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ARTICLE

Ammonium Betaines: Efficient Ionic Nucleophilic Catalysts for the Ring-Opening Polymerization of L-lactide and Cyclic Carbonates

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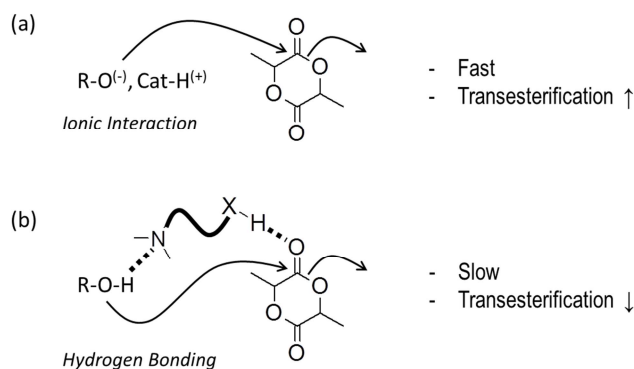
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The ionic nucleophilic character of ammonium betaine catalysts allows for controlling the ROP of L-LA for DP as high as 750 with very narrow dispersity values (≤ 1.18). Compared to ionic nucleophilic and hydrogen-bonding based catalysts for ROP, meta-betaine combines the positive aspects of both processes in terms of kinetics and selectivity. The versatility of ammonium betaines was evidenced by varying the nature of the initiating alcohol and monomer used.

Introduction

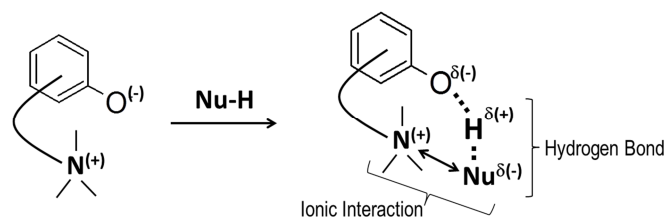
Organic catalysis is becoming an increasingly important segment of organic chemistry and offers a number of advantages over metal-based and bioorganic methods. Like metal complexes and enzymes, small organic molecules have been demonstrated to be efficient catalysts for various chemical transformations¹ including the ring-opening polymerization (ROP) of lactones and cyclic carbonates.^{2,3}

compromise between kinetics and control is principally due to the nature of the active center obtained by strong nucleophilic (\sim ionic) interactions or hydrogen cooperative bonds (Scheme 1). This concept has been nicely demonstrated by Hedrick *et al.* who compared both kinetics and control for the lactide ROP using free nucleophilic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and its benzoic acid (BA) conjugated salt.⁵ While the nucleophilic mechanism promoted by DBU is very fast and uncontrolled (conv. \sim 99% in 30 seconds, $M_w/M_n = \bar{D}_M = 1.6$), the use of the DBU/BA salt implies a cooperative hydrogen bonding system lowering the whole propagating activity (conv. \sim 99% in 24 hours) and improving the overall control of the reaction ($\bar{D}_M < 1.08$).



Scheme 1. Kinetics and control characteristics of a lactide ring-opening process obtained from (a) an ionic mechanism [Cat represents the catalyst] and (b) a cooperative hydrogen bonding mechanism [X = O or N].

Organocatalytic methods for ROP provide a complementary approach to those mediated by metal and enzymes in terms of rate and selectivity.⁴ Governed by either a “supramolecular” or a “superbase” system, nucleophilic metal-free ROP appears to inherently imply a compromise between selectivity and kinetics: highly selective processes lower the general kinetics while highly active systems lower the general control. The



Scheme 2. Ammonium betaine acting as ionic nucleophilic and hydrogen bonding catalyst.

Ammonium betaines have been applied here as bifunctional organic bases capable of recognizing nucleophiles with both ionic and hydrogen bond interactions.^{6,7} Since ammonium betaines have both an ammonium group and an aryloxy group in the same molecule, they can react with pronucleophilic reagents (Nu-H) by hydrogen bonding between H(δ^+) of Nu-H and O(δ^-) of the betaines and by ionic interaction between the ammonium group N(δ^+) and Nu(δ^-).

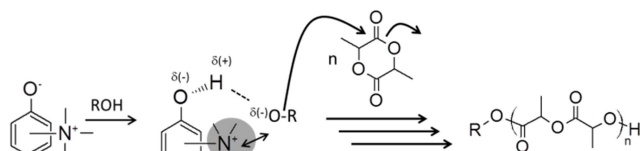
Table 1. Molecular characterizations of poly(L-lactide), poly(ϵ -caprolactone) and polycarbonates prepared by ring-opening polymerizations catalyzed by ammonium betaines.

