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Accelerating effect of crown ethers on the lactide polymerization catalysed by potassium acetate†

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Recent advances in catalysis enriched the toolbox to prepare well-defined polyester materials such as polylactide (PLA). Herein, we report the use of crown ethers to speed up the polymerization of L-lactide (L-LA) initiated by an exogenous alcohol and catalyzed by potassium acetate (KOAc). With KOAc, the crown ethers played a crucial role as a complexing agent, with 18-crown-6 enabling the fastest polymerization kinetics outpacing the one obtained with the pristine catalyst by not less than 73. Experimental results suggested that the 18-c-6 crown ether complexed the KOAc ion pair to *in situ* produce free ions, which was much more appropriate to activate the propagating alcohol for the ring-opening reaction of L-LA.

Introduction

Catalysis is one of the most powerful mechanistic strategies for engineering chemical reactions. The development of new catalytic methods still continues to drive innovation in materials science.^{1,2} Ring-opening polymerization (ROP) is a versatile synthetic method for generating well-defined macromolecules.³ In recent years, many new reaction pathways have been investigated and a range of new catalytic processes for the ROP of heterocyclic monomers, such as lactones, have been developed. Recently, the emergence of organocatalysis offered a number of prospects in the polymer community by proposing advantages and complementarities over metal-based and bio-organic methods.⁴ Organocatalysts complement transition metal-catalysts because of their different mechanisms for effecting bond construction. They were initially thought of and presented as a judicious solution due to their lack of residual metal-contaminants compromising the polymer performance in biomedical and microelectronic applications.⁵ Very recently, a few studies confirmed the relatively low toxicity of some well-known organocatalysts,^{6–8} but exceptions have also been made discrediting their absolute necessity in the

preparation of aliphatic polyesters intended for biomedical use.⁶ In an effort to find non-toxic innovative catalysts for the industrial production of aliphatic polyesters, Isono and Satoh discovered that alkali metal carboxylates represent a very efficient alternative to conventional metal-based catalysts and organocatalysts.⁹ They provide a robust system to produce, on an industrial scale, renewable polymers such as polylactide (PLA), which is a major synthetic bio-based plastic on the market.¹⁰ Computational studies discredited the bifunctional mechanism initially suggested⁹ and concluded that alkali metal carboxylates activate mainly the terminal alcohol moiety during both the initiation and the propagation steps (Fig. 1).¹¹ As experimentally and theoretically demonstrated, the breadth of such activation is a function of both the cation size and the strength of the electron-donating group on the carboxylate moiety, ultimately influencing the rate of the reaction.^{9,11}

When L-lactide (L-LA) is polymerized in bulk at 100 °C, caesium pivalate allows a 74% monomer conversion to be reached in 15 min ($[L-LA]_0/[ROH]_0/[cat.]_0 = 50/1/0.5$).⁹ This demonstrates a very high activity unfortunately detrimental to the control of the ROP as suggested by the tailing effect

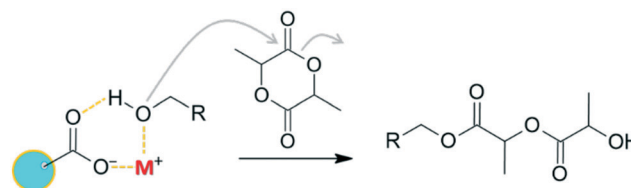


Fig. 1 Simplified polymerization mechanism of lactide from an alcohol (RCH₂OH) catalysed by an alkali metal carboxylate as proposed by Ozen *et al.*¹¹ Coloured items represent the influencing activating factors, i.e., the donating group of the carboxylate moiety (blue sphere) and the size of the metal cation (red M).

