1, 2, 4, 8\}$. (right) Plot of $\ln[LA]_0$ vs $\ln(k_{app})$; k_{app} calculated from the slope of each line.

varying activity as a consequence of different $[LA]_0$. Correlation of this activity dependence on $[LA]_0$ reveals a first-order relationship. Although not shown, a similar manipulation of the $[LB]_0$ concentration would also reveal a first-order dependence on $[LB]_0$. For comparison, with typical first-order chain-growth kinetics, should there be a desire to increase MW, one would do so by decreasing the initiator loading and in doing so would also decrease the activity since the active species ($[P^*]_t$) is in lower concentration. This strategy of two-component manipulation can be used when polymerization is thermodynamically feasible but kinetically slow to push polymerizations to completion, which was demonstrated during the synthesis of high MW PMC, where M/LA/LB ratios of 2000/64/1 were employed to force polymerization of unreactive MC to occur in a reasonable time frame.[9]

Likewise, this strategy can be used to slow down polymerizations of highly reactive monomers to obtain a more controlled system. This is relevant to solvent-free, bulk, or neat polymerizations, which are considered to be more environmentally friendly. Because the LA-stabilized active species cannot interact with the unactivated free monomer, the free monomer is not included in the rate law and can therefore be considered a solvent. Thus (even highly reactive and exothermic), liquid monomers can theoretically be polymerized without solvent to any desired MW if the $[LA]_0$ is appropriately lowered to an extent where polymerization is slow and controlled, and *the inert free monomer, acting as a solvent, will dissipate the heat produced by polymerization and ensuring even mixing.*

Of course, with the conditions illustrated in Figure 7—and in most reported cases—it is reasonable to make the assumption that $[LA]_0 = [M^*]_t$ because in most cases the equilibrium k_1/k_{-1} is shifted far to the right, and most of the LA's time is occupied by coordination to monomer. However, this is not exactly true. The rate-determining step, written as $k_2[M^*]_t[P^*]_t$, contains $[M^*]_t$, which is in fact a function of monomer concentration, solved for by a simple pre-equilibrium approximation:

$$[M^*]_t = \frac{k_1[M]_t[LA]_t}{k_{-1}} \tag{3}$$

Because $[LA]_t$ is in catalytic concentration, its time dependence will be neglected since any change in $[LA]_t$ would be dwarfed by the change in $[M]_t$ for intents and purposes related to the overall rate law. Thus, we can consider $[M]_t$ as the only variable.

$$[M^*]_t = [M]_t\left(\frac{k_1[LA]_0}{k_{-1}}\right) \tag{4}$$

It can be seen from eq 4 that as $[M]_t$ decreases, $[M^*]_t$ decreases. Careful observation of Figure 7 will reveal a slight deviation from linearity near full conversion, which is due to the $[M^*]_t$ dependence on $[M]_t$. Note that the K_{eq} for this modeled system, or the ratio of k_1/k_{-1}, is set simply to 1. Thus, even at a conservative estimate of the LA/monomer coordination affinity, there is substantial constancy to the prior assumptions that $[M^*]_t = [LA]_0$ (as judged by the linearity of the $[M]_t$ vs time plot). We generally assume that this K_{eq} is much higher than 1; therefore, $[M^*]_t = [LA]_0$ is a good assumption. However, we normally judiciously choose solvents for LPP, such as toluene or methylene chloride, because they rarely interact with the LA (except $Al(C_6F_5)_3$ that in the absence of monomer binds toluene and reacts with methylene chloride). If the solvent can foreseeably interact with the LA, then the $[M^*]_t/[M]_t$ equilibrium may be dramatically driven to the left. Likewise, if there is interaction between the LA/LB (Scheme 14), this would also drive the equilibrium to the left. This kind of interaction would present itself as being either first-order or pseudo-first-order with respect to monomer (Figure 8). Figure 8 shows the simulated

