Review

Calixarene-Metal Complexes in Lactide Polymerization: The Story so Far

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ABSTRACT: Polylactide synthetic procedures have lately gained attention, possibly due to their biocompatibility and the environmental problems associated with fossil-fuel-based polymers. Polylactides can be obtained from natural sources such as cassava, corn, and sugar beet, and polylactides can be manufactured in a laboratory using a variety of processes that begin with lactic acid or lactide. One of the most effective synthetic pathways is through a Lewis acid catalyzed ring-opening polymerization of lactides to obtain a well-defined polymer. In this regard, calixarenes, because of their easy functionalization and tunable properties, have been widely considered to be a suitable 3D molecular scaffold for new metal complexes that can be used for lactide polymerization. This review summarizes the progress made in applying some metal-calixarene complexes in the ring-opening polymerization of lactide.

1. INTRODUCTION

The history of calixarenes dates back to 1872, when Adolf von Baeyer reported the reaction between phenol and formaldehyde.[1] After almost 70 years, the compound was termed "calixarene" and its structure was assigned by C. D. Gutsche in 1978, derived from the Latin "calix" meaning vase and describing the cone-shaped conformation which the macromolecule often adopts (Figure 1a).[2,3] Calix[n]arenes possess a
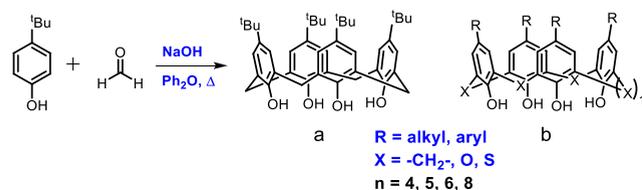
Figure 1. (a) Synthesis and (b) structure of calix[n]arene.

common structure in which *n* represents the number of phenolic units linked together through a methylene group or heteroatom (Figure 1b). The existence of a hydrophobic cavity and the possibility of incorporating a wide variety of analytes create extensive opportunities for their use as catalysts and chemosensors.[4−6] Many catalytically valuable ligands, such as the ubiquitous multidentate salen and porphyrin molecules, act as electron donors in their metal complexes. Like salens and porphyrins, a similar tetradentate dianionic motif is also found in calixarene, where the metal center is coordinated to the lower rim oxygen atoms. An increase in studies on the use of calix[n]arenes as auxiliary ligands in metal catalysts for various transformations is a result of the development of calixarene coordination chemistry. Synthetic protocols toward selectively modified calixarene ligands are straightforward, making these ligands highly attractive for inorganic and analytical chemists. The conformational flexibility, presence of cavities, and ability to concurrently coordinate numerous metal centers are essential characteristics of the higher calixarene systems. Most calix[4]arene systems tend to retain the cone conformation upon metalation, binding to metal centers in both *exo* and *endo* conformations. Nonetheless, calixarene ligands have yet to compete with other multidentate ligands in catalytic applications. One possible explanation for this disparity is that the calixarene ligand exclusively contains hard oxygen donors. Thus, calixarene-based compounds have been utilized as ligands for complexation with a large number of oxophilic metals.[7,8] The presence of only hard *O*-donors also limits the use of calixarene in biomimetic studies.[8] Nonetheless, calixarenes are easily and selectively modified, and high-yield synthetic protocols toward various mono-, di-, or tri-*O*-

substituted ethers and esters are available.[9] Moreover, despite calixarene not exactly taking part in the catalysis, it may have a positive role in many chemical transformations. Calixarenes are frequently used in transition-metal bond activation and catalysis because they give a metal more stability and control over its coordination environment than monodentate ligands.[7−9]

The world's reliance on petroleum-based polymers has grown significantly over time. Polyolefins like polyethylene, polypropylene, polystyrenes, and polyvinyl chloride, polyesters like polyethylene terephthalate, polyamides like nylon, and epoxy (commonly known as plastic) are synthetic polymers made from petroleum hydrocarbons.[10,11] Because of the omnipresent qualities of petroleum-based polymers, they are finding utility in a wide range of applications. These applications include consumer products like appliances, toys, packaging materials, electronics, coatings, and automobile components to name a few.[12,13] These polymers have also gained significant traction in the biomedical field, where they are used in the design and development of implants, monitoring, diagnostic, or therapeutic devices, and drug delivery techniques, among others.[14,15] Petrochemical-based polymers have been extensively used owing to numerous advantages like ease of preparation and low cost. However, the utilization of these polymers poses significant hurdles, which include a paucity of organic compounds as a result of dwindling oil and gas supplies and rising oil and gas prices. Additional effects include toxicity, unaffordable pricing, cross-contamination in recycling, and environmental issues caused by their disintegration. These concerns inspired the search for materials capable of fixing these limitations while retaining the needed qualities for diverse applications. Biocomposites and biopolymers are two materials which have gained recent traction because of their easily adjustable properties.[16−18] Biocomposites from cheap and renewable resources offer significant sustainability and have found use in building materials, the aerospace industry, circuit boards, automotive applications, and the energy sector.[19−21]

Biopolymers have been around for a while now but have generally been held back due to their higher cost and issues with durability. However, the development of improved catalytic systems coupled with rising environmental concerns accompanying the use of petroleum-based polymers has created tremendous interest in alternatives to plastic. One such alternative is a polylactide (PLA) (Figure 2), a polymer of lactic acid which is synthesized either through polycondensation of lactic acid or by ring-opening polymerization (ROP) of lactide (LA).[22−24] The pathway of polycondensation has been found to be less influential, as water is liberated constantly, which is difficult to remove, necessitating harsh conditions to
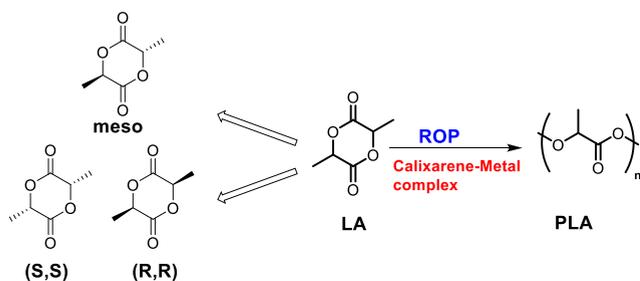
obtain the polymer with a high molecular weight.[25] Hence, the ring-opening polymerization (ROP) of LA has been emphasized, as it allows good control over the molecular parameters like molecular weight, polydispersity index, etc. under mild reaction conditions compared to the polycondensation pathway.[26] PLA and its modified products have received great attention as functional materials due to their biocompatibility, nontoxicity, mechanical stability, durability, and applications.[27,28] Lactide copolymerization with monomers like malic acid or polymers such as polyethylene glycol (PEG) or polyglycolic acid (PGA) has also been explored.[29,30] Although calixarene-metal complexes have found use in many functional group transformations, initially, only a few papers on their application in polymerization were reported.[31−42] An exciting work by Frediani and co-workers in 2008 reported the use of a Ti-calixarene complex in lactide polymerization.[43] After that, several articles have been published in this field by different research groups worldwide.[43−64] Despite some progress in this area and the importance of PLA, no such review has been published to cover the developments (made in this field) critically and also entirely. Thus, this review proposes to not only fill the gap but also provide new insights and analyses of the progress and limitations of different aspects. In this review, we will discuss a few of the protocols adopted to synthesize calixarene-metal complexes, touch upon the structure of a few interesting complexes, and deliberate upon their activity as catalysts for LA ring-opening polymerization.