Entry	BE type	monomer	initiator	solvent	Time (hour)	$[M]_0/[I]_0$	Conv ^a (%)	$M_{n,th}$ (g/mol)	$M_{n,SEC}^a$ (g/mol)	\bar{D}_M^a
1	<i>m</i> -BE	L-LA	/	CHCl ₃	1	/	0	/	0	-
2	<i>m</i> -BE	L-LA	1-PyOH	CHCl ₃	1	50	99	7,400	12,300	1.04
3	<i>m</i> -BE	L-LA	1-PyOH	CHCl ₃	3	100	99	14,500	20,000	1.04
4	<i>m</i> -BE	L-LA	1-PyOH	CHCl ₃	24	250	98	35,500	43,300	1.06
5	<i>m</i> -BE	L-LA	1-PyOH	CHCl ₃	168	750	93	100,000	97,000	1.18
6	<i>m</i> -BE	L-LA	1-PyOH	THF	1	50	74	5,600	6,400	1.06
7	<i>o</i> -BE	L-LA	1-PyOH	CHCl ₃	18	50	87	6,500	10,400	1.04
8	<i>p</i> -BE	L-LA	1-PyOH	CHCl ₃	6	50	89	6,600	11,500	1.04
9	<i>m</i> -BE	L-LA	PEO-OH	CHCl ₃	3	100	99	19,300	26,800	1.04
10	<i>m</i> -BE	L-LA	1,4-butanediol	CHCl ₃	3	100	99	14,300	19,100	1.17
11	<i>m</i> -BE	TMC	1-PyOH	CHCl ₃	24	100	97	10,100	12,800	1.04
12	<i>m</i> -BE	TMC	1-PyOH	CHCl ₃	192	500	99	50,500	48,000	1.47
13	<i>m</i> -BE	TMC-Bn	1-PyOH	CHCl ₃	24	100	98	24,800	13,800	1.10
14	<i>m</i> -BE	TMC-Bn	1-PyOH	CHCl ₃	190	500	99	124,000	44,000	1.11
15	<i>m</i> -BE	ϵ -CL	1-PyOH	CHCl ₃	144	50	5	500	600	1.22
16	<i>m</i> -BE	ϵ -CL	1-PyOH	CHCl ₃	1104	50	100	5,900	26,000	1.49

Conditions: Monomer as L-LA, TMC, TMC-Bn or ϵ -CL 1.8 M in CHCl₃ or THF ($[I]_0/[BE]_0 = 1$). ^a Conversions, experimental molar masses and dispersity values obtained by SEC analyses in CHCl₃, PS standards, 1 ml/min, T = 30°C.

In that situation, the nucleophilic agent is thus recognized and controlled by a hydrogen bond-assisted ionic interaction. It is worth stressing that quantum-chemical calculations (vide infra) indicate that, in the betaine-NuH complexes, there is no full proton transfer between Nu-H and the phenolate. This is illustrated in Scheme 2 representing the complex between the pronucleophile and the aryloxide stabilized by an ionic interaction supplemented by a hydrogen bond.

In our initial investigation, we used (trimethylammonio)phenolate betaine (BE) developed by Sakai⁸ and anticipated that the ionic nucleophilic activity of BE might induce a fast ROP while maintaining a good control over the process (Scheme 3).



Scheme 3. Polymerization of lactide by ammonium betaines.

Results and discussions

Totally inefficient in absence of exogenous alcohol (Table 1, entry 1), the organocatalyzed ROP of L-lactide (L-LA) was first studied with *meta*-(trimethylammonio)phenolate betaine (*m*-BE) in CHCl₃ (1.8 M) at 21°C using 1-pyrenemethanol (PyOH) as the initiator and for an initial *m*-BE-to-PyOH ratio of 1. At a monomer-to-initiator ratio of 50 ($[L-LA]_0/[PyOH]_0$), lactide was converted quantitatively after 1 hour (Table 1, entry 2). The polymerization exhibited the characteristics of a controlled and living reaction, as attested by the linear correlation between

the experimental molar masses (determined by SEC, $M_{n,SEC}$) and the theoretical ones ($M_{n,th}$), complemented by the linear evolution of the semilog plot versus polymerization time (Table 1, entries 2-5, Figure S11). Extremely narrow dispersity values are obtained for polymerization degrees as high as 750 (≤ 1.18). Furthermore, matrix-assisted laser desorption ionization time-of-flight (MALDI-ToF) and differential scanning calorimetry (DSC) analyses clearly show that very low levels of transesterification occur, as evidenced by a repeating unit molar mass of 144.13 Da and a melting enthalpy of 37.39 J/g, respectively (Figure S12).⁹ Finally, examination of the microstructure of a representative P(L-LA) (entry 2, Table 1) by ¹³C NMR spectroscopy reveals a high isotactic polymer with a very low level of stereoregularity (Figure S13).¹⁰

