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Cyclic Polymers

Zwitterionic Polymerization of Lactide to Cyclic Poly(Lactide) by Using N-Heterocyclic Carbene Organocatalysts**

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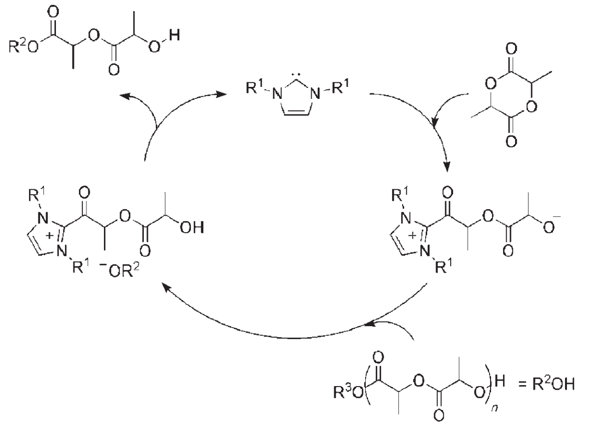
The synthesis of large-ring cyclic structures is a formidable challenge in organic and polymer chemistry. Macrolactones constitute an important class of bioactive natural products;[1] higher-molecular-weight cyclic polymers exhibit unusual physical and solution properties owing to the constraints imposed by tethering of the chain ends.[2,3] A number of synthetic strategies for the synthesis of cyclic structures have been developed that attempt to address both the entropic and enthalpic barriers to cyclization.[1,2]

One of the challenges in the study and application of large-ring macromolecules is the lack of versatile synthetic methods for high-molecular-weight cyclic polymers. The classic approach to the synthesis of ring polymers is the intramolecular cyclization of linear precursors at high dilution.[2] Cyclic polymers can also be formed under ring–chain equilibrium conditions, but as pointed out by Jacobson and Stockmayer, thermodynamic constraints place limits on the molecular weights that can be achieved at equilibrium.[4]

Several clever strategies have been developed for the synthesis of cyclic polymers under kinetically controlled conditions.[2,5] Macrocyclic polyesters have been prepared by using polymer supports onto which the monomer and growing chain are bound; intramolecular cyclization reactions release low-molecular-weight cyclic polymers formed while the linear chains remain attached to the support.[6,7] Kricheldorf and Schwarz developed a kinetically controlled ring-expansion strategy for the synthesis of high-molecular-weight cyclic polyesters from cyclic tin alkoxides.[8] In this approach, the metal alkoxide initiator remains in the product at the end of the reaction, although recent strategies have been devised utilizing intramolecular cross-linking and elimination of the tin initiator.[8–10]

Herein, we report a kinetically controlled synthesis of cyclic polyesters of defined molecular weight and narrow molecular weight distribution by the zwitterionic ring-opening polymerization of lactide with N-heterocyclic carbenes (NHCs). Zwitterionic polymerizations, involving chains with a positively and negatively charged group, have been investigated for many years,[11] but typically yield low-molecular-weight linear polymers because of the high reactivity of the cationic and anionic chain ends.[12] As early as 1960, Swarc posited that zwitterionic polymerizations could produce macrocycles.[13] The zwitterionic polymerization of amino acid *N*-carboxyanhydrides was recently reported to generate low-molecular-weight cyclic polypeptides.[14] Herein we demonstrate that the zwitterionic polymerization of lactide mediated by NHCs leads to macrocyclic polymers of molecular weight up to 26 kg mol^{-1} with narrow polydispersities.

In the presence of alcohol initiators, NHCs[15] are potent organic catalysts for the ring-opening polymerization of cyclic esters to generate well-defined linear polyesters of controlled molecular weights and narrow polydispersities.[16,17] We have proposed a nucleophilic mechanism involving zwitterionic intermediates for NHC-catalyzed transesterification and ring-opening polymerization reactions (Scheme 1).[16–18] To assess the role of zwitterionic intermediates in these polymerizations, we investigated the polymerization of lactide in the absence of alcohol initiators. Remarkably, we found that the



Scheme 1. Proposed mechanism for the ring-opening polymerization of lactide in the presence of alcohol.