2. CALIXARENE-METAL COMPLEXES IN ROP

Metal complexes of calixarenes have received immense attention in the field of catalysis.[31−41] The utilization of a properly designed ligand plays a very important role in the polymerization of LA.[42] Much work has been carried out by using transition-metal complexes of calixarenes, which have proved to be very effective toward the LA polymerization.[43−64] Here we will discuss the synthesis and application of some calixarene metal complexes in the ROP of LA.

2.1. Titanium-Calixarene Complexes in ROP. Frediani's group described the synthesis of the first titanium complex of modified calixarene **1** in lactide polymerization.[43] The dicholorotitanium complex **1** was obtained in 88% yield by treating 5,17-bis-*tert*-butyl-25,27-dihydroxy-11,23-dinitro-26,28-dipropyloxycalix[4]arene with TiCl₄ in hot toluene. The NMR spectra of **1** revealed a C_{2v}-symmetrical structure, confirming the cone conformation (Figure 3). According to single-crystal X-ray diffraction studies, the titanium atom is found in an octahedral ligand environment composed of four oxygen and two chlorine atoms, with the two propylated oxygen atoms occupying trans positions. The polymerizations with catalyst **1** were carried out under solvent-free conditions, and it was found to be more active than other reported

Figure 2. Structures of LA and PLA.
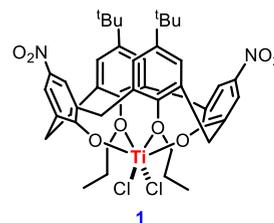
Figure 3. Structure of Cl₂Ti-calixarene complex **1**.

chlorotitanium catalysts. One possible reason given was the presence of two strongly electron withdrawing nitro functional groups, which enhanced the Lewis acidic properties of complex **1**. Another important observation reported by Frediani's group was the role of an external alcohol in reactivity and polymerization. Despite the fact that Ti complex **1** was successful in the polymerization of LA in the absence of any external alcohol activator, the presence of 75 equiv of *n*-BuOH further improved the activity. Under these conditions, PLA was obtained with 98.3% monomer conversion and an excellent polydispersity index (PDI 1.16). One reason for increased activity would be the *in situ* formation of a more labile Ti-dialkoxide complex. The presence of a unique quartet in the methine region (at 5.16 ppm) is indicative of isotactic polylactide formation. The authors report a living polymerization mechanism with catalyst **1**, signifying that the active Ti-metal center is present at the end of the polymerization cycle.

In a continuation of their work on the application of Ti-calixarene complexes in PLA synthesis, Frediani and co-workers in 2010 reported the synthesis of a Cl$_2$Ti-calixarene complex **2** (Scheme 1) and described its use in ROP of *rac*-LA

Scheme 1. Microwave-Assisted ROP
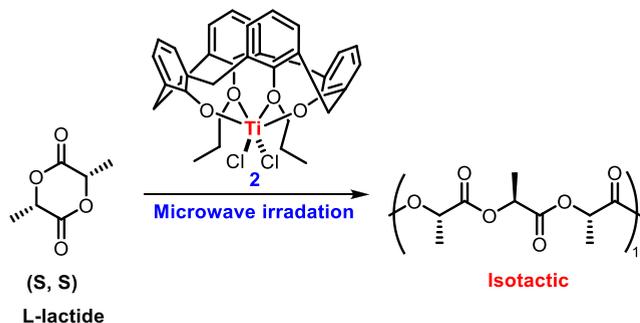
or L,D-LA.[44] To initiate the polymerization reaction, his group opted for two techniques: i.e., microwave irradiation and conventional thermal treatment with complex **2**. In comparison with the other experiments carried out, it was found that microwave energy enhances the polymerization rate. It was also observed that the activity of complex **2** was somewhat higher in the case of rac-LA than for L-LA.[45] The remarkable feature of the polymer formed was the partial isotactic stereoblock microstructure in spite of the C_{2v} symmetry with a conversion of 88% and PDI of 1.23 with conventional heating. The spectrum shows two well-resolved peaks, of equal normalized intensity, at 5.21 and 5.22 ppm representing hexad stereosequences indicating random polymerization. Under microwave-assisted conditions a polymer with a PDI of 1.30 (88% conversion of monomer) was obtained within 80 min. Although lower molecular weights were observed with microwave irradiation (M_w = 27100 and M_n = 20900) compared to those with the conventional method (M_w = 27600 and M_n = 22400), better stereocontrol (isotactic) could be witnessed with microwave heating.

Jason et al. have prepared several structurally diverse metal clusters stabilized by *tert*-butylcalix[8]arene. They noted that the usual deprotection–metalation strategy is ineffective in preparing Ti-calix[8]arene complex **3** (Figure 4). Complex **3** was prepared by directly treating the corresponding calixarene with an excess of Ti(OiPr)$_4$ in THF. The single crystal of complex **3** shows that the two Ti(IV) centers are 3.2876 Å
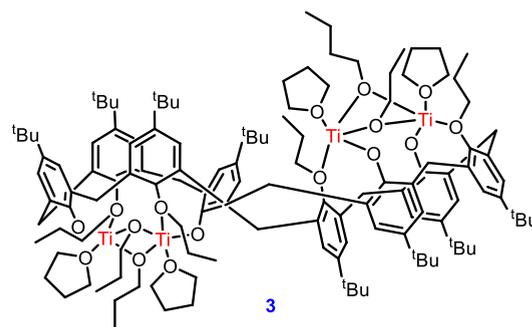
Figure 4. Structure of complex **3**.

apart within half of the molecule. The Ti centers are also supported by two bridging propoxides. The complex was only moderately successful in the polymerization of *rac*-LA, with the maximum *m/z* observed at 1956. The absence of higher molecular weight polymer units was attributed to the competing intramolecular transesterification process.[46] The decreased activity of complex **3** may be due to the higher flexibility of the calix[8]arene scaffold, which allows for unusual binding and less access to the catalytically active core.

Redshaw et al. have synthesized the titanium complexes of a series of functionalized calix[4]arene molecules of the type TiCl$_2$L(O)$_2$(OR)$_2$ (R = Me (**4**), *n*-Pr (**5**), and *n*-pentyl (**6**)), the dimeric compound TiL(O)$_3$(OR)]$_2$(Cl)$_2$ (R = *n*-decyl (**7**)) and Ti(MeCN)ClL(O)$_3$(OMe) (**8**) for the ROP of cyclic esters. For the preparation of complexes **4–6**, the method reported by Taoufik and Bonnamour was followed.[47] In this procedure 1,3-alkoxy calix[4]arene was treated with a THF complex of TiCl$_4$ in toluene and the reaction mixture was stirred at 60 °C for 12 h. Crystallization was done by using CH$_3$CN during workup (Scheme 2). The crystal structure of these complexes indicates that the Ti-metal center resides in a distorted-octahedral geometry with a pinched cone conformation.