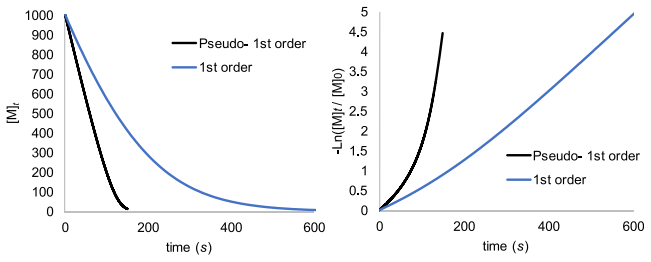

Figure 8. (left) COPASI simulation of LPP according to Scheme 1, with exceptionally low K_{eq}, showing departure from zero-order $[M]_t$ dependence and gradual adoption of first-order $[M]_t$ dependence. Conditions: $(k_1/k_{-1})K_{eq} = \{0.01$ (black), 0.001 (blue); $k_2 = 10$; $k_3 = 100$; $[M]_0 = 1000$; $[LB]_0 = 1$; $[LA]_0 = 1$. (right) First-order plots of both curves, showing a linear fit at $K_{eq} = 0.001$.

curve of a LPP where the M—LA coordination is weak, with the k_1/k_{-1} (or K_{eq}) being 0.01 and 0.001. The former (K_{eq} = 0.01) yields a pseudo-first-order plot, where the $[M]_t$ vs time plot shows a mostly linear curve that becomes nonlinear toward the end of the reaction. The latter ($K_{eq} = 0.001$) is seemingly nonlinear throughout the course of the reaction and has a near ideal fit to the first-order plot ($-\ln([M]_t/[M]_0)$ vs time). Electrophilic ROP of NCAs by B[125] and Zn[126] LAs is an example of pseudo-first-order kinetics, where zero-order kinetics is probably observed early in the reaction, but the propagating amine at the ω-termini interacting with the LA slows down monomer coordination late in the reaction and gives the kinetics some first-order character.

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If the reaction is first order, yet still following the LPP mechanism, the differential concentration of the activated monomer must now be considered in the rate law giving

$$\text{rate} = k_2[\text{P}^*]_t \frac{k_1[\text{M}]_t[\text{LA}]_t}{k_{-1}} \quad (5)$$

Because both LA and LB are at catalytic concentrations and hardly change throughout the course of the reaction, $[\text{P}^*]_t$ and $[\text{LA}]_t$ can be made $[\text{LB}]_0$ and $[\text{LA}]_0$, respectively. Lastly, k_1/k_{-1} can be understood as K_{eq}, the equilibrium constant of coordination, giving

$$\text{rate} = K_{eq}k_2[\text{M}]_t[\text{LA}]_0[\text{LB}]_0 \quad (6)$$

Thus, if the coordination of monomer to LA is weak, or K_{eq} is far less than one, it will follow the above rate law and have first-order dependence on $[\text{LB}]_0$, $[\text{LA}]_0$, and $[\text{M}]_t$. When the K_{eq} is far below 1, there might be a tendency to expect the rds to be coordination, misleading one into thinking the LB is completely uninvolved in the rds and thus not involved in the rate law. This would be an incorrect treatment of the coordination step's nature as an equilibrium. As Figure 9 shows, even when $[\text{M}]_t$ becomes first-order due to weak coordination, there is still a first-order dependence on the LB.

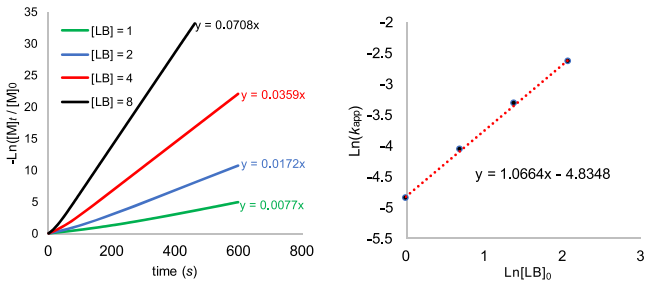


Figure 9. (left) COPASI simulation of LPP according to Scheme 1, with exceptionally low K_{eq} = 0.001, showing first-order plots of $\ln([\text{M}]_t/[\text{M}]_0)$ vs time at different $[\text{LB}]_0$. Conditions $(k_1/k_{-1})K_{eq}$ = 0.001; k_2 = 10; k_3 = 100; $[\text{M}]_0$ = 1000; $[\text{LB}]_0$ = {1, 2, 4, 8}; $[\text{LA}]_0$ = 1. (right) Plot of $\ln(k_{app})$ vs $\ln[\text{LB}]_0$; k_{app} calculated from the slope of each line.

