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# Robust Guanidine Metal Catalysts for the Ring-Opening Polymerization of Lactide under Industrially Relevant Conditions

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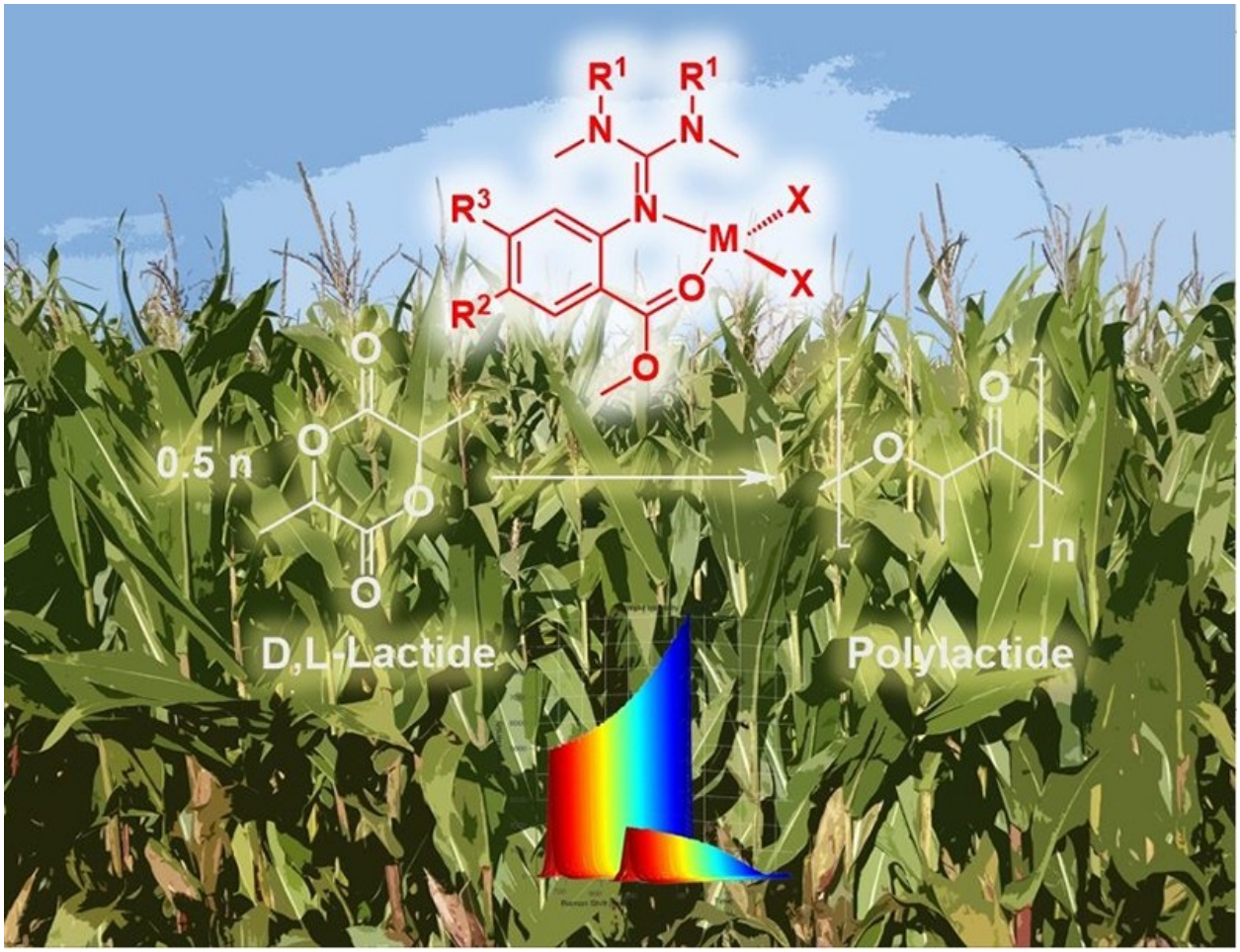

The increasing awareness of sustainability has led to enormous growth of the demand for bio-based and biodegradable polymers such as poly(lactide) (PLA). In industry, polymerization of lactide is currently carried out using tin catalysts (e.g., tin(II) ethyl hexanoate, $Sn(Oct)_2$). Since the catalyst remains in the polymer, it can accumulate in the soil or in the human body after degradation and cause damage due to its toxicity. Therefore, a search for a suitable substitute for this catalyst has been going on for decades. Guanidine metal complexes prove to be excellent catalysts in the polymerization of lactide. They are not only convincing because of their activity and the synthesis of high molar mass polymers, but also show a high robustness against high temperatures, oxidation as well as residual protic impurities in the monomer. Herein, key zinc and iron guanidine complexes are discussed with respect to their apparent rate constant ($k_{app}$) and rate constant of propagation ($k_p$), produced molar masses and the mechanism involved.