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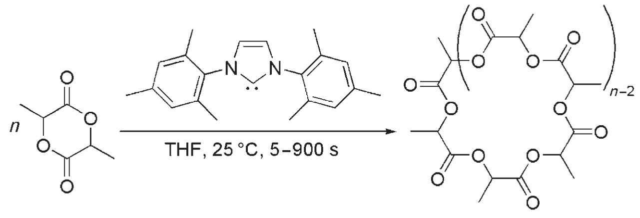
polymerization of lactide by NHCs without alcohol yields cyclic poly(lactide)s (PLAs) of defined molecular weight, even at relatively high monomer concentrations (0.6–1.0 M in tetrahydrofuran (THF)). The polymerization of *rac*-lactide with 1,3-dimesitylimidazol-2-ylidene (IMes)[19] occurs rapidly (5–900 s) at room temperature to yield PLAs with molecular weights from 7 to 26 kg mol^{-1} (Table 1). Polymerizations were terminated by the addition of carbon disulfide, an aprotic trapping agent for the carbene. The resulting cyclic polymers were isolated simply by precipitation without the need for elaborate purification procedures.

Table 1: Selected data for cyclic poly(lactide)s prepared by using IMes.



Entry	*t* [s]	M/I[a]	Conv. [%][b]	M_n [kDa][c]	PDI[d]
1	30	100	75	15 (8.4)	1.16
2	10	100	35	7.3 (4.2)	1.15
3	60	200	73	18 (11)	1.17
4	20	200	32	9.9 (5.8)	1.28
5	900	200	92	26 (15)	1.35
6[e]	120	100	90	22[f]	1.27

[a] Monomer-to-initiator ratio; $[M]_0 = 0.6$ M. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Number average molecular weight, determined by gel permeation chromatography (GPC) calibrated with polystyrene standards. Corrected molecular weights[20,21] are presented in parentheses. [d] Polydispersity index, determined by GPC calibrated with polystyrene standards. [e] Sample purified by precipitation. [f] Weight average molecular weight determined by light scattering.

The cyclic structure of the products was determined by a combination of techniques, including ^{1}H nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, and comparisons of the solution properties of the cyclic polymers with their linear congeners. For example, polymerization of L-lactide at room temperature with IMes at a monomer-to-initiator (M/I) ratio of 100 proceeded in 30 % conversion after 5 seconds. No end groups were observed in the ^{1}H NMR spectrum of the resulting PLA. The matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum of this sample shows molecular ions for the sodium- and potassium-complexed cyclic PLAs; no evidence for linear structures was observed for molecular ions less than *m*/*z* 10000 (Figure 1). The MALDI-TOF mass spectrum reveals signals for cyclic polymers separated by 72 mass units (corresponding to the mass of half a lactide unit), thus indicating that both odd- and even-numbered cyclics are formed.

Further evidence for the cyclic structure of these PLAs was provided by gel-permeation chromatography (GPC) utilizing a light-scattering detector and viscometer. The PLAs obtained in the absence of alcohol elute later than those of the same molecular weight prepared in the presence of alcohol initiators (Figure 2a). This result is considered indicative of a cyclic structure, as ring polymers have smaller hydrodynamic volumes than their linear analogues.[22] Viscosity measurements with a light-scattering detector coupled to a viscometer show that PLAs prepared in the absence of alcohol have lower intrinsic viscosities than those prepared from alcohol initiators (Figure 2b). This result is also consistent with a cyclic structure, as the intrinsic viscosities of cyclic polymers are less than those for linear polymers of the same molecular weight. The ratio $[\eta]_{\text{cyclic}}/[\eta]_{\text{linear}}$, obtained from the Mark–Houwink plot, is approximately 0.7, which is in good agreement with theoretical predictions and experimental findings on other cyclic polymers.[22,23]