Scheme 2. Synthesis of Titanocalixarene Complexes 4–6
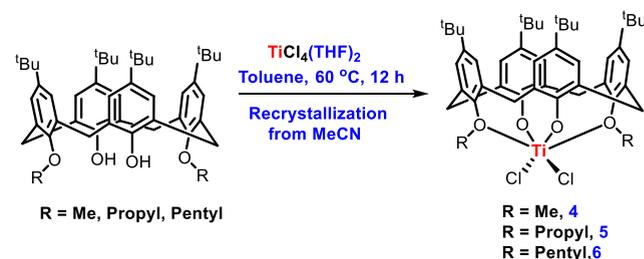
Interestingly, in the case of 1,3-*n*-decyl-functionalized calixarene, a choloro-bridged dimer was obtained, in which each Ti center is best described to be present in a distorted-octahedral geometry (Scheme 3).

Redshaw's group also prepared many other titanocalixarene complexes for their catalytic study of ROP in cyclic esters using a modified Floriani procedure.[48] Consequently, the treatment of 1,3-dimethoxy calix[4]arene with TiCl$_4$(THF)$_2$ in hot toluene (60 h) followed by refluxing with acetonitrile (24 h) afforded orange-red crystals of complex **8** on cooling (Scheme 4).

All of the complexes were investigated for their ability to catalyze the ROP of *rac*-LA. It was reported that the catalyst

Scheme 3. Synthesis of Titanocalixarene Complex 7

R = Decyl
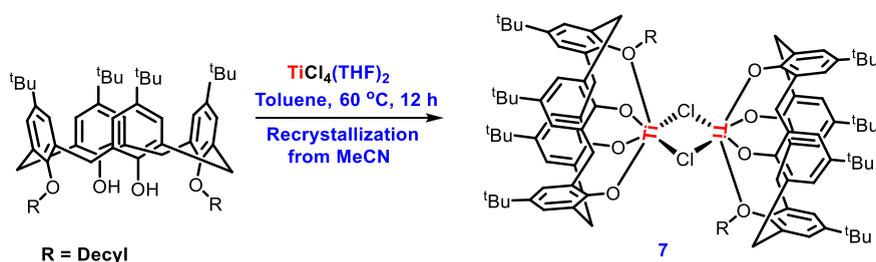
Scheme 4. Synthesis of Titanocalixarene Complex 8
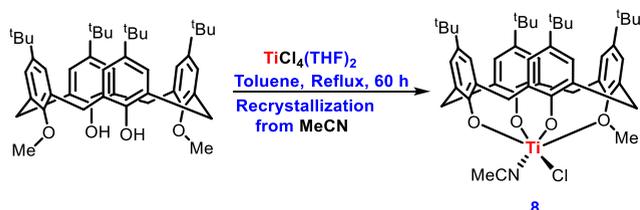
systems **4**−**8** were inactive at 80 °C even when the reaction mixture was stirred for 24 h. At an elevated temperature (130 °C), almost quantitative conversion was observed with complexes **4**−**6** and **8** (95%, 97%, 95%, and 95%, conversions, respectively), while only moderate conversion (65%) could be realized with complex **7**. Ring-opening polymerization was carried out with complexes **4** and **5**, which yielded the heterotactic polymers (P_r 0.46 and 0.42, respectively), and with complexes **6**−**8** isotactic materials were obtained (Scheme 5). Interestingly, catalyst **8** was also found to be active even in air, with complete conversion being observed.

Scheme 5. Microstructures of Heterotactic and Isotactic PLA
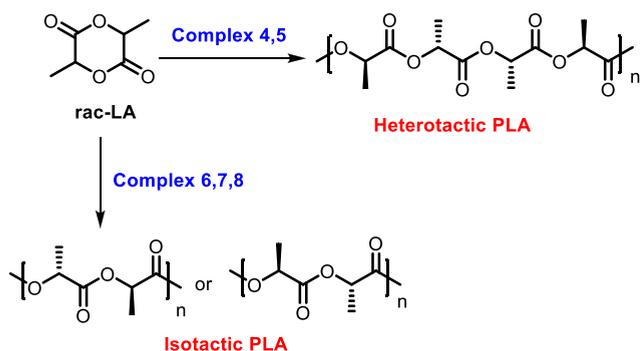
Very recently, Redshaw and co-workers synthesized Ti complexes of calix[6]arene and calix[8]arene (**9**−**13**) and screened them in the ROP of cyclic esters both in air and under an inert atmosphere. The catalyst **9** was prepared by direct treatment of calix[6]arene with 2 equiv of TiCl$_4$ in hot toluene followed by workup with acetonitrile. In each case, the two pseudo-octahedral Ti(IV) ions are bound to a calix[6]-arene ligand via three phenolate oxygens, while the Cl, CH$_3$CN and H$_2$O molecules are facial (Figure 5, complex **9**).

Treatment of calix[6]arene with TiF$_4$ (3 equiv) and extraction into MeCN provided complex **10**. The pseudo-octahedral Ti centers of the two macrocyclic units in complex
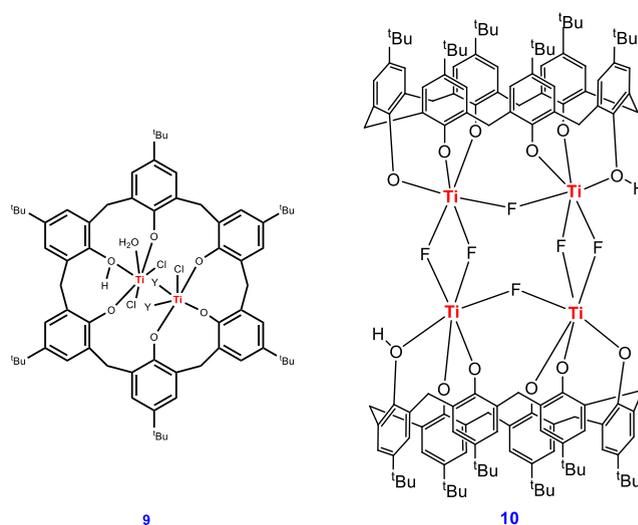
Figure 5. Structures of complexes **9** (Y = CH$_3$CN) and **10**.

10 are connected to each other through an F bridge. The central core consists of two Ti$_2$F$_2$ diamonds that connect the calixarenes, while the two fluoride ions connect the Ti centers (Figure 5, complex **10**).

The reaction of *p*-tert-butylcalix[8]arene with 4 equiv of TiCl$_4$ in refluxing toluene and workup with MeCN furnished small red crystals of **11** in moderate yield. The X-ray diffraction studies show a complex where Ti is occupying a pseudo-octahedral position with trans Cl and MeCN groups, while the other Ti centers are square-pyramidal with apical Cl ligands. Treatment of *p*-tert-butylcalix[8]arene with 4 equiv of TiI$_4$ followed by workup in dichloromethane afforded the dark red complex **13**. Similarly, the analogous complex **12** could be realized with TiBr$_4$ (Figure 6). Interestingly, the molecular structure of the prepared compounds revealed a ladder-like complex similar to that observed for the chloride and iodide systems.