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observed in the SEC traces of the resulting PLAs. Moderately less active, alkali metal acetates (including Li^+ , K^+ and Cs^+ cations) promote the ROP of L-LA in a controlled manner with turnover frequency (TOF) values increasing with the increasing cation size of the catalysts.⁹

The unique property of macrocyclic crown ethers as complexing agents is their high affinity for alkali metal ions depending on their size and the diameter of the hole in the centre of the polyether rings. Thermodynamics of the cation–macrocyclic crown ether interaction have shown that the ΔH^0 and ΔS^0 values for complexation are usually negative and small.¹² Consequently, the sign and value of the free energy depend on the absolute temperature which, contrary to homogeneous systems, forces the complex to release the free cations in heterogeneous media.¹³ From their different investigations, Isono and Satoh demonstrated that the control of the L-LA from alkali metal acetates was achieved at 100 °C.⁹ In such conditions, the polymerization medium is heterogeneous since the L-LA ROP could be promoted by crystallization of the product PLA.¹⁴ Considering that the complexation of alkali metal acetates with appropriate crown ethers, in a homogeneous medium, shifts the equilibrium between ion pairs (e.g., contact and solvent separated) to free ions,¹⁵ we reasoned that in solution, the presence of crown ethers would further accelerate the polymerization.

Herein, we report the accelerated ROP of L-LA catalyzed by potassium acetate, which is complexed by a crown ether in THF. As it will be shown, the apparent rate constant of the propagation of L-LA catalysed with potassium acetate ($k_{\text{app,K}}$) increases not less than 73 times when the 18-crown-6 ether is present ($k_{\text{app,K+18-c-6}}/k_{\text{app,K}} = 73$). The substantial increase of the rate of polymerization allowed us to replace less efficient caesium acetate ($k_{\text{app,Cs}}/k_{\text{app,K}} = 15$) by a much cheaper catalytic complex.

Results and discussion

In the frame of our work, potassium acetate (KOAc) was selected as a representative catalyst. It presents the advantages of being a food preservative (labelled in European Union by the E number E261) and is cheaper than the commercially available caesium acetate (CsOAc). Moreover, the diameter of the potassium cation (2.66 Å) perfectly fits with the hole size of the 18-crown-6 ether (2.6–3.2 Å)¹⁶ which is also the cheapest crown ether available. Finally, because KOAc will be used at a relatively low concentration ($[\text{KOAc}]_0 \sim 0.01 \text{ M}$), comparison of the stability constants of the Na^+ , K^+ and Cs^+ cations – each with the crown of optimum ring size – reveals that K^+ is the strongest by at least one order of magnitude.¹⁷

Prior to any polymerization in the presence of crown ethers, the ROP of L-LA was first carried out with pristine KOAc at an initial monomer concentration ($[\text{L-LA}]_0$) of 1 M and from a benzyl alcohol (BnOH) initiator. The L-LA ROP was performed in THF at 21 °C at an initial $[\text{L-LA}]_0/[\text{BnOH}]_0/[\text{KOAc}]_0$ of 40/1/0.5. Kinetic plot gave a straight line in the semilogarithmic coordinates (Fig. 2) attesting that the number of growing chains does not change appreciably

during the ROP.[‡] As compared to a polymerization proceeding with CsOAc (under the same experimental conditions, Fig. 2), the reaction appears very slow, reaching a monomer conversion of 13.5% within 92 hours. By ignoring the initiation process and using the general accepted kinetics, the linearity of these plots is consistent with a polymerization process that is first order in L-LA and can be described by an apparent rate constant (k_{app}) equal to $\ln([\text{LA}]_0/[\text{LA}]_t)/t$.

In accordance with the conclusions drawn in bulk at 100 °C,⁹ the apparent rate constant of L-LA polymerization catalyzed by CsOAc ($k_{\text{app-Cs}}$) appears to be higher than the apparent rate constant of L-LA ROP catalyzed by KOAc ($k_{\text{app-K}}$). In THF at 21 °C and for a $[\text{cat.}]_0 \sim 0.01 \text{ M}$, the L-LA polymerization is 15 times ($k_{\text{app-Cs}}/k_{\text{app-K}} = 2.4 \times 10^{-2} \text{ h}^{-1}/1.6 \times 10^{-3} \text{ h}^{-1} = 15$) more rapid with CsOAc than with KOAc (Table 1). This is fully consistent with the theoretical calculations indicating that the larger cation leads to faster reactions.¹¹ Motivated by this difference in the polymerization rate observed in THF, we hypothesized that the addition of crown ethers would lead to even faster polymerizations by complexing the K^+ cation of the KOAc ion pair. Ion pairs are indeed considered to be at chemical equilibrium with their free ions. If the exact nature of KOAc in THF (i.e., “tight” or “loose” ion pair) is outside the scope of this manuscript, it is known that their equilibrium is considerably displaced to free ions by adding crown ethers.^{15,18} Thus, by complexing K^+ , the free acetate anions will exhibit a more important nucleophilic character in favour of the basic activation mechanism proposed.