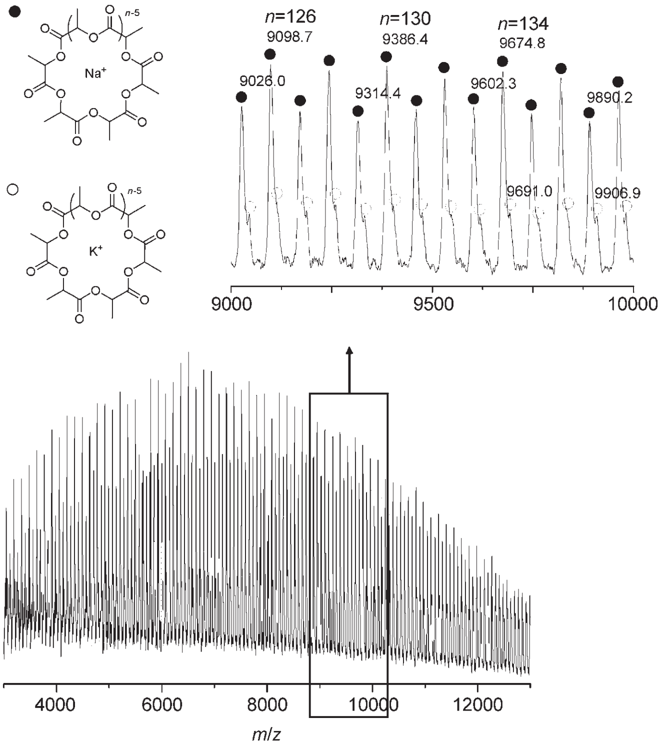


Figure 1. MALDI-TOF mass spectrum of cyclic poly(lactide).

The hydrodynamic radii of the chains R_h of PLAs prepared both in the absence and presence of alcohol initiators were determined by dynamic light scattering (DLS) experiments in acetone. In this solvent, the hydrodynamic radius for the cyclic polymer is estimated to be $R_{h,\text{cyclic}} = 4.5 \pm 0.1$ nm, and for the linear polymer $R_{h,\text{linear}} = 4.8 \pm 0.2$ nm. The ratio $R_{h,\text{cyclic}}/R_{h,\text{linear}} = 0.89 \pm 0.04$ for these two samples is within the range of values reported in the literature ($R_{h,\text{cyclic}}/R_{h,\text{linear}} = 0.86$–$0.90$).[22,24] These data suggest that the cyclic polymers generated by our synthetic procedure are not concatenated. Furthermore, thermogravimetric analysis (TGA) studies on these samples suggest that cyclic PLAs are more thermally stable than linear PLAs of similar molecular weight. Comparison of the stability of linear and cyclic PLAs by isothermal TGA revealed 18 % weight loss for the linear polyester whereas only 11 % weight loss was observed for the cyclic polyester after 3 h at 225 °C.

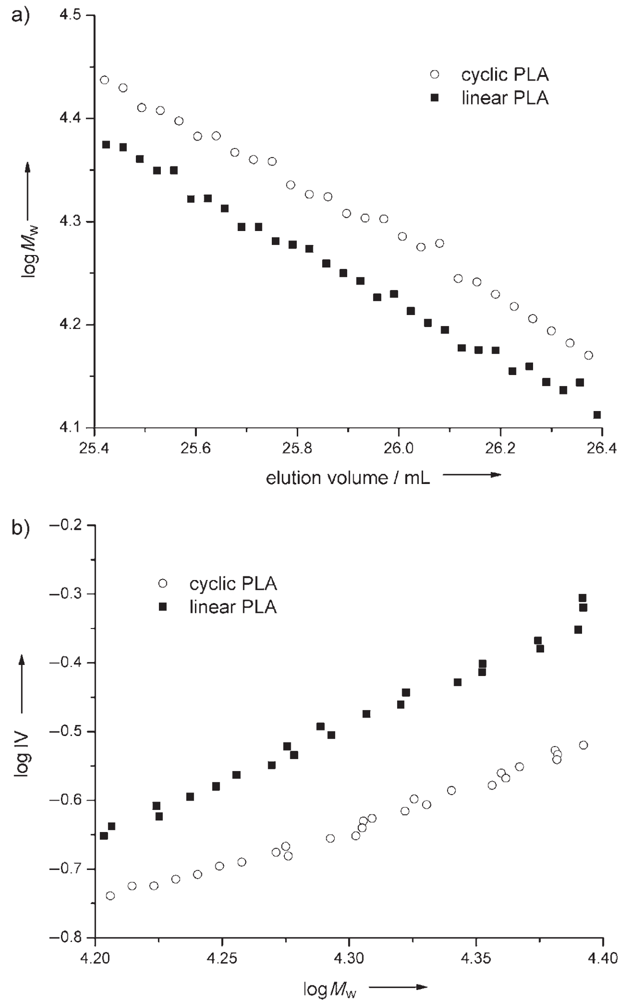
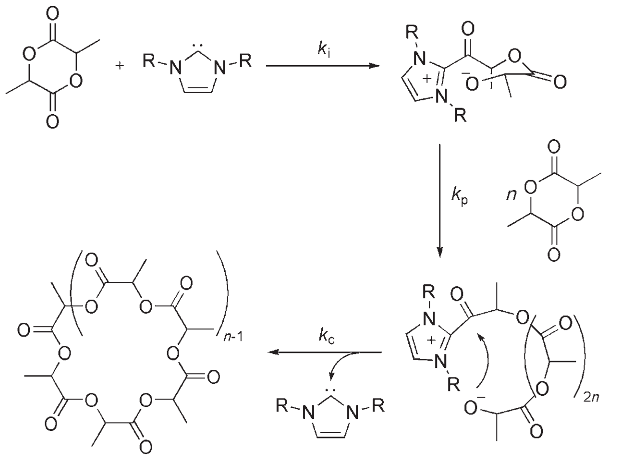