## 1. Introduction

The current debate in society about our environment also affects the way we are dealing with petrochemically derived plastics. Their synthesis from finite petroleum resources and the high level of contamination by plastic residues in our oceans and habitats has led to a search for substitutes.[1] Therefore, bioplastics have received more and more attention and, with a production capacity of 2.11 million tons in 2018, they account for one percent of the entire plastics market.[2] However, no distinction is made here as to whether the bioplastics are merely bio-based and/or, biodegradable or have both properties. Bio-based and biodegradable polymers like poly(lactide) (PLA), poly(hydroxyalkanoate) (PHA) as well as starch blends and materials made from cellulose combine both properties and have successfully found their way into the markets.[3] PLA is the most promising material since its physical and mechanical properties are similar to poly(ethylene terephthalate) (PET), poly(propylene) (PP) and poly(styrene) (PS). Another advantage of the polyester is that it can be processed using conventional methods. The polymer can be applied in extrusion, foaming, injection molding and blow molding.[4] The material is used in the packaging industry, in disposable tableware, in textile production and in the medical sector. Due to its good biocompatibility, PLA is used as suture material in surgical dressing and as an implant.[5] PLA is produced by polymerization of the monomer lactide, the cyclic diester of lactic acid. The bacterial fermentation of corn and sugar beets first produces pyruvate, which is then converted into lactic acid. After oligomerization and a thermal cracking process, lactide is obtained.[6] Due to two stereocenters *meso*-LA, D-LA and L-LA are possible dimers. Since the natural isomer of lactic acid is L-lactic acid, mainly L-LA is produced. After the fermentation process, lactide is usually contaminated with water, residual lactic acid, oligomers and *meso*-lactide. In the industrial process the lactide is therefore purified to avoid possible side reactions and termination reactions during polymerization of the monomer. The company *Total Corbion PLA* states the following impurities after its purification process: Water: less than 0.03%, *meso*-LA less than 0.03%, free acid 7 meq $kg^{-1}$.[7] The quality is called "technical grade quality" or "non-purified lactide". In scientific literature, however, in toluene recrystallized lactide or single/multiple sublimated lactide is mostly used, making it difficult to compare academic results with industrial requirements and methods.[8] The polymer synthesis occurs *via* a ring-opening polymerization (ROP). In contrast to the polycondensation of lactic acid which results technically in the same polymer, the ROP of lactide achieves a narrow and controlled molar mass distribution and avoids side reactions.[9] The obtained PLA polymer is degradable under industrial composting conditions and meets the requirements of the European standard EN 13432, thus closing the life cycle of lactide, ensuring a $CO_2$-neutral emission.[10]

The different stereoconfigurations of the monomer allow different tacticities in the polymer. This enables to obtain various material properties by controlling the stereoconfiguration during polymerization. Thus, semicrystalline atactic PLA, isotactic material with a high crystallinity, syndiotactic PLA and stereoblock PLA (sc-PLA) can be obtained.[11] The tunability of this bio-based and biodegradable polymer and its good processability on existing machines makes the material an excellent substitute for petrochemical-based plastics.

### 1.1. Mechanism of the polymerization

The ring-opening polymerization of lactide can basically take place according to five different reaction mechanisms. A distinction is made between cationic, anionic, organocatalytic ROP, the coordination-insertion mechanism (CIM) and the activated monomer mechanism.[9,12] In the cationic mechanism, alkylating and acylating agents as well as Lewis acids are used for ring-opening.[13] However, this form of ring-opening does not allow control over the polymerization and is therefore not considered a living polymerization.[14] In contrast, the anionic polymerization exhibits a living character. Using metal alkoxides and strong bases/nucleophiles as catalysts, controlled molar masses with narrow dispersities can be obtained.[15] Nevertheless, the stereoinformation is lost during the polymerization and the microstructure of the polymer cannot be controlled. The third option to open the cyclic diester are organocatalysts. *N*-heterocycles carbenes,[16] guanidines such as triazabicyclodecene (TBD),[17] amines and phosphinimines possess a high potential to open and polymerize lactide or other cyclic esters such as ε-caprolactone and δ-valerolactone.[17] However, the best control over the molar masses of the polymers, the physical and mechanical properties as well as the micro-

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structure is achieved with a polymerization according to the Coordination-Insertion Mechanism (CIM). Here, metal salts and metal complexes are used as catalysts. Molar masses can be adjusted by changing the monomer-to-initiator ratio ([M]/[I]).[18] The mechanism starts with the coordination of the carbonyl oxygen atom of the lactide to the metal center (Figure 1). This initiating step activates the monomer and enables the nucleophilic attack of an alkoxide group, guanidine or water to the carbonyl carbon atom of the cyclic diester. Followed by an insertion of the monomer in the previous metal-oxygen bond, the lactide ring opens. Thus, a new alkoxide group is formed which allows the propagation of the polymer chain. Polymerizations according to CIM can be described as pseudo-first order kinetics.[19] The concentration of the initiator remains constant during polymerization, which is why it can be integrated with the reaction constant and expressed as the apparent rate constant $k_{app}$ [Eq. (1)]:

$$v = -\frac{d[M]}{[dt]} = k_p \cdot [M] \cdot [I] = k_{app} \cdot [M] \quad (1)$$

After integrating, Eq. (2) is obtained:

$$[M]_t = [M]_0 \cdot e^{-k_{app} t} \quad (2)$$

$$X_i = \frac{[M]_0 - [M]_t}{[M]_0} \quad (3)$$

Using the conversion $X_i$ [Eq. (3)] in the logarithm of Eq. (2), Eq. (4) is obtained:

$$\ln\left(\frac{[M]_0}{[M]_t}\right) = \ln\left(\frac{1}{1-X_i}\right) = k_{app} \cdot t \quad (4)$$

Eq. (4) shows that by plotting the logarithmic monomer concentration against the reaction time, the rate constant $k_{app}$ can be determined. For a more detailed description of the polymerization, $k_{app}$ values are then determined at different initiator concentrations and plotted against the respective initiator concentration used. Thus, the rate constant of propagation ($k_p$) is determined from the slope of the regression [Equation (1)]. This rate constant ($k_p$) enables a better comparison between the catalyst systems investigated, provided that the reaction conditions such as temperature and quality of the monomer are identical. The coordination-insertion mechanism is often hard to distinguish from the "activated monomer" mechanism, which is also controlled by metal complexes. While CIM needs an initiating group like benzyl alcohol, for the activated monomer mechanism an inactivation of the catalyst with benzyl alcohol can be observed.[12]