To demonstrate the importance of their ring size, 15-c-5 and 18-c-6 crown ethers were selected as KOAc partners for the L-LA ROP ($[\text{KOAc}]_0/[\text{crown}]_0 = 1$). Because THF appears as an excellent solvent for potassium salts to form stable 2:1 complexes with 15-c-5,¹⁸ another polymerization reaction was

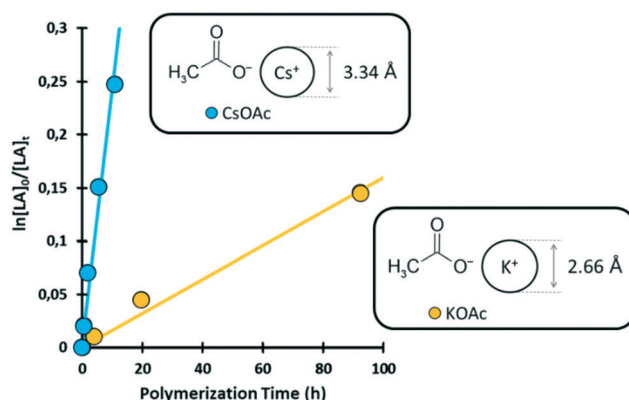


Fig. 2 Semilogarithmic plots of the L-LA polymerizations initiated with BnOH and catalysed with KOAc (●) and CsOAc (●). Reaction conditions of the polymerizations: $[\text{L-LA}]_0/[\text{BnOH}]_0/[\text{cat.}]_0 = 40/1/0.5$, $[\text{L-LA}]_0 = 1 \text{ M}$, THF solvent, 21 °C.

‡ Kinetic details including the linear regressions and R^2 values are presented in the ESI† for clarity.

Table 1 Apparent rate constants (k_{app}) of the L-LA polymerization^a

Entry	Catalyst	k_{app} (10^{-3} h^{-1})
1	CsOAc	24
2	KOAc	1.6
3	KOAc/15-c-5	8.5
4	KOAc/(15-c-5) ₂	38.5
5	KOAc/18-c-6	117.5

^a Determined from the semilogarithmic plots of L-LA polymerizations initiated with BnOH and catalysed with different catalysts. Reaction conditions of the polymerizations: $[\text{L-LA}]_0/[\text{BnOH}]_0/[\text{cat.}]_0 = 40/1/0.5$, $[\text{L-LA}]_0 = 1 \text{ M}$, THF solvent, 21 °C.

also carried out using a $[\text{KOAc}]_0/[\text{15-c-5}]_0$ molar ratio of 0.5 (Fig. 3). All polymerizations in the presence of crown ethers showed accelerated behaviour, with 18-c-6 exhibiting the highest catalytic activity with KOAc ($k_{app-K+18-c-6} = 117.5 \times 10^{-3} \text{ h}^{-1}$, Table 1).

Polymerizations in the presence of 1 eq. of 15-c-5 ($k_{app-K+15-c-5} = 8.5 \times 10^{-3} \text{ h}^{-1}$) and 2 eq. of 15-c-5 ($k_{app-K+(15-c-5)_2} = 38.5 \times 10^{-3} \text{ h}^{-1}$) were slower compared to those with 18-c-6, requiring 23.7 hours and 4.6 hours to reach ~18% L-LA consumption, respectively.

As compared to the pristine KOAc, the cooperative work of crown ethers resulted in one-stage polymerization kinetics, generating well-defined PLAs with predictable molecular mass (M_n) and narrow dispersity index ($\mathcal{D} = M_w/M_n \leq 1.25$). As represented by the KOAc/18-c-6 complex, the obtained M_n increases linearly suggesting the maintained end-group fidelity throughout the polymerization process (Fig. 4).