Figure 2. a) Plot of logarithm of molecular weight versus elution time b) Double logarithmic plot of intrinsic viscosity (IV) versus molecular weight.

Several features of these zwitterionic polymerizations are noteworthy.[11,12,14] First, in contrast to other known zwitterionic polymerizations, high-molecular-weight cyclic polymers are generated with high selectivities. Analysis of the GPC traces of aliquots of the reaction mixtures at 14% and 73% conversion reveal only monomer and cyclic polymer with no evidence for other cyclic oligomers. Moreover, polymerization of optically pure L-lactide with IMes generated crystalline cyclic poly(L-lactide), which indicates that the polymerization proceeds with retention of stereochemistry. The facile synthesis of crystalline cyclic PLAs should enable investigations of the influence of topology on the crystalline behavior of linear and cyclic polyesters.

Notably, these NHC-mediated zwitterionic polymerizations display a remarkable degree of control and exhibit some features of living polymerizations. Plots of molecular weight (M_n) against monomer conversion are linear (see Figure S1 in the Supporting Information) with a nonzero intercept. The polydispersity index is less than 1.3 for polymerizations with conversions less than 90% (Table 1, Figure S1). Kinetic studies are consistent with the polymerization of lactide from zwitterionic species whereby the initiation rate (formation of zwitterions, k_i) is slower than the propagation rate (k_p, Scheme 2). Conventionally, narrow polydispersities are expected when $k_i \geq k_p$; nevertheless, fast initiation is a sufficient, but not necessary, condition for narrow molecular size distributions.[25] Modeling of the kinetics as a living polymerization with slow initiation yields estimates for $k_p = 16\,\text{M}^{-1}\text{s}^{-1}$ and $k_i = 0.46\,\text{M}^{-1}\text{s}^{-1}$.[26,27] Simulations of the evolution of molecular weight with conversion illustrate that when the initiation rate is slower than the propagation rate, the initiation period results in higher molecular weights at low conversions than those predicted simply on the basis of the monomer/initiator ratio and conversion (see Figure S8 in the Supporting Information).



Scheme 2. Proposed mechanism for NHC-mediated zwitterionic polymerization of lactide.

The increase in molecular weight with conversion and the narrow polydispersities for conversions less than 90% imply that macrolactonization to generate the cyclic polymer and free carbene is slower than propagation, which would mean that few chains are reinitiated from carbenes liberated upon macrolactonization. Furthermore, the observation of odd-numbered cyclic PLAs and the increase in polydispersity index at high conversion are consistent with either competitive transesterification reactions of the propagating zwitterions[28] (whereby the transesterification rate is slower than the propagation rate) or transesterification reactions of the cyclic polymers by the zwitterions or carbenes. Further studies are underway to elucidate the polymerization mechanism, particularly the details of the macrolactonization step.