The efficiency of (pseudo)ionic and hydrogen bond-assisted catalysts is highly dependent on the solvent polarity. Although a solvent such as THF highly favors the nucleophilic mechanisms, the use of CHCl₃ strengthens reactions relying on cooperative hydrogen bonding. Quite interestingly, only a slightly faster polymerization was observed in CHCl₃ compared to that performed in THF (Table 1, entry 6), supporting the ionic nucleophilic nature of the *m*-BE and demonstrating the crucial role of the phenolate as a hydrogen acceptor. Moreover, upon addition of 1.3 mol% of *m*-BE in CDCl₃, the chemical shift of the $-CH_2OH$ in PyOH goes downfield from 5.37 to 5.45 ppm while the acidic hydroxyl proton shifts upfield from 1.95 to 1.72 ppm, indicative of a hydrogen bond modulation between the catalyst and the alcohol initiator (Figure S14). Molecular mechanics (MM) and molecular dynamics (MD) simulations have then been performed to provide further insights into the polymerization mechanism. In particular, the nature of the interactions between the monomer, the initiator

and *m*-BE was investigated. To simplify the computational process, the simplest alcohol, i.e., methanol, has been used as

the initiator and put in close contact with the oxygen atom of *m*-BE to allow hydrogen bonding.

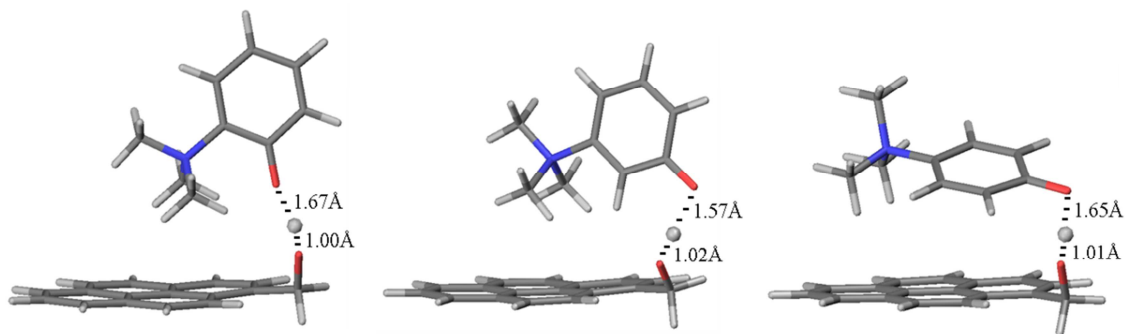


Figure 1. Representation of the B97D/6-31G(d,p) optimized complexes made of PyOH and betaine isomers (*ortho*, *meta*, and *para*, from left to right).

Three different starting positions have been considered for the L-LA monomer: (i) with one carbonyl group pointing to the positively-charged trimethylammonium group; (ii) on top of the betaine molecule; and (iii) in close contact with the carbon atom in the *para* position of the nitrogen atom of *m*-BE (Figure SI5). After an initial geometry optimization, those complexes have been introduced in a simulation box (30 Å x 30 Å x 30 Å) containing chloroform molecules (density = 1.48) and 5 ns-long MD runs were performed. The calculations show unambiguously: (i) an interaction between the oxygen of *m*-BE and the hydrogen of the alcohol group of the methanol molecule, as evidenced by the short distance between them throughout the dynamics (Figure SI6), (ii) no specific interaction between the L-LA monomer and the nitrogen atom of *m*-BE since L-LA appears to move freely around the betaine molecule during the MD simulations (Figure SI6). Consistently, FTIR experiments do not show any shift of the carbonyl band of L-LA (1754 cm⁻¹) in the presence of *m*-BE, confirming the lack of specific interactions between the monomer and the catalyst (Figure SI7).