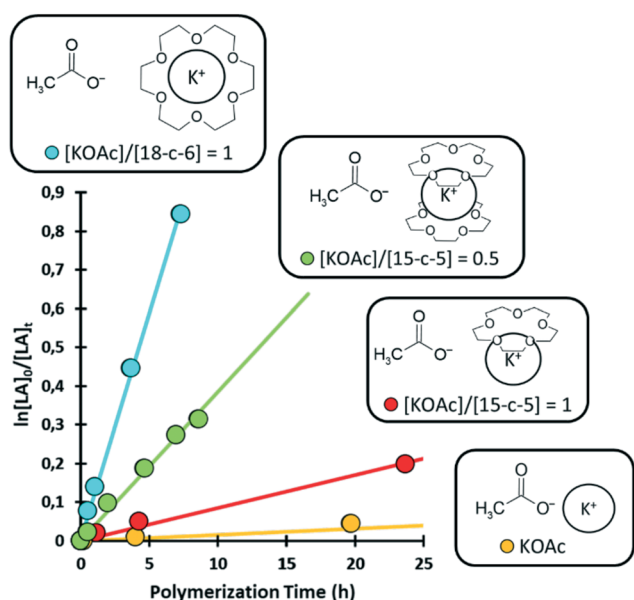


Fig. 3 Semilogarithmic plots of the L-LA polymerizations initiated with BnOH and catalysed with KOAc (●), $[\text{KOAc}]_0/[\text{18-c-6}]_0 = 1$ (●) and $[\text{KOAc}]_0/[\text{15-c-5}]_0 = 1$ (●) and 0.5 (●). Reaction conditions of the polymerizations: $[\text{L-LA}]_0/[\text{BnOH}]_0/[\text{cat.}]_0 = 40/1/0.5$, $[\text{L-LA}]_0 = 1 \text{ M}$, THF solvent, 21 °C.

Previous computational studies concluded that the main function of the alkali metal carboxylate – at least when polymerizations are performed in bulk – is to activate the terminal alcohol moiety.¹¹ Therefore, we hypothesized that the 18-c-6 crown ether, by transforming K^+, OAc^- ion pairs into free ions in solution, allows the nucleophilic behaviour of the acetate to be exacerbated. As such, the crown ether helps to promote the acetate–(propagating) alcohol binding, facilitating the L-LA polymerization. To verify our hypothesis, the polymerization kinetics was studied in another solvent. The selection of the solvent plays an important role as it may disrupt the acetate–alcohol interaction and slow down the overall process. Chloroform (CHCl_3) is known to exhibit acidic behaviour, which should minimize the H-bonding interaction between the (propagating) alcohol and the catalyst.¹⁹ As expected, as compared to the same polymerization performed in THF ($[\text{L-LA}]_0/[\text{BnOH}]_0/[\text{KOAc}]_0/[\text{18-c-6}]_0 = 40/1/0.5/0.5$, $[\text{L-LA}]_0 = 1 \text{ M}$), a clear deceleration was observed in CHCl_3 (Fig. 5, left). Alongside the results obtained in THF, the efficiency of the polymerization is demonstrated by the good linearity between the experimental molar masses, determined by SEC analyses, and the L-LA conversion (Fig. 5, right). Rather slow, the high selectivity of the KOAc/18-c-6 complex in CHCl_3 was also revealed by matrix-assisted laser desorption/ionization time-of-flight