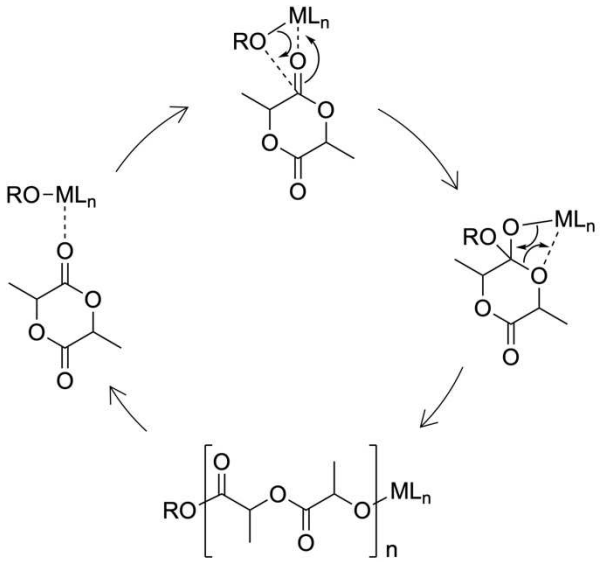


**Figure 1.** Coordination-insertion mechanism (CIM) for the ROP of lactide.

### 1.2. Catalysts for the ROP of lactide

In the industrial production of PLA, tin(II) ethyl hexanoate (Sn(Oct)$_2$) is the favored catalyst. This compound is better known as tin octanoate and is able to produce polymers with molar masses of up to 1.000.000 g mol$^{-1}$ *in bulk*.[20] Studies by Duda *et al.* show that the addition of alcohol as co-initiator results in an equilibrium between the Sn(Oct)$_2$ and a monoalkoxide species up to a bisalkoxide (Scheme 1).

The monoalkoxide significantly increases the polymerization rate compared to pure Sn(Oct)$_2$.[21] After the polymerization the catalysts remains in the polymer and can accumulate in soil after degradation. In addition, tin residues in the polymer can interact

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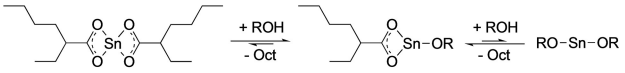
Sonja Herres-Pawlis studied Chemistry at the Universities of Paderborn and Montpellier and performed her PhD studies on bioinorganic copper complexes. After postdoctoral work on bioinorganic chemistry at Stanford University, she turned for her habilitation at the TU Dortmund (2012) towards sustainable polymerization chemistry. In 2011, she was appointed as associate professor for coordination chemistry at LMU, in 2015 she moved to RWTH Aachen University to take over the Chair of Bioinorganic Chemistry. In 2011 and 2014 she was awarded prizes for her efforts in lactide polymerization.




**Scheme 1.** Equilibrium of $Sn(Oct)_2$ and an alcohol as coinitiator. Left: $Sn(Oct)_2$, middle: the monoalkoxide species (highly active), right: the bisalkoxide.[20]

with the organism when PLA is used in the human body.[22] The catalyst is classified as harmless by the American Food and Drug Agency (FDA), but the toxicity of tin(II) compounds is well known although less toxic than Sn(IV) compounds. Hence alternatives for industrial use are urgently required. In recent years, a wide variety of catalysts have been developed for the polymerization of lactide. Metal complexes stand out in the literature due to their number and performance.[23] Some systems were convincing due to their extraordinary control and activity in polymerization like dincuclear zinc catalysts from Williams *et al.*[24] and the control of the tacticity (microstructure).[25] Several complexes containing Mg, Al,[26] Ti,[27] Zr,[27c,28] Zn,[29] Sn[21,30] and rare earth metals[31] have been prepared and successfully tested in the ROP of lactide.[23] Nevertheless, only a few catalysts are able to polymerize under industrially relevant conditions and do not bring along an intrinsic toxicity. Five criteria for an industrial relevant catalyst were formulated by Feijen *et al.* in 2011: the ligand should be commercially available and thus inexpensive, the synthesis of the complex should succeed in high yields, they should show a high activity in the polymerization *in bulk* and the polymerization should take place in high conversion with high molar masses and narrow dispersities.[26d] In order to gain biocompatibility of the catalysts, mainly zinc catalysts have been developed in the last two decades. The good biocompatibility of the metal, low costs and the formation of colorless and stable complexes have proven to be particularly advantageous.[32] Besides these criteria, the ligand design plays an important role. Anionic ligands in complexes promote a high sensitivity to moisture. With regard to the residual water and lactic acid in the lactide, stable complexes are therefore required.

Here, ligands with neutral donors are considered more advantageous. Zinc and calcium complexes with carbenes,[33] trispyrazolylmethane ligands,[34] phosphinimine ligands,[35] bipyridine and phenanthroline ligands,[36] pyrrolidine and pyridylamine ligands[37] as well as polyamine stabilized sodium aryloxide ligands[38] have been developed in the past. However, most systems catalyzed lactide polymerization only under inert conditions and in solution due to their sensitivity to air, moisture and high temperatures. Davidson *et al.* succeeded in 2009 in synthesizing a zinc complex with an anionic Schiff-base ligand scaffold (**1**), which converted unsublimed lactide ([M]/[I] = 300:1) to 80% of the corresponding polymer in 30 minutes at 130 °C (Figure 2).[39] PLA with molar masses of up to $M_n = 41200\ g\,mol^{-1}$ and dispersities of $Đ = 1.43$ were obtained. Furthermore, air and moisture stable mononuclear zinc Schiff-base complexes (**2**) were tested in the ROP of recrystallized L-lactide under industrial relevant conditions. Molar masses of up to $90000\ g\,mol^{-1}$ have been obtained.[40] Robust zinc complexes with tridentate Schiff base-like ligands (**3**) converted 78% of technical grade *rac*-LA after 42 min at a [M]/[I] ratio of 500:1. With molar masses of $M_n = 71000\ g\,mol^{-1}$ the polymers were suitable for industrial processing. Schiff-base ligand complexes (**4**) were developed by Jones *et al.* in 2018 and successfully used in the polymerization of lactide.[41] Once recrystallized lactide was used at a very low catalyst concentration ([M]/[I]/[BnOH] = 10000:1:100) with the addition of a coinitiator and successfully polymerized in a short time at 150 °C and 180 °C. With TOF values of up to $100000\ h^{-1}$ the catalyst is classified as extremely active under industrial conditions. In addition to this development of zinc complexes for the ROP of technical grade lactide, a non-toxic germanium complex (**5**) has recently been synthesized, which proved to be active in ring-