In summary, we have described a zwitterionic strategy for the controlled synthesis of high-molecular-weight cyclic PLAs with narrow polydispersities. The selectivity for the formation of high-molecular-weight macrolactones, even at relatively high monomer concentrations, is likely a consequence of the enforced proximity of the zwitterionic chain ends. This efficient macrolactonization step is conceptually related to Corey's strategy for generating macrolactones from zwitterionic intermediates.[29,30] As this process for forming cyclic polyesters is fast, highly efficient, atom-economical, and conducted at relatively high concentrations, it represents an expedient route to novel topologies of biodegradable polyesters derived from renewable resources.

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[1] A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.
[2] J. A. Semlyen in *Cyclic Polymers*, 2nd ed. (Ed.: J. A. Semlyen), Kluwer Academic Publishers, Dordrecht, **2000**, pp. 1–46.
[3] T. McLeish, *Science* **2002**, *297*, 2005–2006.
[4] H. Jacobson, W. H. Stockmayer, *J. Chem. Phys.* **1950**, *18*, 1600–1606.
[5] C. W. Bielawski, D. Benitez, R. H. Grubbs, *Science* **2002**, *297*, 2041–2044.
[6] B. R. Wood, P. Hodge, J. A. Semlyen, *Polymer* **1993**, *34*, 3052–3058.
[7] M. H. Chisholm, J. C. Gallucci, H. Yin, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 15315–15320.
[8] H. R. Kricheldorf, G. Schwarz, *Macromol. Rapid Commun.* **2003**, *24*, 359–381.
[9] H. R. Kricheldorf, M. Al-Masri, G. Schwarz, *Macromolecules* **2002**, *35*, 8936–8942.
[10] H. Li, A. Debuigne, R. Jérome, P. Lecomte, *Angew. Chem.* **2006**, *118*, 2322–2325; *Angew. Chem. Int. Ed.* **2006**, *45*, 2264–2267.
[11] D. S. Johnston, *Adv. Polym. Sci.* **1982**, *42*, 51–106.
[12] G. Odian, *Principles Of Polymerization*, 4th ed., Wiley-Interscience, Hoboken, **2004**.
[13] M. Swarc, *Makromol. Chem.* **1960**, *35*, 132–158.
[14] H. R. Kricheldorf, C. von Lossow, G. Schwarz, *Macromolecules* **2005**, *38*, 5513–5518.
[15] D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–91.
[16] G. W. Nyce, T. Glauser, E. F. Connor, A. Möck, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2003**, *125*, 3046–3056.
[17] S. Csihony, D. A. Culkin, A. C. Sentman, A. P. Dove, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 9079–9084.
[18] An alcohol-activation mechanism has also been proposed: M. Movassaghi, M. A. Schmidt, *Org. Lett.* **2005**, *7*, 2453–2456.
[19] A. J. Arduengo III, H. V. R. Dias, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.
[20] A. Kowalski, A. Duda, S. Penczek, *Macromolecules* **1998**, *31*, 2114–2122.
[21] M. Save, M. Schappacher, A. Soum, *Macromol. Chem. Phys.* **2002**, *203*, 889–899.
[22] J. Roovers, 2nd ed. (Ed.: J. A. Semlyen), Kluwer Academic Publishers, Dordrecht, **2000**, pp. 347–384.
[23] Although the viscosity data cannot rule out the presence of small amounts of linear contaminants, the MALDI-TOF mass spectrum shows no evidence for linear contamination for molar masses less than 10 kg mol^{-1}.
[24] W. W. Graessley, Polymeric Liquids and Networks: Structure and Properties, Garland Science, New York, **2003**.
[25] L. Gold, *J. Chem. Phys.* **1958**, *28*, 91–99.
[26] L. F. Beste, H. K. Hall, Jr., *J. Phys. Chem.* **1964**, *68*, 269–274.
[27] D. C. Pepper, *Eur. Polym. J.* **1980**, *16*, 407–411.
[28] R. Szymanski, *Macromol. Theory Simul.* **1998**, *7*, 27–39.
[29] E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616.
[30] E. J. Corey, D. J. Brunelle, P. J. Stork, *Tetrahedron Lett.* **1976**, *17*, 3405–3408.