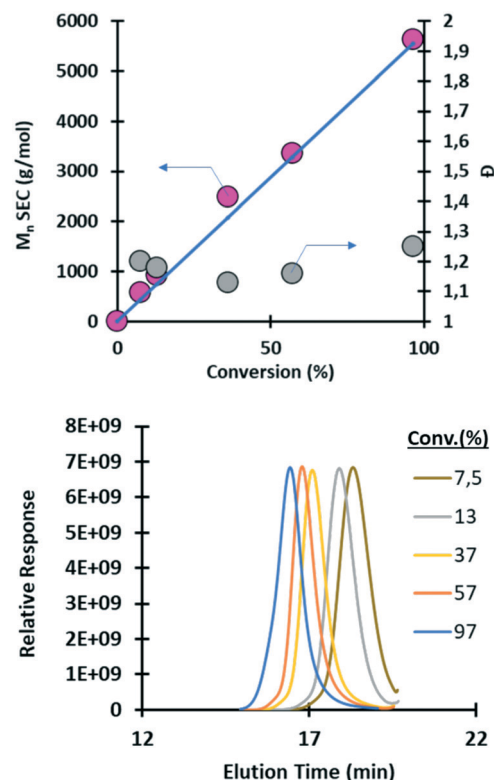


Fig. 4 Top: SEC experimental M_n and dispersity as a function of the conversions recorded during the KOAc/18-c-6 complex-catalysed ROP of L-LA in THF at 21 °C. Theoretical M_n in blue. Reaction conditions: $[\text{L-LA}]_0/[\text{BnOH}]_0/[\text{KOAc}]_0/[\text{18-c-6}]_0 = 40/1/0.5/0.5$; $[\text{L-LA}]_0 = 1 \text{ M}$. Bottom: associated SEC traces.

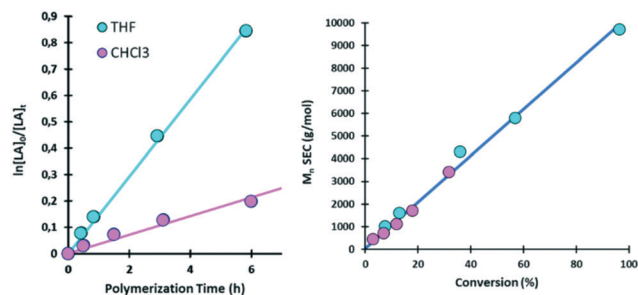


Fig. 5 Left: Semilogarithmic plots of the L-LA polymerizations initiated with BnOH and catalysed with $[KOAc]_0/[18-c-6]_0 = 1$ in THF (●) and $CHCl_3$ (●). Reaction conditions of the polymerizations: $[L-LA]_0/[BnOH]_0/[KOAc]_0/[18-c-6]_0 = 40/1/0.5/0.5$, $[L-LA]_0 = 1$ M, 21 °C. Right: Uncorrected SEC experimental M_n as a function of the conversions recorded during the L-LA polymerizations initiated with BnOH and catalysed with $[KOAc]_0/[18-c-6]_0 = 1$ in THF (●) and $CHCl_3$ (●).

mass spectrometry (MALDI-ToF MS). Fig. 6 shows the sample obtained after 22 hours of reaction (conv. $\sim 32\%$, $M_{nSEC} = 3400$ g mol $^{-1}$). The primary population is formed with molecular ions with a mass corresponding to the potassium ion of lactic acid-repeating PLA end-capped with a BnOH molecule.

In order to further elucidate the catalytic mechanism, binding interactions were studied through diffusion-ordered spectroscopy (DOSY) (Fig. 7). The addition of L-LA into the THF- d_8 solution of an equimolar mixture of KOAc and 18-c-6 resulted in a decrease in its diffusion coefficient by 28%, suggesting a partial interaction between the monomer and

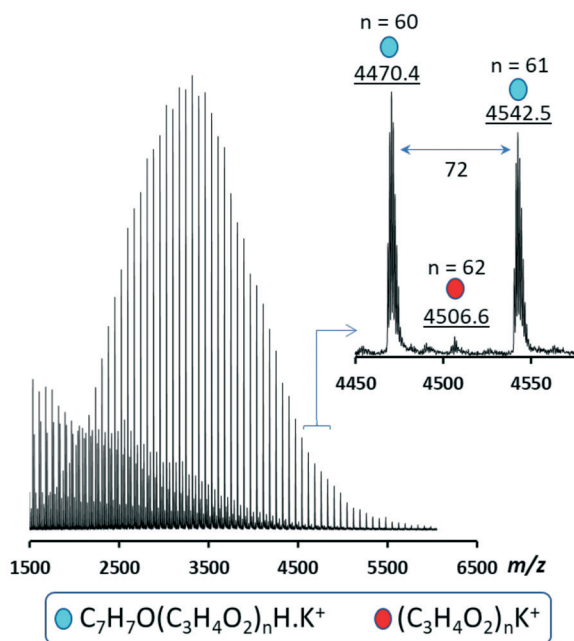


Fig. 6 MALDI-ToF MS of PLA obtained by the L-LA ROP initiated with BnOH and catalysed with $[KOAc]_0/[18-c-6]_0 = 1$ in $CHCl_3$. Reaction conditions of the polymerizations: $[L-LA]_0/[BnOH]_0/[KOAc]_0/[18-c-6]_0 = 40/1/0.5/0.5$, $[L-LA]_0 = 1$ M, 22 hours, 21 °C.