All of the catalysts were screened under different reaction conditions (for a brief overview, see Table 1). Among all the catalysts prepared, only complex **9** was found to be highly active toward the polymerization of *rac*-LA with a conversion of 87%, and the syndiotactic bias (P_r) of 0.51 suggested atactic polylactide formation.[49,50] Regardless of the reaction conditions investigated, no reaction was detected while using **10** and **11** and the bromide complex **12**. In contrast, a 11% conversion was observed when catalyst **13** was used even after 24 h.

2.2. Zinc-Calixarene Complexes in ROP. From enzymatic transformations to asymmetric organic synthesis, zinc complexes are at the heart of a wide range of catalytic
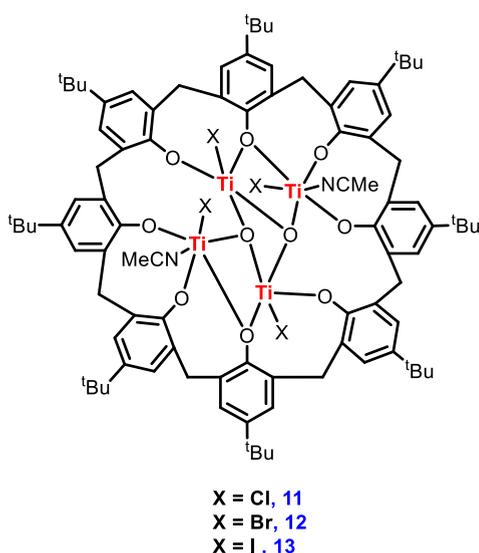
Figure 6. Structures of complexes **11**−**13**.

Table 1. Catalyst Screening for ROP of *rac*-LA

entry	complex no.	*rac*-LA:Ti:BnOH	*T* (°C)	time (h)	conversion (%)
1	**9**	500:1:3	130	24	87
2	**9**	500:1:3	130	1	33
3	**10**	250:1:4	130	24	
4	**11**	500:1:2	130	24	
5	**12**	250:1:1	130	24	
6	**13**	250:1:1	130	24	11

processes.[51,52] Both bi- and monometallic Zn complexes have been found to be active in LA polymerization. In 1996 Raston and co-workers reported the formation of an unusual bimetallic Zn complex when calixarene 1,3-dimethyl ether was treated with 2 equiv of Et₂Zn.[53,54]

Vigalok et al. in 2004 synthesized and studied a variety of bimetallic alkyl zinc complexes of 1,3-alkylated calix[4]-arenes.[55] They envisaged that the small methyl substituent might favor flipping in the calixarene scaffold, and thus much of their work was on larger 1,3-substituted calix[4]arenes. A series of bimetallic Zn complexes were prepared by treating appropriately substituted calix[4]arene with 2 equiv of Et₂Zn in toluene at room temperature (Scheme 6).

The alkyl-incorporated complexes **14** and **15** containing two Zn atoms share the same aryl oxide framework; calixarene trapping protects one of the alkyl zinc fragments from an attack of the organic substrate. It has been observed that the ethyl zinc group is a comparatively poor nucleophile and less
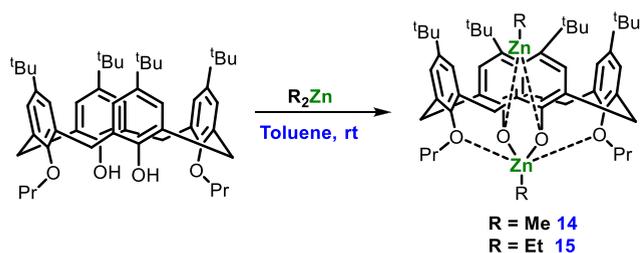
reactive than Zn-alkoxide, therefore moving from an ethyl zinc to a methyl zinc initiating group drastically improved the performance of the catalyst.[56] Ring polymerization was carried out in toluene at a temperature above 60 °C to produce PLA with low polydispersity and a conversion rate of 98% (Scheme 7). To ensure that conformational changes in calixarene did not play a significant role in catalysis, they also prepared complexes **16**−**18** (Figure 7) and checked the efficiency in the ROP of L-lactide. The results indicated that the catalyst activity depended only on the external alkyl group (behaving as an initiator for reaction) and was independent of the alkyl zinc group inside the calixarene cavity.

Redshaw and co-workers explored the use of the calix[4]-arene and the oxacalix[3]arene ligand in the preparation of the corresponding Zn complexes and reported their use in ROP of cyclic esters.[57] The authors identified the effect of additional chain transfer agents and the tactility of the resulting polymers. The synthesis of several new zinc-containing calix[4]arene complexes (**19**−**21**) is outlined in Scheme 8.

Among the synthesized complexes, only **19** was found to be more active for the ROP of *rac*-LA at high temperature (100 °C) with 90% conversion and P_r = 0.62, but the molecular weight of the polymer was found to be lower than expected. One of the possible reasons for this could be the unwanted trans-esterification reaction occurring at that temperature. Replacing the pentafluorophenyl group with an amide group (N(SiMe₃)₂) in **19** afforded complex **20**, which was found to be more effective with 64% conversion and P_r = 0.54 at room temperature and the polymer molecular weight was near the expected value. While complex **21** differs from complex **20** by substitution of Zn-N(SiMe₃)₂ with a sodium cation, it was not found to be active under the same reaction conditions. The group also synthesized an oxacalix[3]arene complex for the first time, the synthetic scheme of which is given in Scheme 9. After removing the volatiles from a reaction between 3 equiv of Zn(C₆F₅)₂·toluene and oxacalix[3]arene at room temperature, compound **22** was formed. However, while attempting crystallization from hot acetonitrile, ring opening and rearrangement of the parent oxacalix[3]arene were observed. Compound **22** was found to be active in ROP at high temperature, leading to the possibility of ring opening of the parent oxacalix[3]arene and rearrangement.

Rawat et al. in 2019 reported for the first time a monometallic Zn complex of an oxygen-depleted *p-tert*-butylcalix[4]arene ligand in the ROP of *rac*-LA.[58] Complex **23** was synthesized in quantitative yield by treating 1,3-bis(pyrazole)-*p-tert*-butylcalix[4]arene with ZnEt₂/Zn-(HMDS)₂ in toluene at 110 °C. According to a qualitative study, the oxygen of the 1,3-phenols has substituted the two ethyl groups of the reagent, indicating the development of a monometallic Zn complex. Diffusion NMR studies further confirmed the structure of monometallic Zn complex **23** with diffusion constants for the complex and ligand of 0.4926 × 10^{-5} and 0.4979 × 10^{-5} cm² s⁻¹, respectively (Scheme 10). The coordination mode in complex **23** was verified by preparing the ¹⁵N-labeled equivalent of **23** and studying its ¹⁵N NMR. Complex **23** was found to be effective when ROP was carried out in toluene at 110 °C, which afforded the polymer with a molecular weight of 29 kDa and a PDI of 1.78.