There is a kinetic limitation related to the dilution of the LP catalyst. Because the rds involves a statistical collision between M* and P*, dilution of the system results in rapid second-order decay of activity. Or, in other words, dilution of the system decreases the concentration of two factors in the rate law. Figure 10 illustrates the rapid decay in activity as both the

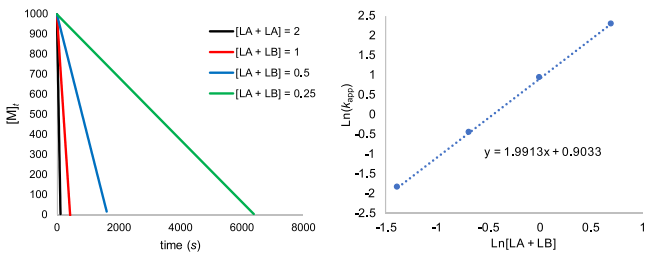
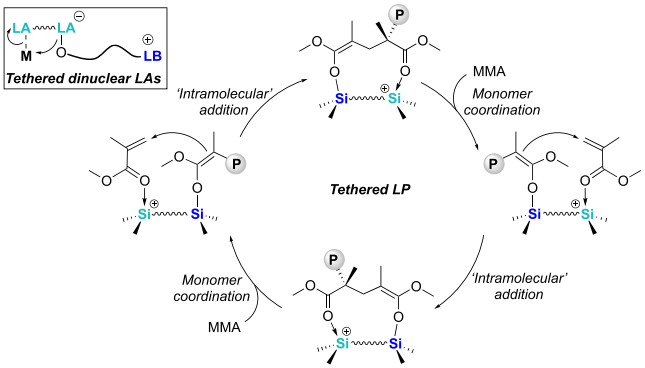


Figure 10. (left) COPASI simulation of LPP according to Scheme 1, showing rapid second-order decay of activity when both LA and LB are diluted: $K_{eq}(k_1/k_{-1})$ = 10; k_2 = 10; k_3 = 100; $[\text{M}]_0$ = 1000; $[\text{LB}]_0$ = $[\text{LA}]_0$ = {1; 0.5; 0.25; 0.125}. (right) Plot of $\ln(k_{app})$ vs $\ln[\text{LB}]_0$; k_{app} calculated from the slope of each line.

LA and LB are diluted, while keeping monomer concentration constant. In terms of component ratios, this series represents M/LA/LB = {1000/1/1; 2000/1/1; 4000/1/1; 8000/1/1}. The log/log plot on the right shows the expected second-order dependence on the sum of LA + LB. This makes high turnover numbers difficult to achieve with LPP in a timely manner. Because it makes economic sense to use extremely low catalyst loadings, this aspect of LPP seems limited. Nonetheless, the immortal LPP reported by Zhang was capable of polymerizing MMA at a M/LA/LB ratio of 20,000/2/1 and achieved 89% conversion in 48 h.[56]

A strategy to overcome this limitation is to covalently tether two LAs together (Scheme 17). By doing so, one LA is used to

Scheme 17. A Strategy Overcoming the Bimolecular Nature of the Addition Step Designed for "Intramolecular" Addition via the Proximity Effect



stabilize the growing polymer chain while the other activates the incoming monomer. By tethering the two LAs, the activated monomer is always in proximity to the active species. The rds is reliant on conformation and proximity of two tethered components as opposed to a statistical collision between them. We demonstrated this mechanism for MMA polymerization using a tethered dinuclear silylium/SKA LA/LB catalyst.[81]

4.2. Sequential Addition Block Copolymerization.

One important question still left for the discussion of LPP kinetics is the conflicting LA effect on polymerization activity. One argument suggests that stronger LAs will provide a higher degree of stabilization for the active (enolate or alkoxide) species, thus decreasing activity. A second argument suggests that stronger LAs will provide a higher degree of activation for the incoming monomer, thus increasing activity. If both of these arguments were of equal importance, then the strength of the LA would not affect the activity of polymerization. At least for conjugate addition polymerization, it seems as though LA activation of the incoming monomer has more of an effect on activity than LA stabilization of the enolate. One important clue that suggests this conclusion is the comparison of the two LA congeners $B(C_6F_5)_3$ and $Al(C_6F_5)_3$. $Al(C_6F_5)_3$, being a stronger LA, is orders of magnitude faster than $B(C_6F_5)_3$ when employed in LPP of MMA and its cyclic analogue, γ-methyl-α-methylene-γ-butyrolactone. From this outcome, we can conclude not only that stronger LAs yield higher activities but also that the character of the activated monomer has a much higher influence on the activity than the character of the enolate.