Since similar conclusions hold when considering the *ortho*- and *para*-betaine isomers in the simulations, L-LA ROPs were carried out with both *o*-BE and *p*-BE to compare the substitution effect of the phenolate anion on the polymerization kinetics (Table 1, entries 7 and 8). First, we observed that *o*-BE is the less active isomer (87% conversion in 18 hours), presumably due to the steric hindrance introduced by the quaternary ammonium on the phenolate anion. In contrast, positioning the ammonium group in the *para* position of the betaine restores the phenolate anion accessibility but reduces the ionic interaction with the initiating alcohol; this isomer leads to an intermediate kinetic behavior (89% conversion in 6 hours). Such results thus tend to support the important role of the ammonium group on the phenolate anion activity toward the hydrogen bonding and ionic nucleophilic activation of the propagating alcohol center.

In order to rationalize the different kinetics of the betaine isomers, complexes made of PyOH and betaine isomers have been optimized at the density functional theory level (B97D/6-

31G(d,p)). Interestingly, while the OH bond length of PyOH remains almost constant whatever the isomer (1.00 Å, 1.01 Å, and 1.02 Å for complexes involving the *ortho*, *para*, and *meta* isomers, respectively), the interaction between the phenolate anion and the proton of PyOH is stronger for the *meta* compared to the *ortho* and *para* isomers, as evidenced by the reduced distance between these two atoms (1.57 Å for the complex involving the *meta* isomer vs. 1.67 Å and 1.65 Å for its counterparts with the *ortho* and *para* compounds, respectively), see Figure 1. The high selectivity of the polymerizations thus appears to be intimately linked to the formation of hydrogen bonds while the drop in the polymerization rates going from the *meta* to the *para* and *ortho* isomers is rationalized by a decrease in the strength of the hydrogen bonds and hence in the reduced ionic character of the nucleophile.

To demonstrate the versatility of the *m*-BE catalyst, a variety of alcohols was used, such as 1,4-butanediol and poly(ethylene oxide) monomethyl ether (PEO-OH) (M_n = 5,000 g/mol) (Table 1, entries 9 and 10). ROPs were conducted in CHCl₃ at r.t. for a targeted DP of 100. Conversions of 99% were obtained after 3 hours with very low Đ_M (≤ 1.17). In the case of the PEO-OH initiator, the SEC revealed the formation of a block copolymer without unreacted macroinitiator (Figure SI8). The ¹H NMR spectrum (Figure SI9) of the PLLA generated from the symmetrical 1,4-butanediol shows beside signals of the methine main-chain protons (δ 5.0-5.3) those due to the CH₂ groups of the initiator incorporated into the centre of each PLLA chains (δ 4.15, H_b) going along with signals of capping lactoyl end-groups (δ 4.35, H_c). The ratio integrations (H_b/H_c) equals 1.93. This is close enough to 2, and indicates that the LA ROP is expected to proceed from both hydroxyl groups of the initiator leading ultimately to a symmetrical structure.

The ring strain of L-LA clearly provides a driving force for the ROP and also a kinetic preference for the polymerization over the transesterification. However, the extraordinary selectivity of the *m*-BE was also demonstrated for both trimethylenecarbonate (TMC) and benzylester trimethylenecarbonate (TMC-Bn) ROPs. The results (Table 1,

entries 11-14) indicate that the polymerization of TMC and TMC-Bn gives no evidence of transesterification ($\bar{D}_M \leq 1.1$) when a DP of 100 is targeted. Higher DPs such as 500, characterized by an extended polymerization time (~200 hours), imply however a slight increase of the \bar{D}_M as far as TMC ROP is concerned. As is the case for the hydrogen bonding mechanism,¹¹ these data suggest that the low dispersity values and exceptional control observed are a consequence of the selective transesterification of cyclic monomers relative to open chains. BEs are effective catalysts for alcohol activation, at least sufficiently to promote both polymerizations of LA and TMC-based monomers in an acceptable period of time. This alone is insufficient activation to quickly effect the ROP of ϵ -caprolactone (ϵ -CL) (entries 15-16, Table 1). As for other organic bases efficient in alcohol activation,¹² a simultaneous activation of the CL carbonyl group (by a thiourea surrogate for example) would be of help to improve the general polymerization kinetics.

Conclusions

In summary, ammonium betaines exhibit an exceptional selectivity in the ring-opening polymerization of L-lactide and cyclic carbonates. The *meta* isomer (*m*-BE) induces a more pronounced ionic nucleophilic activation of the initiating and propagating alcohol site, allowing for a very rapid polymerization process while maintaining excellent control. When compared to representative nucleophilic¹¹⁻¹³ and hydrogen-based systems,^{12,14-20} *m*-BE combines the positive aspects of both processes in terms of kinetics and selectivity.

Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures, selected MALDI-ToF, FT-IR and NMR spectra, selected DSC and SEC traces, starting geometries and time evolution of selected geometrical parameters]. See DOI: 10.1039/b000000x/

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