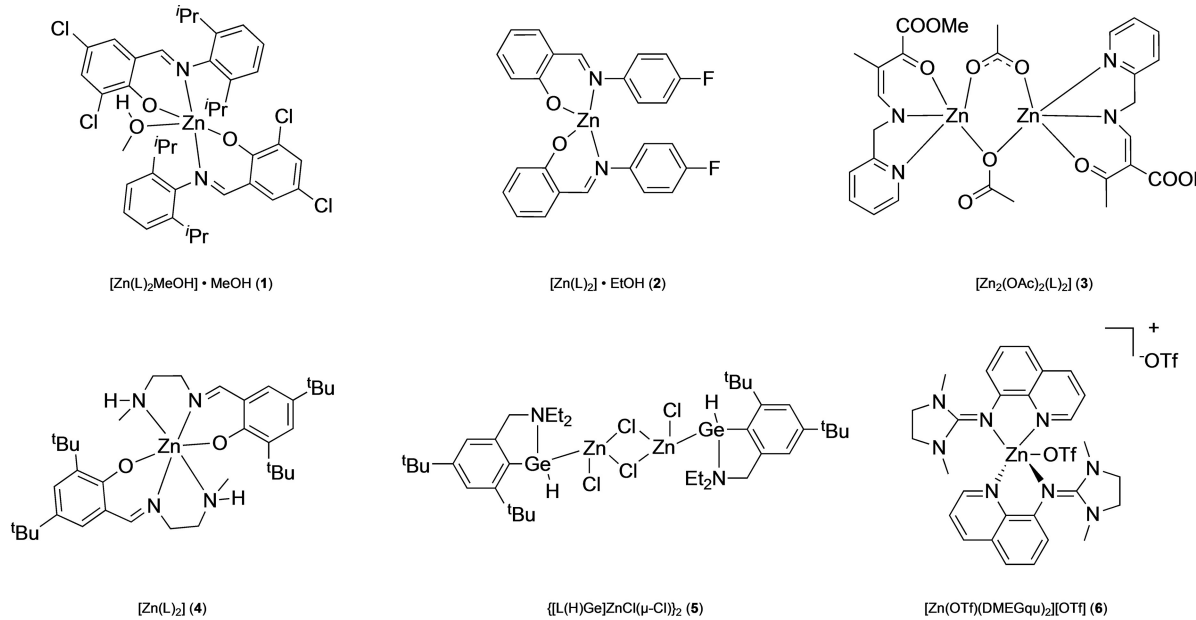



**Figure 2.** Zinc and germanium complexes for the ring-opening polymerization of lactide under industrially relevant conditions.

opening polymerization.[42] Kinetic investigations showed that the germanium atom is the active center of the polymerization and that a CIM mechanism is proceeding. With a rate constant twice as high as the one of tin octanoate and molar masses of up to 100000 g mol$^{-1}$, this complex has a high potential as a substitute for existing tin catalysts in industry.

## 2. Guanidine metal complexes as catalysts

Guanidine metal complexes for the ROP of lactide showed a great advantage in recent years. With a $pK_s$ value of 13.6, guanidines are neutral ligands with a high basicity and a high donor strength. They can form metal complexes with a wide variety of coordination geometries. Their rather outstanding donor properties are based on the stabilization of the protonated guanidinium species over the three nitrogen atoms of the guanidine moiety. Guanidine complexes are used not only in the ROP of lactide, but also in the atom transfer radical polymerization (ATRP) of styrene,[43] in the modelling of tyrosinase[44] complexes and the entatic state[45] involving the metals copper and iron. First results of various *N,N* guanidine zinc complexes were summarized in a review by Herres-Pawlis *et al.* in 2012 and form the first generation of guanidine metal complexes for lactide ROP.[46] At that time, the quinoline-guanidine bis-(chelato) triflato complexes [Zn(OTf)(TMGqu)$_2$][OTf] and [Zn(OTf)(DMEGqu)$_2$][OTf] (**6**) showed the highest activities in the ROP of technical grade lactide.[47] Conversions of >90% and molar masses of up to 77000 g mol$^{-1}$ were obtained after 24 h (Table 1). Mechanistic investigations also showed that the guanidine ligand is able to open the lactide ring analogous to metal-alkoxide complexes. In the following we summarize the development of guanidine metal complexes since then and their use in the ROP of lactide under industrial relevant conditions.