What follows is the interesting application of this concept to sequential addition block copolymerizations. When two

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monomers of varying activity are employed for sequential addition copolymerization, there is a compatibility factor that limits the degree of control obtained in these reactions. If we consider an A−B diblock copolymerization, where A is a slow monomer and B is a fast monomer, the reaction would begin by initiation of a solution of A, which would then run to completion. Because the activity of B (which will be defined as $k_{p,B/B}$) is much higher than that of A ($k_{p,A/A}$), there would be a crucial crossover step having its own activity ($k_{p,A/B}$), which we will refer to as the crossover reaction. The crossover reaction can be thought of as an initiation step, and it is well-known that if the rate of initiation is noticeably lower than the rate of propagation for any given polymerization, the dispersity will broaden. Similarly, in a block copolymerization, if the crossover reaction $k_{p,A/B}$ is less active than propagation $k_{p,B/B}$, the dispersity will broaden. Physically, this can be imagined as one single chain crossing over and propagating rapidly while the other chains are still waiting to cross over. Thus, in any copolymerization of two monomers with different activity, a dispersity increase will be observed if the slow monomer is polymerized first. This can be circumvented by simply polymerizing the fast monomer first. However, for more sophisticated architectures such as A−B−A copolymerizations, the slow/fast crossover is unavoidable.

If the aforementioned argument (that the character of the incoming monomer has the most influence on activity) is true, then what follows is that for any copolymerization, regardless of individual monomer reactivity, $k_{p,A/B}$ will be similar to or equal to $k_{p,B/B}$ since the activity is not as much influenced by the enolate of A, but more so by the activated monomer B. Thus, any two vinyl monomers can be compatibilized for block copolymerization, even those of differing reactivity, to obtain clean crossover reactions and narrow dispersities.

Although never discretely conceptualized until now, examples that can be thought of as demonstration of this concept have already existed. For example, Zhang et al.[5] reported the synthesis of well-defined A−B−A BCPs of PMMA-*b*-PBnMA-*b*-PMMA with $Đ$ as low as 1.10 and the reverse BCP PBnMA-*b*-MMA-*b*-PBnMA (BnMA = benzyl methacrylate) with an equally low $Đ$ of 1.09. Similarly, Lu copolymerized vinylbenzyl methacrylate (VBMA) chemoselectively with MMA to make a diblock with $Đ$ as low as 1.17 (slow/fast).[141] Recently, we reported the sequential addition of highly reactive acrylates ^{n}BA (*n*-butyl acrylate) and ^{t}BA (*tert*-butyl acrylate), affording high MW (M_n = 200 kg/mol) P^{t}BA-*b*-P^{n}BA-*b*-P^{t}BA with $Đ$ as low as 1.08. More recently, Zhang et al. synthesized a 53-block copolymer of alternating PMMA-*b*-PEMA-*b*-PMEMA-*b*-PEEMA pattern (EMA: ethyl methacrylate; MEMA: 2-methoxyethyl methacrylate; EEMA: 2-ethoxyethyl methacrylate), a current record to date, with $Đ$ = 1.22 after 53 sequential additions.[23]

4.3. Compounded Sequence-Control Block Copolymerization. Most recently,[19] we developed a strategy that exploits LPP kinetics to implement compounded sequence-control (CSC) block copolymerizations from one-pot mixed comonomers (Figure 11). This strategy relies on the two-step LPP propagation mechanism that involves coordination followed by bimolecular conjugate addition (Scheme 1). Because the addition step is rate-determining, the monomer coordination process has time to establish an equilibrium prior to the rds. When more than one monomer is present, the LA then has time to select the preferable comonomer for coordination prior to the rds and thus biases which monomer