2.3. Magnesium-Calixarene Complexes in ROP. Magnesium compounds show exceptionally high activity[59] for the ROP of *rac*-LA compared to their zinc counterparts.[59−61] However, the use of calix[4]arene-Mg complexes in this area

Scheme 6. Bimetallic Zn-Calixarene Complexes 14 and 15

Scheme 7. Polymerization of L-Lactide with Complexes 14 and 15

R = Me, **14**
R = Et, **15**

with **14**
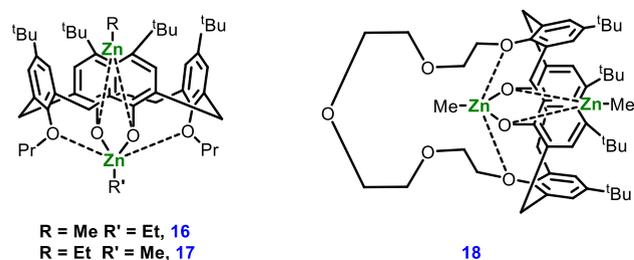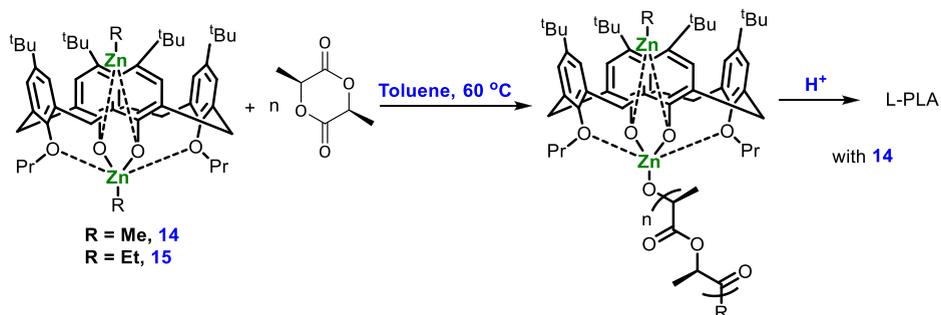
Figure 7. Complexes 16—18.

R = Me R' = Et, **16**
R = Et R' = Me, **17**

18

remains scant. Monoanionic ligands are preferred for reactions with Mg precursors. They invariably result in a metal with a viable nucleophilic group for ROP, which may explain why calix[4]arenes are seldom used.

Redshaw in 2014 reported the synthesis of heterobimetallic complex **24** and monometallic Mg complex **25**.[62] For the synthesis of complex **24**, lithiation of 1,3-dipropoxy-*p-tert*-butylcalix[4]arene was carried out with nBuMgBr in THF and, for complex **25**, tripropoxy-*p-tert*-butylcalix[4]arene was treated with *n*-Bu₂Mg (Scheme 11). By using a single-crystal XRD technique, it was reported that both complexes exist in a cone conformation with the Li atom (in **24**) residing in the cavity of the calixarene. Both of the catalysts were proven to be effective for the ROP of *rac*-LA, with complex **24** showing a

Scheme 9. Synthesis of Complex 22

22
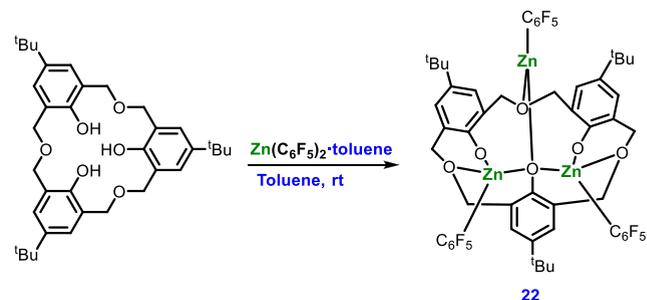
Scheme 10. Synthesis of Complex 23

23
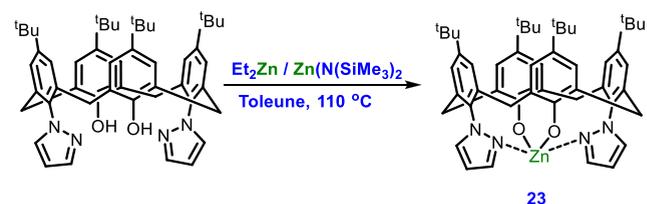
conversion of 94%, while complex **25** displayed a conversion of 99%.

Scheme 8. Synthesis of Complexes 19—21

19

(i) NaH, THF, rt
(ii) ZnCl₂, THF, rt
(iii) Na(N(SiMe₃)₂)
     THF, rt

20

21
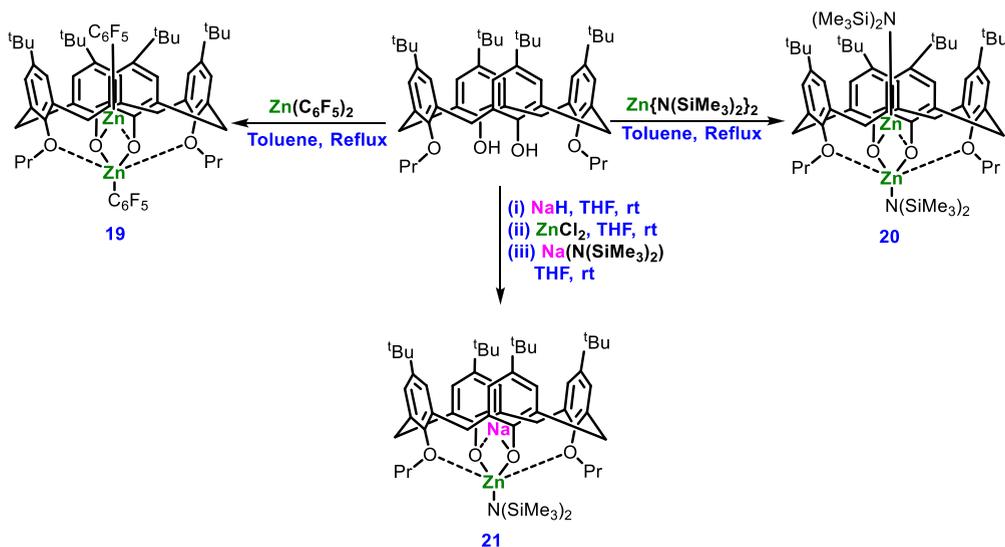
Scheme 11. Synthesis of Complexes 24 and 25
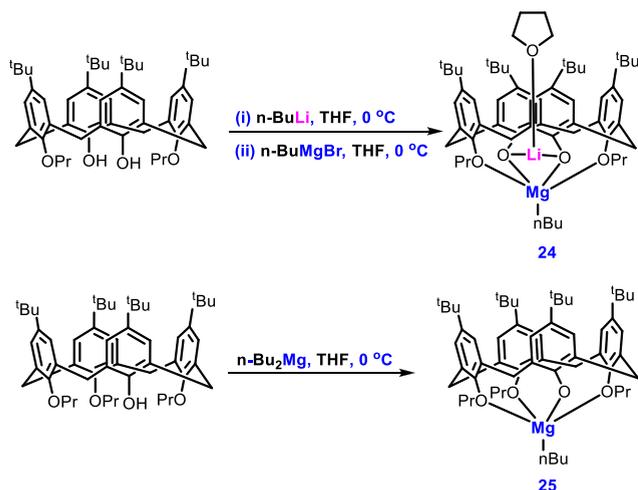
Initially, the polymerization of *rac*-LA was attempted by using benzyl alcohol as an activator. However, this led to the formation of methyl-(*R,S*)-lactate instead of the desired PLA product. The author reported that using 1 equiv of MeOH in combination with catalyst **24** resulted in greater activity for the ROP of *rac*-LA in CH$_2$Cl$_2$ than any other solvent. Other alcohols as activators were also found to be ineffective. In contrast to **24**, compound **25** showed increased activities in THF and toluene, rather than CH$_2$Cl$_2$, with conversions of 97%, 99%, and 55%, respectively. For catalyst **25**, the addition of alcohols (i-PrOH, *t*-BuOH, or BnOH) other than MeOH led to increased activities, particularly when BnOH was used, which gave a 92% conversion of *rac*-LA in 3 min. PLA obtained from both catalysts had a respectable PDI of 1.19 with catalyst **24** and 1.25 with catalyst **25**.