### 2.1. *N,N* donor guanidine ligand systems (2$^{nd}$ generation)

Six different guanidine zinc complexes were presented in 2016 (Figure 3).[48] Besides the two guanidine units (tetramethylguanidine = TMG and dimethylethylene = DMEG), ethylene (**7**, **8**) and propylene (**9**, **10**) bridges as well as an aromatic (**11**, **12**) backbone were used to investigate the influence of the bridging unit on the activity in the ROP. Thus, kinetic measurements for the polymerization of non-purified lactide using the complexes **7**–**12** were performed. The polymerization was carried out without stirring the reaction mixture in reaction vessels which were placed in an oven at 150 °C. With values between $5.0\times10^{-6}$ s$^{-1}$ (**12**)—$3.3\times10^{-5}$ (**10**) s$^{-1}$ ([M]/[I] = 500:1) the complexes showed moderate

**Table 1.** Polymerization data for lactide with guanidine metal complexes and Sn(Oct)$_2$.

| Catalyst | Conditions | $k_p$ [L mol$^{-1}$ s$^{-1}$] | $k_{app}$ [s$^{-1}$] | time [min] | conv. [%] | $M_{n,theo}$ [g mol$^{-1}$] | $M_n$ [g] [g mol$^{-1}$] | $Đ$ [g] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 6 | [a] | – | – | 1440 | 92 | 66200 | 77000 | 2.1 | [47b] |
| 7 | [a] | – | $1.5\times10^{-5}$ [e] | 830 | 64 | 46000 | 19400 | 1.52 | [48] |
| 8 | [a] | – | $1.7\times10^{-5}$ [e] | 830 | 59 | 42500 | 18200 | 1.21 | [48] |
| 9 | [a] | – | $2.2\times10^{-5}$ [e] | 830 | 70 | 50400 | 15600 | 1.55 | [48] |
| 10 | [a] | – | $3.3\times10^{-5}$ [e] | 830 | 94 | 67700 | 13000 | 1.77 | [48] |
| 11 | [a] | – | $5.0\times10^{-6}$ [e] | 830 | 27 | – | – | – | [48] |
| 12 | [a] | – | $5.0\times10^{-6}$ [e] | 830 | 21 | – | – | – | [48] |
| 13 | [a] | – | $3.6\pm0.3\times10^{-5}$ [e] | 360 | 60 | 43200 | 14000 | 1.59 | [49] |
| 14 | [a] | – | $5.7\pm0.3\times10^{-5}$ [e] | 360 | 71 | 51100 | 16000 | 1.72 | [49] |
| 15 | [a] | – | $3.4\pm0.2\times10^{-5}$ [e] | 360 | 64 | 46000 | 21500 | 1.62 | [49] |
| 16 | [a] | – | $5.8\pm0.3\times10^{-5}$ [e] | 360 | 79 | 56900 | 20000 | 1.53 | [49] |
| 17 | [a] | – | $3.0\pm0.2\times10^{-5}$ [e] | 420 | 63 | 45400 | 20000 | 1.47 | [49] |
| 18 | [a] | – | $3.3\pm0.2\times10^{-5}$ [e] | 360 | 63 | 45400 | 19000 | 1.62 | [49] |
| 19 | [a] | – | $3.3\pm0.3\times10^{-5}$ [e] | 360 | 69 | 49700 | 25500 | 1.57 | [49] |
| 20 | [a] | – | $2.9\pm0.3\times10^{-5}$ [e] | 360 | 69 | 49700 | 16000 | 2.21 | [49] |
| 21 | [a] | – | $9.9\times10^{-5}$ [e] | 120 | 64 | 46000 | 20000 | 1.70 | [50] |
| 22 | [a] | – | $7.3\times10^{-5}$ [e] | 120 | 55 | 39500 | 5100 | 1.72 | [50] |
| 23 | [a] | – | $12.8\times10^{-5}$ [e] | 120 | 62 | 44500 | 13000 | 1.74 | [50] |
| 24 | [b] | $10.95\times10^{-3}$ | $1.26\pm0.07\times10^{-4}$ [e] | 90 | 52±2 | 37400 | 49400 | 1.4 | [51] |
| 25 | [b] | $9.48\times10^{-3}$ | $1.09\pm0.10\times10^{-4}$ [e] | 90 | 52±2 | 37400 | 35000 | 1.4 | [51] |
| 26 | [b] | $7.26\times10^{-3}$ | $1.01\pm0.10\times10^{-4}$ [e] | 90 | 53±2 | 38200 | 46900 | 1.5 | [51] |
| 27 | [b] | $8.25\times10^{-3}$ | $1.03\pm0.15\times10^{-4}$ [e] | 90 | 55±2 | 39600 | 42600 | 1.6 | [51] |
| 28 | [b] | – | $6.7\times10^{-5}$ [e] | 90 | 48 | 33800 | 34600 | 1.4 | [52] |
| 29 | [c] | – | $2.39\pm0.005\times10^{-4}$ [e] | 53 | 25 | 18000 | 43900 | 1.4 | [52] |
| 30 | [c] | $4.11\times10^{-2}$ | $4.92\times10^{-4}$ [e] | 36 | 68 | 49000 | 85500 | 1.5 | [52] |
| 31 | [c] | $6.10\pm0.34\times10^{-2}$ | $8.82\pm0.1\times10^{-4}$ [e] | 120 | 81 | 58300 | 71000 | 1.4 | [52] |
| 32 | [c] | – | $0.3\times10^{-5}$ [e] | 960 | 25 | 18000 | 5300 | 1.8 | [54] |
| 33 | [c], [d] | $9.2\pm0.01\times10^{-2}$ [d] | $5.46\pm0.49\times10^{-4}$ [c,e] | 60 | 83 | 59800 | 35500 | 1.5 | [54] |
| 34 | [c], [d] | $55.4\pm0.02\times10^{-2}$ [d] | $43.5\pm3.5\times10^{-4}$ [c,e] | 1.6 | 69 | 49700 | 46800 | 1.5 | [54] |
| Sn(Oct)$_2$ | [d] | $8.4\pm0.02\times10^{-2}$ | $9.88\times10^{-4}$ [f] | 25 | 69 | 99360 | 168000 | 1.9 | [54] |