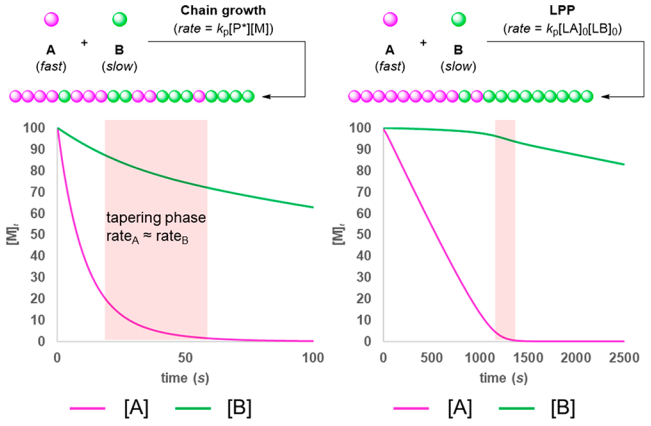
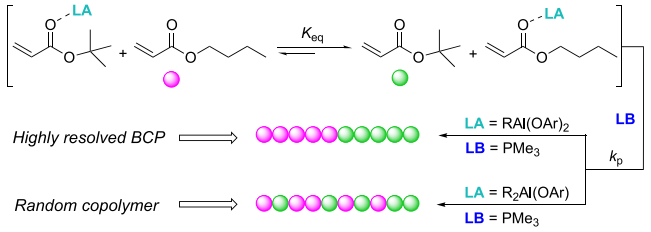


Figure 11. COPASI simulation (left) of chain-growth one-pot copolymerization of A (fast) and B (slow) monomers according to rate = k_p[P*]$_t$[M]$_t$, showing first-order decay in both A and B and (right) LPP of one-pot copolymerization of A and B monomers, with K_{eq} = 30, according to Scheme 1, showing zero-order decay of A, while B is locked out of the reaction until depletion of A. Conditions: (for both) $k_{p,A/A}$ = 0.1; $k_{p,A/B}$ = 0.01; $k_{p,B/B}$ = 0.0033; $k_{p,B/A}$ = 0.05; [M]$_0$ = 100; [I]$_0$ or [LB]$_0$ = 1; (for LPP only) ([A*][B]/[B*][A]) K_{eq} = 30, [LA]$_0$ = 1.

is available for the rds (Scheme 18). This scenario differs from metal-mediated coordination−addition polymerization, where

Scheme 18. Illustrated K_{eq} Differentiation



coordination typically is the rds and is immediately followed by addition,[142] which does not allow enough time for a prior equilibrium (K_{eq}) to establish.

Additionally, any propagating active species, when exposed to two different monomers with inherently different reactivity, will have some selectivity toward one monomer over the other (differing propagation rates, k_p), resulting in a tapered or gradient copolymer structure. The shaded area in Figure 11 marks the tapering phase at which point rate$_A$ is approximately equal to rate$_B$, resulting in a significant tapering effect (sequence error) for any typical first-order chain-growth polymerization. This "natural" k_p selectivity is also present in LPP but occurs during the rds of bimolecular addition. Therefore, there are two different events of selectivity occurring at two different steps. If these two events operate constructively (i.e., the same monomer is selected for during coordination and propagation), the two selectivity probabilities will compound (thus the name *compounded sequence control*, Figures 12 and 13). This compounded thermodynamically biased prior K_{eq} and kinetically differing k_p sequence control, unique to LPP, drastically suppresses the tapering effect (i.e., no sequence error until very late in the copolymerization, see Figures 11), thereby enabling the synthesis of highly resolved BCPs.[19]

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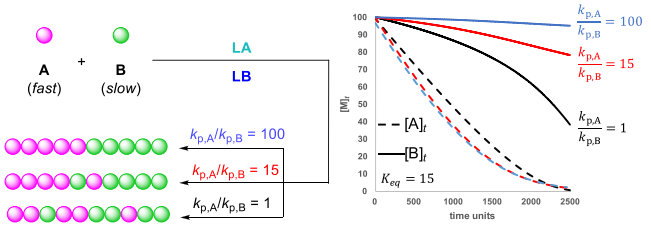