2.4. Potassium-Calixarene Complexes in ROP. Wu et al. based their synthesis of K-calixarene complexes on the fact that potassium is nontoxic and calix[4]arenes show a good inclusion effect. They were able to synthesize four calix[4]-arene potassium complexes and reported their use in the ROP of *rac*-LA.[63] Complex **26** was prepared in 50.7% yield by the treatment of distal functionalized 1,3-dipropoxy *tert*-butyl calix[4]arene and KN(SiMe$_3$)$_2$. Complex **27** could be obtained from **26** in moderate yield (34.5%) by reacting with 18-crown-6 in a mixed solvent of toluene and THF at room temperature. On the other hand, direct treatment of the ligand with KN(SiMe$_3$)$_2$ and 18-crown-6 also afforded the desired complex **27** (Scheme 12).

Unsurprisingly, complex **26** showed a cone conformation with one K atom at the exo position with the second K atom

occupying the endo position. Complex **26** also shows aggregation, due to which several active sites were possible, and as expected **26** was active in ROP. The oxygen atoms of crown ether caps the potassium ion in an exo position in complex **27**. The other K atom, as in complex **26**, is occupying the cavity of the calix[4]arene. Four oxygen atoms of the calix[4]arene ligand and two oxygen atoms of 18-crown-6 are sandwiched around the possible catalytic center. A quantitative conversion in ROP of *rac*-LA was observed within 3 min when a 200:1:2 monomer:catalyst:activator ratio was used with a complex concentration of 2.0 mM in 5.0 mL of toluene at room temperature, while the same reaction consumed 5.5 h in CH$_2$Cl$_2$ to reach a 97% yield, and only 95% lactide could be converted to polymer in THF within 10 h. It was discovered that, when 1.0 equiv of BnOH was used as an activator, the molecular weights of the final polymers were lower than predicted, which may be due to a cyclization side reaction caused by the phenoxy groups. To suppress the side reactions, polymerization was conducted with 2, 5, and 10 equiv of BnOH to good effect with a conversion as high as 98%, but with an increasing concentration of activator the polymer was obtained as a wider PDI of 1.48.

Compounds **28** and **29** were prepared from *tert*-butyl calix[4]arene with the aim to synthesize other bimetallic complexes bearing a crown ether as a second auxiliary ligand. Structural analysis with NMR and single-crystal XRD indicated the formation of the dinuclear complex **28**. The rotation of two phenoxy groups leads to a quick transformation equilibrium reaction in solution (Figure 8). On the other hand, **29** is a
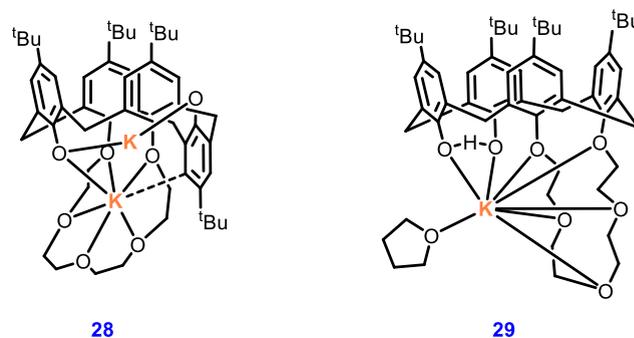
Figure 8. Structures of complexes **28** and **29**.

stable mononuclear complex, possibly due to intramolecular hydrogen bonding; consequently, it shows substantially lower activity in ROP. Complex **28**, which contains a 1,3-substituent crown moiety, is also a highly active catalyst for the ROP of *rac*-LA with 2 equiv of BnOH as a coinitiator, but final polymer

Scheme 12. Synthesis of Complexes 26 and 27
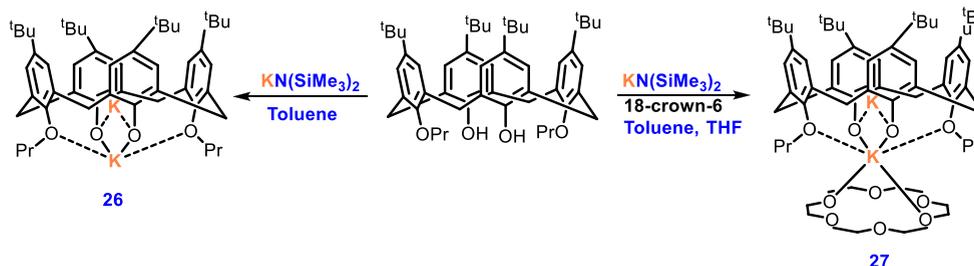
molecular weights were smaller than expected ($M_{n,cal}$ 12900 g/mol; $M_{n,obs}$ 6200 g/mol), possibly due to some side reactions, like transesterification and/or cyclization. It was observed that a 10-fold increase in the amount of BnOH led to faster polymerization, partially suppressing the side reactions due to phenoxides. The molecular weights of polymers were found to be closer to the calculated M_n now ($M_{n,cal}$ 2900 g/mol; $M_{n,obs}$ 2700 g/mol); the dispersity values of the polymers were also low.

2.5. Zirconium Complexes. Zr complexes are of particular interest in the ROP of cyclic esters due to their low toxicity and high reactivity in contrast to the corresponding Ti complexes in the polymerization process. Researchers have used a bridge between the different phenolic groups of the calixarene scaffold to minimize the number of conformers that the ligand could attain and to keep the metal atoms in an open catalytic pocket. As a result, Neri and colleagues developed the di-Zr 1,5-bridged calix[8]arene complex **30** with a xylene functionality, which they used in the ROP of cyclic esters. The polymerization results were then compared with those obtained using a mono-Zr complex featuring a calix[4]arene ligand.