[a] Solvent-free melt polymerization, technical grade *rac*-LA, reaction vessel, 150 °C, conversion determined by $^1$H NMR spectroscopy. [b] Solvent-free melt polymerization, technical grade *rac*-LA, Schlenk tubes, 150 °C, 260 rpm, conversion determined by $^1$H NMR spectroscopy. [c] Solvent-free melt polymerization, technical grade *rac*-LA, steel reactor with *in situ* Raman technology to determine $k_{app}$ values; 150 °C, 260 rpm, final conversion determined by $^1$H NMR spectroscopy. [d] Solvent-free melt polymerization, recrystallized L–LA, steel reactor with *in situ* Raman technology to determine $k_{app}$ values; 150 °C, 260 rpm, final conversion determined by using $^1$H NMR technology. [e] [M]/[I] = 500:1. [f] [M]/[I] = 1000:1. [g] Determined by GPC (THF).

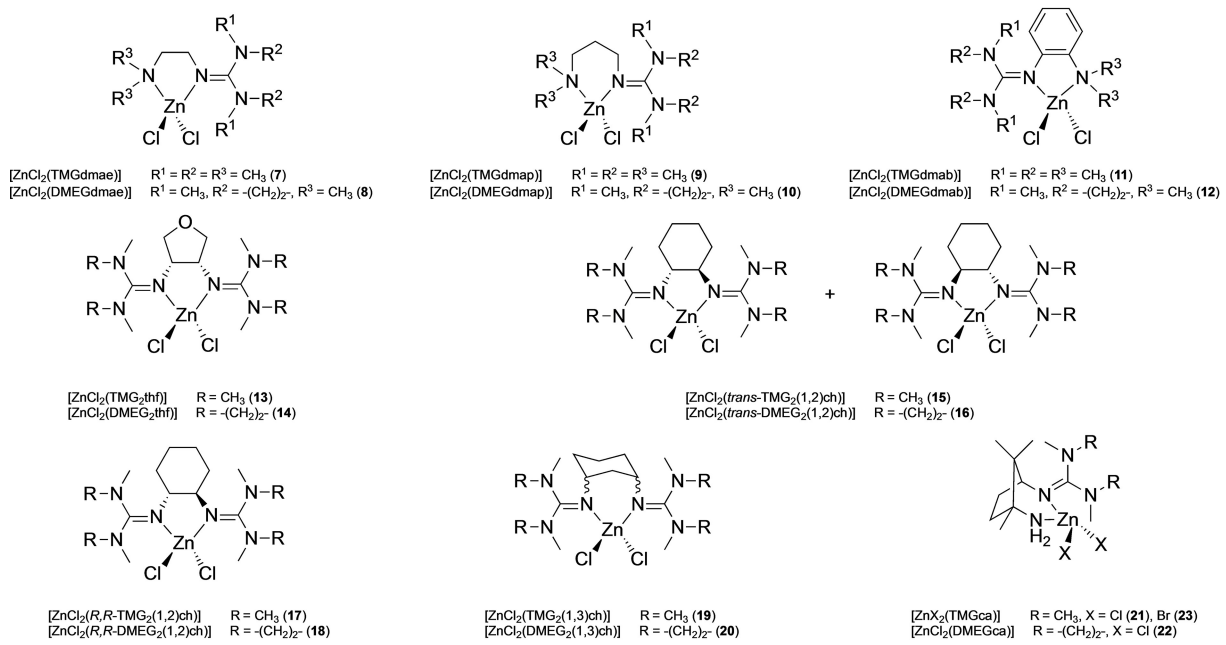



**Figure 3.** *N,N* donor guanidine metal complexes (2nd generation) for the ROP of lactide under industrially relevant conditions.

polymerization rates. The highest molar masses with $M_n =$ 19400 g mol$^{-1}$ were obtained with complex **7**. Mechanistic investigations with benzyl alcohol as coinitiator showed the alcohol as the end group on the polymer, hence, a coordination-insertion mechanism was proposed. The higher activity of the aliphatic complexes **7**–**10** in comparison with the aromatic systems (**11**, **12**) could be explained by higher interaction energies of the *N* atoms to the zinc calculated by NBO analysis with DFT.

Eight more zinc chloride complexes containing aliphatic and achiral bisguanidine ligands were published in 2017.[49] The aim of these investigations was to control the stereo-configuration in the polymer and to increase the polymerization rate in the ROP of technical grade lactide. Tacticity studies of the obtained polymers by catalytic polymerization of technical grade *rac*-LA with the complexes **13**–**20** showed values of $P_r = 0.51$ (**17**)−0.56 (**14** & **20**). With respect to these data it is clear that only atactic PLA was produced. Kinetic measurements showed that using the complexes **13**, **14** and **16**, apparent rate constants with values of $k_{app} = 3.6 \pm 0.3 \times 10^{-5}$ s$^{-1}$ (**13**)−$5.8 \pm 0.3 \times 10^{-5}$ s$^{-1}$ (**16**) can be obtained. Compared to the systems **7**–**12**, the values are in the same order of magnitude. Besides the investigation of the systems in the ROP of technical grade lactide, kinetic measurements of recrystallized lactide with/without addition of the coinitiator benzyl alcohol were performed. In this case the kinetic data were measured by *in situ* FT–IR spectroscopy. In contrast to the previous catalysis results of the polymerization of lactide with guanidine zinc complexes, here the reaction mixture was stirred at 140 °C with 400 rpm. At a [M]/[I]/[BzOH] ratio of 1000:1:10, a $k_{app}$ value of $7.2 \times 10^{-5}$ s$^{-1}$ (**14**) was obtained, so that a significant increase in reactivity could be achieved by adding the coinitiator.