Figure 12. Comparative simulation of CSC-LPP at different reactivity ratios. Conditions: ([A*][B]/[B*][A]) K_{eq} = 30; $[M]_0$ = 100; $[LA]_0$ = 1; $[LB]_0$ = 1; (blue) $k_{p,A/A}/k_{pB/B}$ = 100: $k_{p,A/A}$ = 1; $k_{p,A/B}$ = 0.1; $k_{p,B/B}$ = 0.01; $k_{p,B/A}$ = 0.5; (red) $k_{p,A/A}/k_{pB/B}$ = 15: $k_{p,A/A}$ = 1; $k_{p,A/B}$ = 0.2; $k_{p,B/B}$ = 0.066; $k_{p,B/A}$ = 0.5; (black) $k_{p,A/A}/k_{pB/B}$ = 1: $k_{p,A/A}$ = $k_{p,A/B}$ = $k_{p,B/B}$ = $k_{p,B/A}$ = 1. The *X*-axis is artificially scaled so that each run can be evenly overlaid.

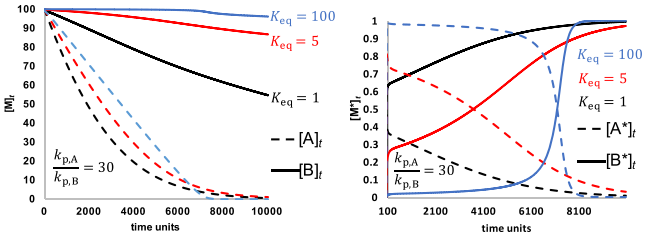

Figure 13. Comparative simulation of CSC-LPP at different K_{eq}, with monomer depletion vs time (left) and activated monomer vs time (right). Conditions: $[M]_0$ = 100; $[LA]_0$ = 1; $[LB]_0$ = 1; $k_{p,A/A}$ = 0.1; $k_{p,A/B}$ = 0.01; $k_{p,B/B}$ = 0.0033; $k_{p,B/A}$ = 0.05; (blue) ([A*][B]/[B*][A]) K_{eq} = 100; (red) K_{eq} = 5; (black) K_{eq} = 1. The *X*-axis is artificially scaled so that each run can be evenly overlaid.

To demonstrate the equal importance of both prior K_{eq} and differing k_p, we have performed a thorough simulation study to isolate each variable. In Figure 12, we show three reactions, all containing the same K_{eq} = 15, but with differing reactivity ratios. For all reactions, the reactivity ratios represent the $k_{p,A/A}/k_{p,B/B}$ ratio, or the ratio of the homopolymer k_p's, and can be measured. Thus, the cross-polymerization rates ($k_{p,A/B}$ and $k_{p,B/A}$) are considered *and important* but chosen judiciously and arbitrarily for the purposes of the simulation study, and we have not endeavored to measure them experimentally. Thus, it can be seen from Figure 12 that various degrees of selectivity derived from differing propagation rates lead to different levels of block resolution.

In a similar fashion, the reactivity ratios, $k_{p,A/A}/k_{p,B/B}$, were kept constant at 30 while the K_{eq} was manipulated (Figure 13). Here, we see a similar trend where a higher K_{eq} results in higher block resolution. Notably, at K_{eq} = 100, the B monomer is completely locked out of polymerization until A has been depleted. Likewise, for this reaction, A shows an almost perfectly linear conversion vs time plot from start to finish. This can be attributed to the constancy of the $[A^*]_t$ shown on the right, where due to a high K_{eq} value, its concentration does not significantly change over the course of the polymerization until the very end. In contrast, when K_{eq} = 5, such constancy is not observed, and the $[A^*]_t$ is much more variable, leading to lower block resolution. This contrasts starkly with the K_{eq} = 1 case, where $[A^*]_t$ is virtually always less than $[B^*]_t$, resulting in a poor block resolution reminiscent of a typical chain-growth polymerization (Figure 11).