The dinuclear heteroleptic complex **30** was obtained by protonolysis of 1,5-bridged calix[8]arene with 2 equiv of Zr(IV) *tert*-butoxide in toluene (or THF) at room temperature (Figure 9). The mononuclear Zr complex **31**, with a chemical
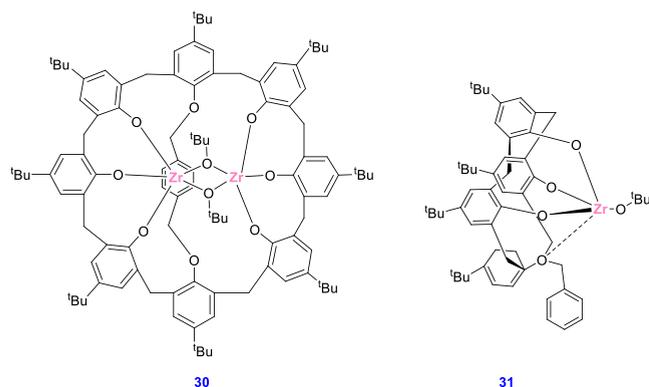
Figure 9. Structures of Zr complexes **30** and **31**.

environment as similar as possible to that of the dinuclear complex **30**, was also prepared and tested for polymerization of *rac*-LA to verify the importance of two close Zr atoms. The derived complex (**31**) was synthesized by metathesis with 1 equiv of Zr(IV) *tert*-butoxide.

Using a monomer/initiator ratio of 100:1, complex **30** was screened in the ROP of *rac*-LA at various temperatures. It was observed that, with increasing temperature, the activity improved rapidly, and at 100 °C polymerization was completed in 30 min, with a turnover frequency of 194 h^{-1}. Complex **30**, which possesses C_{2v} symmetry, having Zr atoms lying in the vicinity, was highly active in the ROP of *rac*-lactide. One of the reasons for this could be the backbiting of the growing polymer chain that promotes a chain reaction. DFT calculations proved that chain folding in complex **30** was exergonic, while that of complex **31** was slightly endergonic. Hence, all polymerization reactions carried out by complex **31** led to polymers with monomodal and narrow molecular weight distributions (PDI = 1.10−1.30).[64]

3. MECHANISTIC ASPECTS OF ROP BY CALIXARENE-METAL COMPLEXES

As previously mentioned, the ROP of LA is the best way to achieve the synthesis of a high-molecular-weight PLA. In comparison to polycondensation, ROP of LA can generate a polymer with a wide molecular weight range by regulating monomer purity and synthesis conditions without the use of a chain coupling agent or an azeotropic method. Various ions initiate ring-opening polymerization, which is a type of chain-growth mechanism for the polymerization of cyclic monomers. The terminal end of a polymer, as the reactive center of propagation, divides the system into anionic ROP, cationic ROP, and radical ROP. For PLA, the cyclic monomer (lactide, which is the cyclic dimer of lactic acid) is attacked by the terminus of the growing polymer chain leading to propagation (Figure 10). It should also be mentioned that alcohols as
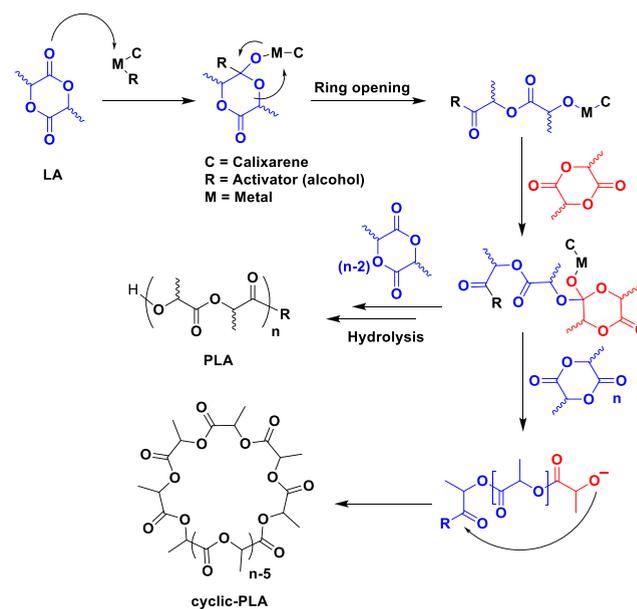
Figure 10. General mechanism for the ROP of LA.

activators are likely to react with the metal−halogen bonds to result in a metal-alkoxide. Such species are known to be faster catalysts in the ROP of cyclic esters. In the case of Zn complexes **14**, **15**, and **23**, an external alcohol (or activator) was not required to initiate ROP.[53−58] Talatta et al. reported that the bimetallic or multimetallic calixarene complexes show higher activity than the corresponding monometallic analogues, clearly indicating that a cooperative interaction between two metals is a determinant for controlling the performance of ROP.[64] Generally, alcohol is needed as an initiator in the lactide polymerization process that is facilitated by metal complexes. Through ligand exchange, the alcohol first reacts with metal centers to generate metal-alkoxides. The catalyst's metal atom then briefly coordinates with the exocyclic carbonyl oxygen of the lactide, increasing both the carbonyl group's electrophilicity and the nucleophilicity of the initiator's alkoxide group. Then, the lactide's acyl-oxygen bond breaks, permitting insertion into the catalyst's metal−oxygen bond (alkoxide). The polymer is created by repeatedly introducing new lactide molecules into the metal−oxygen link.

Table 2 describes the efficiency of various calixarene-based catalysts in lactide polymerization presented in this review: the

Table 2. Summary of Calixarene-Based Catalysts in Lactide Polymerization

entry	catalyst	PDI	M_w (g/mol)	ref
1	1	1.16	42000	43
2	2	1.23	22400	44
3	3	not reported	not reported	46
4	4	1.68	13520	49
5	5	1.94	11170	49
6	6	2.09	15770	49
7	7	1.04	22040	49
8	8	1.94	69950	49
9	9	1.29	8190	50
10	14	1.06	143000	56
11	15	1.45	72000	56
12	19	1.26	1440	57
13	20	1.13	8970	57
14	23	1.78	29000	58
15	24	1.19	1790	62
16	25	1.25	14800	62
17	26	1.42	13400	63
18	27	1.21	13400	63
19	28	1.08	2700	63
20	29	1.06	2800	63
21	30	1.23	705	64
22	31	1.14	2363	64

catalyst number, PDI, and molecular weight (M_w) of the polymer formed and corresponding references are provided.