With molar masses of $M_n = 15000$ g mol$^{-1}$, however, an application in industrial processing is not possible.

In the following, camphor-derived guanidine zinc complexes were presented as catalysts for lactide ROP.[50] At 150 °C and a [M]/[I] ratio of 500:1, rate constants between $k_{app} = 7.3 \times 10^{-5}$ s$^{-1}$ (**22**) −$12.8 \times 10^{-5}$ s$^{-1}$ (**23**) were determined. Thus complex **23** shows the highest activity of the guanidine zinc complexes with *N,N* donors. The polymerization yielded 62% PLA after two hours and molar masses of $M_n = 13000$ g mol$^{-1}$. If the [M]/[I] ratio was increased to 1000:1, molar masses of $M_n = 56000$ g mol$^{-1}$ could be obtained. Tacticity measurements showed that despite the chirality of the complex mainly atactic polymer is formed with values of $P_r = 0.54$–0.58. For mechanistic elucidation, MALDI-ToF measurements were also carried out, in which ethoxy end groups, formed by the precipitation of polymers in ethanol, and OH groups, formed by the initiation of water residues in the monomer, were detected.

### 2.2. *N,O* donor guanidine ligand systems (3rd generation)

While the focus was for a long time on *N,N* donor guanidine zinc complexes, our group has also investigated the field of neutral *N,O* donor guanidine ligands starting in 2017 (Figure 4).[51] The first hybrid guanidines of this kind consist of an aromatic backbone with a guanidine unit as substituent and a methyl ester in *ortho* position. The resulting guanidines TMGasme and DMEGasme were used to form the corresponding tetrahedral guanidine zinc complexes with zinc chloride (**24** & **25**) and zinc bromide (**26** & **27**), in which the imine nitrogen atom of the guanidine unit and the carbonyl oxygen atom of the methyl ester coordinate to the zinc ion. The aim of the catalytic investigations of these complexes in the ROP of technical grade lactide was to determine the influence of the two guanidine units and the different halide ligands. The kinetic studies were, unlike most experiments of the

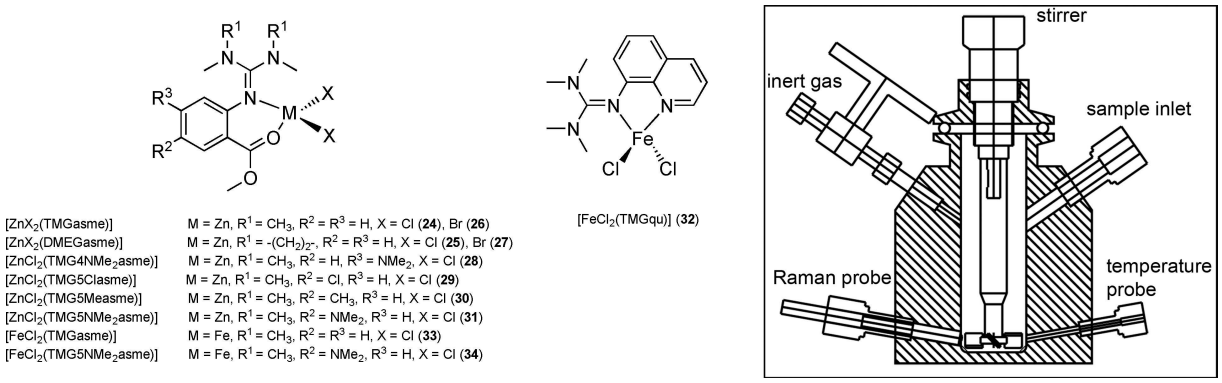



**Figure 4.** Left: *N,O* and *N,N* donor guanidine metal complexes (3rd generation) for the ROP of lactide under industrially relevant conditions. Right: Reactor with *in situ* Raman spectroscopy for *bulk* polymerization of lactide.

*N,N* donor class, performed in Schlenk tubes under stirring in an oil bath to ensure homogenization during polymerization. For complex **24**, catalytic measurements were also performed with *in situ* Raman spectroscopy. By observing the characteristic band for the ring vibration of lactide at 650 $cm^{-1}$ and the characteristic vibration of the C–O backbone of polylactide at 870 $cm^{-1}$, the conversion was monitored. Evaluation of the $k_{app}$ determination by Schlenk tubes with Raman technology yielded similar values, but Raman spectroscopy allows a more detailed progress of the polymerization which is key for these faster systems.

With a $k_p$ value of $9.48\times10^{-3}$ $L\,mol^{-1}\,s^{-1}$ (**25**), the *N,O* guanidine zinc complexes proved to be the fastest robust zinc catalysts in the ROP of non-purified lactide at that time. Due to the obtained molar masses of up to $M_n = 49400$ $g\,mol^{-1}$ (**24**), industrially processable colorless polymer was obtained. Further mechanistic investigations *via* $^1H$ NMR spectroscopy showed that the guanidine ligand of the complex is able to open the lactide ring and thus initiates the polymerization. The polymerization studies showed that the different halides and guanidine moieties do not influence the polymerization activity.