Thus, with ^{n}BA and ^{t}BA, two reactive acrylate homologues, sequence control was achieved with the MAD/PMe_3 LP.[19] The K_{eq} value using MAD as the LA, representing preference between MAD/^{n}BA and MAD/^{t}BA structures in equilibrium, was found to be ∼16 at RT. Likewise, using independent kinetic studies, we found the $k_{p,A/A}/k_{p,B/B}$ value to be ∼30. Thus, when a one-pot copolymerization of the equimolar mixture of ^{n}BA and ^{t}BA was executed, nearly ideal block resolution (<3% sequence errors) was achieved. Additionally, A−B−A tri-BCPs were also synthesized in two steps by initiating polymerization on the entire sum of the slow monomer (^{t}BA) and adding the fast monomer (^{n}BA) at 50% conversion. We expect this methodology to be widely applicable and are currently expanding the monomer scope to other polar conjugate monomers. With ^{n}BA being a highly desirable soft middle block (glass-transition temperature = −40 °C), we expect that ^{n}BA will be compatible with most vinyl esters and will conveniently always be the fast monomer since being an electron-rich and uncrowded acrylate it will always be the preferential LA binder (K_{eq}) and the fastest (k_p) monomer. Consequently, A−B−A tri-BCPs of all other conjugated esters—such as methacrylates, α-methylene lactones, crotonates, and sorbates—should be feasible with ^{n}BA as the soft middle block.

Hypothetical extrapolation of this concept leads to many intriguing possibilities. (1) Two-step A−B−A triblocks include the aforementioned *slow−fast−slow* triblock and equally feasible *fast−slow−fast* triblocks involving initiation of a *fast*/*slow* comonomer mixture, followed by addition of a second quantity of the fast monomer. (2) The A−B−A tri-BCPs should be made in one-pot by initiating polymerization on a mixture of comonomers with using a dinuclear LB. (3) The one-pot A−B−C triblock copolymerization should also be feasible with three different monomers of sufficient variety as well as a number of two-step A−B−C−A and A−C−A−B tetrablocks. (4) Careful application of flow chemistry could allow for the continuous synthesis of highly sophisticated multiblock copolymers. As for diblock copolymerizations, this method not only saves an addition step but also saves a purification step, as two monomers can be packaged in the same container, presumably with some form of a stabilizer, and purified in a one-pot setup.

5. SUMMARY AND OUTLOOK

In summary, we have presented here an account of the progression of LPP from its emergence to the present, highlighting the mechanistic advancements of each milestone and tracing the advantageous elements back to the fundamental concepts. We hope to leave the reader with not only a fundamental understanding of LPP but also ideas for how to exploit the unique features of LPP to conquer future polymerization challenges. Here we want to emphasize the following four most important concepts of LPP. (1) LPP tames the highly reactive active species and focuses both the reactivity on LA-activated monomers and selectivity of the stabilized active species against side reactions. (2) Tunability of both LA and LB components compounding with a vast library of component structures provides access to a massive degree of tunability. (3) The synergy and cooperativity between the acidic and basic catalytic sites of readily available and judiciously constructed LPs can be exploited on demand to control the polymerization characteristics. (4) The unique two-step mechanism of coordination followed by propagation affords access to additional levels of control including precise tuning of polymerization activity, polymer MW, and

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comonomer sequence as well as manipulation of active monomer before the rds.

Lastly, we offer our perspectives on *three selected challenges* still facing LPP, thereby highlighting future opportunities in this exciting, yet still young and relatively unexplored territory. We frame these challenges with the following three questions. (1) Can we advance LPP to effect polymerization of nonpolar olefins? Currently, LPP is void of reports on α-olefins such as ethylene and propylene, and LP structures appropriate for olefin polymerization have yet to be observed. The key aspect of the design is elucidation of LA structures that can effectively active an olefinic monomer to result in an active species that can chain propagate. (2) Can we overcome catalyst dilution effects inherent to the bimolecular intermolecular addition rds under dilute conditions by performing LPP "intramolecularly"? LPP by dinuclear LPs with covalently tethered LAs could potentially not only affect kinetics of reaction but also have chemoselective and stereoselective implications that inflame the imagination (cf. Scheme 17). (3) How can we develop stereoselective LPP? Although LPP has demonstrated complete chemoselectivity for several types of multifunctional monomers, stereoselective LPP remains an unmet challenge. The influence on the transition state afforded by LA stabilization and LA activation leads one's imagination to hypothetical stereoselective mechanisms. We expect our recently reported CSC mechanism[19] to be fruitful in the synthesis of many highly sophisticated and otherwise unattainable BCPs as well as stereosequencing and kinetic stereoresolution.