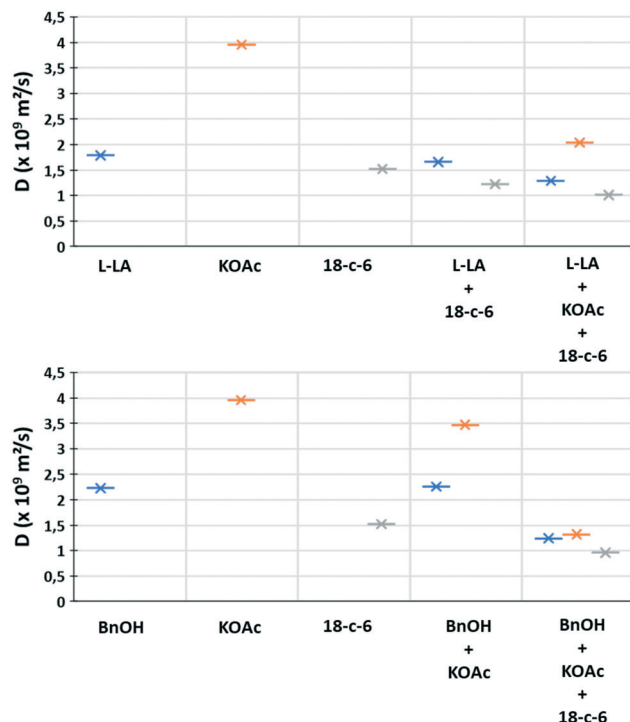


Fig. 7 Diffusion coefficients determined by DOSY NMR in THF- d_8 at 27 °C. Reagent concentrations ~ 50 –200 mM.

the catalytic complex. Note that without KOAc, no molecular interaction was observed between L-LA and 18-c-6.

Very interestingly, the addition of KOAc to a solution of BnOH in THF- d_8 led to negligible changes in the diffusion coefficient of the alcohol, suggesting a really weak molecular interaction. In contrast, by adding an equimolar amount of 18-c-6 to the BnOH/KOAc mixture, diffusion coefficients of all the three molecules decrease, validating the hypothesis that the KOAc/18-c-6 complex interacts more efficiently with the alcohol. This enhancement of interactions is consistent with the experimental results showing an elevated rate of the L-LA ring-opening reaction when KOAc is complexed by 18-c-6. This validates the hypothesis that the generation of acetate free ions activates more efficiently the propagating alcohol during the ROP process implying an impressive modification of the apparent rate constant by a factor of 73. This effect also originates from non-negligible activation of the L-LA monomer through coordination with the complexed potassium cation, at least in THF.

Conclusions

We reported the accelerating effect of crown ethers on the L-lactide ring-opening polymerization catalysed by potassium acetate (KOAc). Crown ethers, and more especially 18-crown-6, promote the *in situ* generation of free ions from the KOAc ion pair, resulting in fast polymerization kinetics when reactions are performed in THF. The rapid polymerization enabled us to prepare poly(L-lactide) materials in an efficient manner. This work enriches the toolbox of mechanistic

strategies to prepare one of the major synthetic bio-based plastics on the market from a cheap, non-toxic and commercially available catalytic complex.

Author contributions

O. C. conceived the project and designed the experiments. S. M. performed the majority of the experiments and data analysis. Q. De R. participated in the experiments. J. D. W. performed the MS analysis and data analysis. C. H. performed the NMR (DOSY) experiments and data analysis. The manuscript was written by O. C. and edited by all the co-authors.

Conflicts of interest

There are no conflicts to declare.

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