Variation of this successful carboxy-guanidine system, the influence of different electronic substituents on the aromatic skeleton was studied recently.[52] Different "asme" (German: Anthranylsäuremethylester, English: methyl anthranilate) derivatives with electronically donating and withdrawing substituents were introduced in *para*- and *meta*-position to the guanidine unit. While the electron-donating dimethylamine group in *meta*-position (**28**) to the guanidine unit tended to slow down polymerization compared to the unsubstituted "asme" system (**25**), the polymerization rate increased by a factor of 6 when the dimethylamine group was introduced in *para*-position to the guanidine unit. The electron-withdrawing chlorine substituent in the *para*-position (**29**) doubled the rate of polymerization in comparison to the unsubstituted system, which could be explained by the increase in Lewis acidity at the zinc atom. The substitution of a methyl group in *para* position (**30**) quadrupled the rate compared to **25**. The novelty of the project was that almost all polymerizations were recorded in a self-designed steel reactor with *in situ* Raman technology based on the reactor design developed by Liauw *et al.* (Figure 4).[53] Thus, the corresponding polymerizations could be monitored with a time resolution of seconds. The now fastest complex **31** with $k_p = 6.10 \pm 0.34 \times 10^{-2}$ $L\,mol^{-1}\,s^{-1}$ reached a conversion of 81% already after 2 h with a [M]/[I] ratio of 500:1. Molar masses of $M_n = 71000$ $g\,mol^{-1}$ were obtained. With $Đ = 1.4$, the polymerization can be described as well controlled. In addition to the studies with technical grade *rac*-lactide, polymerizations with recrystallized and sublimed lactide were carried out, with no changes in the catalysis activity. To elucidate the operating mechanism, polymer in the presence of a coinitiator was prepared which was characterized *via* MALDI-ToF analysis. It was found that both the alcohol and the ligand were identified as endgroups and therefore act as initiators for the polymerization. Besides, the complex was found at the chain end which is why a CIM mechanism was proposed.

While the literature is full of zinc complexes as catalysts for the ROP of lactide, iron was given less attention than zinc. Polymerization data of iron complexes with bis(pyrazolyl)-bipyridinyl-methane ligands showed low activity in the ROP of technical grade lactide.[55] In 2019, three guanidine iron complexes for lactide polymerization were synthesized with $FeCl_2$ using the three best guanidine ligands TMGqu, TMGasme and TMG5NMe$_2$asme from zinc chemistry for lactide polymerization.[54] In all three obtained complexes tetrahedral coordination was present by the corresponding hybrid guanidine and the two chloride ligands. First kinetic studies with technical grade *rac*-LA at a ratio of [M]/[I] = 500:1 showed a conversion of 25% for **32** after 16 h. The complex [FeCl$_2$TMGasme] (**33**) achieved a conversion of 83% and molecular weights of $M_n = 35500$ $g\,mol^{-1}$ in 60 min. By introducing the dimethylamine group in *para*-position to the guanidine unit (**34**), the activity could be increased by a comparable factor regarding the corresponding zinc system (**31**). Already after 1.4 min a conversion of 66% was reached. In addition, polymers with molecular weights of $M_n = 77300$ $g\,mol^{-1}$ were obtained. These initial polymerization data were followed by more in-depth kinetic investigations of **33** and **34**, which were, however, carried out with once recrystallized lactide to ensure a constant purity of the monomer. In order to make an accurate comparison with the catalyst Sn(Oct)$_2$, kinetic studies were carried out with Sn(Oct)$_2$ under identical polymerization conditions. The rate constant of propagation $k_p$ was determined and showed that the two iron

complexes are not only several times faster than their zinc equivalents, but also exceed the polymerization rate of $Sn(Oct)_2$. While **33** with a $k_p$ value of $9.2 \pm 0.01 \times 10^{-2}$ L mol$^{-1}$ s$^{-1}$ is slightly faster than $Sn(Oct)_2$ with $k_p = 8.4 \pm 0.02 \times 10^{-2}$ L mol$^{-1}$ s$^{-1}$, **34** with $k_p = 55.4 \pm 0.02 \times 10^{-2}$ L mol$^{-1}$ s$^{-1}$ is 6.5 times faster than $Sn(Oct)_2$. This means that a biocompatible solution has been found for the toxic catalyst tin octanoate currently used in industry. Plotting of the molar masses against the respective conversion showed that the polymerization is proceeding in a controlled manner. With the data of the MALDI-ToF analysis it was also shown that the complex, the ligand, as well as OH groups are found at the chain end. In addition to residual water in the monomer, the ligand is therefore able to open the lactide ring, which led to the conclusion that the guanidine iron complex **33** corresponds to a well-defined catalyst and that the polymerization proceeds according to a CIM mechanism.

## 3. Conclusion and Outlook

In this mini-review, the second and third generation of guanidine metal complexes as catalysts for the ring-opening polymerization of technical grade lactide were summarized. While the developed guanidine zinc complexes with *N,N* donors showed moderate results, the use of *N,O* donor hybrid guanidines opened up a new avenue for the ligand design. Several zinc complexes showed high activities in the ROP of lactide, requiring the development of new methods for kinetic monitoring of the polymerization. By designing a steel reactor and using *in situ* Raman technology, the rate constant of propagation $k_p$ could be determined more accurately under stirring and with much less effort than before. In addition to the zinc complexes, the synthesis of corresponding iron complexes and their catalytic investigation have shown that *N,O* donor hybrid guanidine iron complexes have a much higher activity than *N,N* donor guanidine zinc complexes and the catalyst $Sn(Oct)_2$ currently used in industry. With the development of a robust catalyst with higher activity than $Sn(Oct)_2$, an important step towards a biocompatible alternative has been taken. In addition to the catalytic activity, the catalyst also convinced by the formation of polymers with high molecular masses. Mechanistic investigations revealed that the complex polymerizes as a well-defined catalyst and follows a CIM mechanism. In future projects these very active and robust systems will be tested in the ROP of other cyclic esters. In addition to homopolymerization, application in copolymerizations of other cyclic esters will be investigated, for example with ε-caprolactone, in order to construct different material properties of the biodegradable polymers.

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## Conflict of Interest

*The authors declare no conflict of interest.*

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