4. SOME RECENT EXAMPLES OF CATALYSTS USED IN ROP OF LA

Stannous octoate ($Sn(Oct)_2$) has been extensively used in industry for the ROP of LA due to its solubility in a monomer

Scheme 13. Synthesis of PLA Using Stannous Octoate

L-lactide   L-PLA
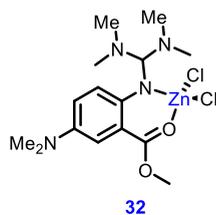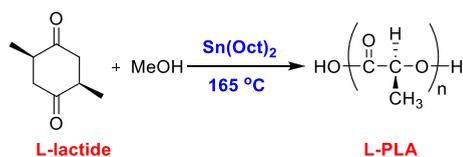
Figure 11. Structure of complex 32.

melt, high reaction rate, and potential to generate higher molecular weight polymers.[65] Morris et al. were the first to study the role of alcohols as initiators in the ROP of LA. His group has utilized different alcoholic systems (1-dodecanol, 1-octanol, methanol) and studied the effect on yield, thermal properties, and stability in the presence of $Sn(Oct)_2$ as a catalyst. It was observed that methanol was found to be an effective initiator, which afforded the polymer in an 89% yield,
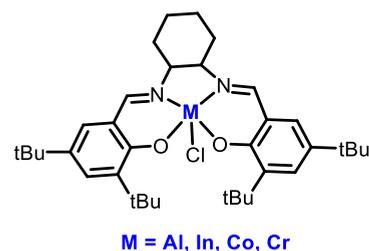
Figure 12. Structure of complex 33.
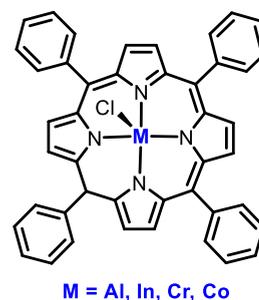
Figure 13. Structure of complex 34.

with an M_n value of 11800 g/mol and a PDI of 1.22 (Scheme 13).

Guanidines are neutral ligands of high donor strength capable of forming metal complexes with a wide variety of coordinations. Guanidine-based metal complexes have proven to be superior catalysts in lactide polymerization sustainability and decreased toxicity. They are stable at high temperatures in the presence of residual protic impurities, show promising activity, and lead to a high-molecular-mass polymer.[66] Many Zn- and Fe-guanidine complexes have been synthesized and examined toward the ROP of LA, but complex 32 was found to be the most effective with a PDI of 1.4 and M_n of 71000 g/mol (Figure 11).

Phomphrai and co-workers explored the use of cyclohexylsalen-ligated metal complex 33 (M = Al(III), In(III), Cr(III), and Co(III)) in ROP of LA. The catalytic system is comprised of a metal complex, initiator, and epoxide as solvent. All the complexes were examined for ROP, but the (Cy-salen)InCl complex showed the highest activity and afforded a polymer with a PDI of 1.23 and a molecular weight of 4300 Da (Figure 12). One possible reason for this could be the larger ionic radius of In; hence, the coordination environment of the ligand affects the rate of polymerization.[67]

Phomphrai et al. also reported the synthesis and application of several metal complexes of tetraphenylporphyrin (TPP) in the ROP of LA (Figure 13). The (TPP)AlCl catalyst is one of the few reported complexes to be active in polymerizing rac-LA at room temperature, leading to a isotactic polylactide. The ionic initiator PPN^+Cl^- was proven to have higher catalytic activity compared to a neutral initiator such as pyridine or DMAP, and among the many metal complexes, Cr-TPP 34 was found to be the most active, producing polymers with a good PDI (1.08) and molecular weight (5150 Da).[67]

Although ROP of LA is the method of choice, Yamaguchi in 1995 reported high-molecular-weight synthesis (300000 Da) of PLA by polycondensation of L-lactic acid with Sn powder at 130 °C.[68] Kimura et al. also reported a polycondensation route to high-molecular-weight poly(L-lactic acid) from L-lactic

Table 3. Some Notable Catalysts Used in Lactide Polymerization

S.No.	Catalyst	PDI	M W (g/mol)	Reference
1.		1.13	1500	70
2.		1.25	51500	71
3.		1.05	42000	72
4.		1.06	15440	73
5.		1.17	39500	74
6.		1.13	11300	75
7.		1.22	48000	76
8.		-	4600	77
9.		-	82300	78
10.		1.58	33800	79
11.		1.15	6990	80
12.		1.63	14000	81
13.		1.12	22800	82
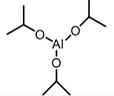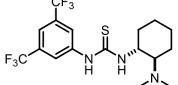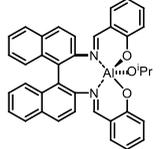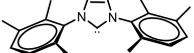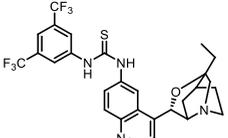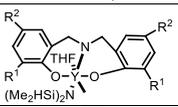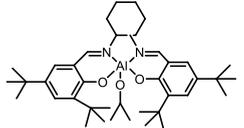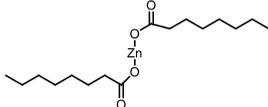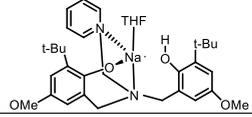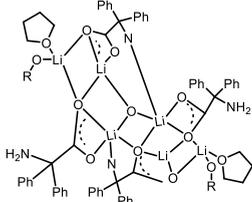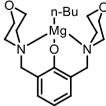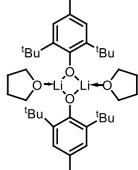
acid.[69] In their protocol, a lactic acid melt was created by heat treatment at around 105 °C in the presence of a binary system of Sn(II) chloride hydrate/p-toluenesulfonic acid and further heating at 150 °C (10−30 h) for polycondensation. This route gave a polycondensate with a high molecular weight (2×10^4) in a relatively short reaction time. The polymer formed by this procedure was comparable to the poly(L-lactic acid) obtained by ring-opening polymerization of L-lactide.[69] Although the FDA has approved Sn and its salt as a food additive, the toxicity of most tin compounds is a significant disadvantage in biomedical applications. Table 3[70−82] gives a few examples of notable catalysts used for polylactide preparation.

■ CONCLUSION

The production of PLA using different metal-based calixarene complexes, which have been known in the past few decades, are reported in this review. Due to the unique properties possessed by PLA, like biodegradability, biocompatibility, and mechanical stability, it offers a wide range of applications in packaging units, textile industries, and medicinal fields. Ring-opening polymerization (ROP) is an efficient and convenient method for the synthesis of high-molecular-weight polylactide. These calix[n]arene-metal complexes offered advantages such as a high yield and PDI and a shorter reaction time. Comparing the different catalyst systems also show that complexes having more than one metal center may not always be more efficient in ROP. For instance, monometallic complexes **25**, **29**, and **31** are more efficient (better PDI and higher molecular weight) when compared to their multimetallic counterparts. There is a huge scope for the extension of the applications of calixarene-metal complexes in polymerization, since only a limited number of metals such as Zn, Ti, Mg, K, and Zr incorporated with a calixarene scaffold have been reported. Others metals like Li, Fe(III), Cr, and Co may also be employed for lactide polymerization, but no previous reports are available. Predominantly, the controlled ROP could lead to a polymer with specific and needed properties (e.g., refractive index, molecular weight), making it a very important catalyst in polymer synthesis nowadays.

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The manuscript was written through the contributions of all authors.

Notes

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