To demonstrate the potential of the CSC mechanism to meet the above-described third challenge, here we present a hypothesized scenario that zwitterionic or dual catalytic LPP modes could be capable of not only CSC of different monomers but also stereosequence control and stereoselection of enantiomeric or diastereomeric mixtures such as lactides,[143] diolides,[144] and fused bicyclic lactones.[115,116,145] For example, a racemic mixture of methyl diolide, DL^{Me} (4,8-dimethyl-1,5-dioxocane-2,6-dione), mixed with an enantiopure C_1- or C_2-symmetric LA would result in an equilibrium bias between DL^{Me}/LA structures: K_{eq} = [(*S*)-DL^{Me}·LA][(*R*)-DL^{Me}]/([(*R*)-DL^{Me}·LA][(*S*)-DL^{Me}]. Thus, subsequent initiation and propagation would result in a highly resolved isotactic stereoblock poly(3-hydroxybutyrate) (P3HB) through the proposed enantioselective LPP (Figure 14). For comparison, the recent system[146] that exploits chiral Salen−yttrium complexes to effect stereosequencing of *rac*- and *meso*-DL^{Me} differentiates between (*R*)- and (*S*)-DL^{Me} carbonyls by preferential coordination of the chiral monomer to the chiral yttrium. However, the first-order kinetics of that reaction implies that coordination is the rds which consequently suggests that chain addition follows immediately after coordination. Thus, only the forward coordination rate constant k_1 (association of monomer to Y) matters and not the reverse reaction k_{-1} (dissociation of monomer from Y). In other words, there is not enough time for a true thermodynamic equilibrium bias to establish. Furthermore, the coordination−insertion mechanism only affords one degree of differentiation, while LPP affords two degrees of differentiation (preferential coordination K_{eq} and preferential propagation k_p) which, if operating constructively, leads to CSC of *rac*-DL^{Me}. By the same token, this important stereocontrolled, biased prior equilibrium in the case of LPP of *meso*-DL^{Me} should also result in the stereoselective LPP to form syndiotactic P3HB (Figure 14).

In closing, narrated in this Perspective are the many important advances already made so far in the field of LPP over the past ten years. These, coupled with LPP's intriguing future opportunities and reasoned fascinating possibilities also outlined in this Perspective, show LPP's growing potential to be a broadly useful polymerization method to solve modern polymer synthesis problems.

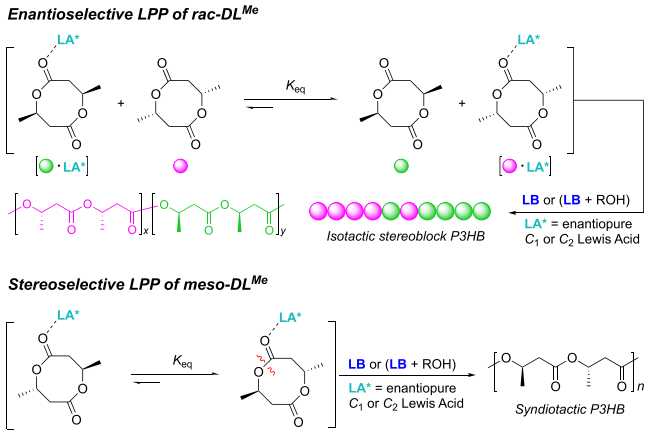

Figure 14. Postulated stereoselective LPP of *rac*-DL^{Me} and *meso*-DL^{Me}.

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Notes

The authors declare no competing financial interest.

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Eugene Chen received his Ph.D. degree from The University of Massachusetts in 1995. After a postdoctoral stint at Northwestern University, he joined The Dow Chemical Company, where he was promoted to Project Leader. He moved to Colorado State University in 2000, where currently he is a University Distinguished Professor, the John K. Stille Endowed Chair in Chemistry, and the Millennial Professor of Polymer Science and Sustainability. His current research interests encompass broadly the areas of polymer science, sustainable chemistry, and homogeneous catalysis.

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