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Catalyst Chelation Effects in Organocatalyzed Ring-Opening Polymerization of Lactide

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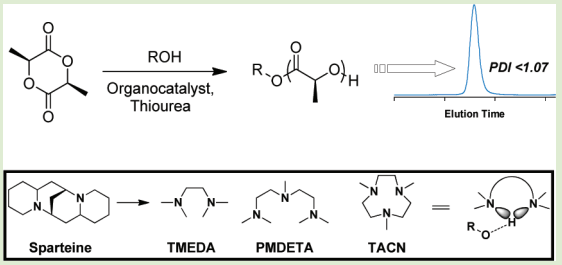
Supporting Information

ABSTRACT: (−)-Sparteine is a proven organocatalyst for the ring-opening polymerization (ROP) of L-lactide, which affords polymers of controlled molecular weight and narrow polydispersity. The recent worldwide shortage of (−)-sparteine has necessitated the identification of simple and cost-effective replacement ROP catalysts. A series of commercially available molecules was first identified through molecular modeling and then subsequently investigated for polymerizing L-lactide. The modeling proved very useful at predicting spatial relationships and nitrogen geometries that greatly aided in the rapid identification of various alkyl amines as alternative organocatalysts.



The naturally occurring lupin alkaloid, (−)-sparteine, is most commonly isolated from cytisus scoparius (scotch broom).[1,2] As a chiral diamine, it was originally used in various asymmetric reactions such as lithiations, substitutions, and carbometalations.[2−6] Its utility in the aforementioned reactions can be attributed to its tetracyclic bis-quinolizidine ring system that effectively locks both nitrogens into an ideal metal chelating conformation (Figure 1).[7] Additionally, (−)-sparteine has proven itself to be an extremely effective catalyst for ring-opening polymerizations (ROP).[8−10] The same attributes that made it an excellent metal ligand, optimal spacing of intramolecular nitrogens and their corresponding fixed lone pair orientations, also allowed it to engender ROP by coordination of initiating/propagating alcohols (Figure 1). Furthermore, (−)-sparteine's mild basicity provided sufficient nucleophilic activation while encouraging virtually no deleterious transesterification.[11] As a consequence of this low basicity, polymerizations catalyzed by (−)-sparteine required a cocatalyst to provide accelerated reaction kinetics.[12] Additionally, no experimentally discernible differences in reaction rate or polymer tacticity have been observed when polymerizing either enantiomerically pure or racemic lactide monomers while using (−)-sparteine.[8,13] This result revealed that catalyst chirality had essentially no effect on the polymerization reaction (Figure 2a).

With so many research applications and an abundant plant source, it is very surprising that (−)-sparteine has become difficult if not impossible to acquire. This scarcity prompted us to seek alternatives to fill the void caused by the (−)-sparteine shortage. Computational modeling suggested that (−)-sparteine surrogates could be identified by their requisite spatial conditions and nitrogen lone pair orientations. We performed B3LYP/6-31+G*[14−22] density functional geometry optimizations with a continuum dielectric model for CH_2Cl_2 using IEF-cPCM,[23,24] as implemented in GAMESS-US.[25,26] Examination of (−)-sparteine's geometric structure shows nitrogen atoms spaced at approximately 3.02 Å with lone pairs oriented 44° above the *N*−*N* plane (Figure 2b); we surmised that replication of these values would produce new ROP catalysts. Herein, the identification of commercially available amines able to mimic (−)-sparteine and produce controlled polymerizations of L-lactide is presented.

Because (−)-sparteine does not have any resonance enhanced basicity (e.g. DBU and TBD),[28] its catalytic activity was expected to originate from rigid nitrogen spacing and lone pair orientation rather than increased proton association. This prompted the modeling of various multiamino compounds for comparison against the (−)-sparteine metric (Figure 3). The first compound evaluated was *N*,*N*,*N*″,*N*′-tetramethylethylenediamine (TMEDA). Through free rotation about its various σ-bonds, TMEDA was calculated to have an active conformation with nitrogens spaced approximately 3.07 Å apart with an orientation angle of 60°. These values are a relatively close approximation of (−)-sparteine (Table 1); however, upon experimentation,[29] TMEDA proved to catalyze L-lactide polymerizations at a much slower rate (85% conversion after 24 h). This result was explained because TMEDA must adopt a thermodynamically unfavorable eclipsed conformation in order to assume its active state. To test this supposition *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane[30] (TMDAC) was evaluated. Unfavorable 1,3-diaxial interactions force the vicinal nitrogens into an equatorial conformation increasing its relative time spent in the catalytic state. Similar to TMEDA the catalytic conformation exhibited nitrogens spaced 2.90 Å with an orientation angle of 54°. When used to polymerize L-lactide, it

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proved effective but still required a protracted reaction time (2 h) in comparison to (−)-sparteine (Table 1).

An alternative strategy for the amplification of catalytic activity was to increase the relative amount of active states. Through the addition of an alkyl amine, exemplified by *N*,*N*,*N*′,*N*″,*N*″-pentamethyl diethylenetriamine (PMDETA), it was envisioned that more active conformations would be created thus encouraging faster kinetics. Calculations confirmed that in fact PMDETA could achieve more catalytic states by its terminal nitrogens independently adopting active forms. Modeling further showed that the central nitrogen was spaced 3.18 Å from its respective outer nitrogen having an orientation angle of 58°. Upon polymerizing L-lactide, PMDETA was found to be considerably faster producing full conversion in 1.5 h. This concept was further explored by evaluating tris[2-(dimethylamino)ethyl]amine (Me_6TREN). The addition of yet another dimethylaminoethane group served to change the calculated active confirmation such that the nitrogen atoms were spaced 3.25 Å apart with an orientation angle of 60°. Despite it having the greatest divergence from the (−)-sparteine dimensions, Me_6TREN proved to be even faster than PMDETA, catalyzing full conversion of L-lactide in under 15 min.

Because restricting degrees of freedom and increasing active states both accelerated polymerization kinetics, their combination was expected to further bolster catalytic activity. A molecule combining these principles was found using 1,4,7-trimethyl-1,4,7-triazacyclononane (TACN). This compound had nitrogen atoms spaced 3.03 Å apart with an orientation angle of 53°, the closest replication of (−)-sparteine values of any catalyst tested. Not surprisingly, it showed the fastest polymerization kinetics demonstrating full conversion in less than 10 min.

For further comparison, both 1,4-diazabicyclo-[2.2.2]octane (DABCO) and triethylamine (TEA) were evaluated. DABCO has a suitable nitrogen spacing of 2.58 Å; however, its lone pairs are oriented in opposite directions (180°) preventing chelative proton association. As a consequence, slow activity was observed for this catalyst (85% conversion after 24 h). To ensure intramolecular chelative effects (a manifestation of N−N spacing and orientation angle) were vital to catalytic activity, TEA with only a single nitrogen was used to polymerize L-lactide. After 24 h, only 78% monomer conversion was found. Thus, the activity of TEA is slower than all other chelating catalysts investigated.[8]

To replicate the catalytic ability of (−)-sparteine, a prospective surrogate must also show exceptional fidelity. Sparteine became a ROP catalyst of choice because it showed minimal ability to promote deleterious transesterification and epimerization reactions. The absence of chain transfer events can be attributed to its mild basicity, as stronger bases such as TBD and DBU demonstrate rapid and extensive transesterifications. Because (−)-sparteine generally does not undergo such reactions, it produces extremely narrow polydispersities (polylactide commonly is produced, <1.08 PDI). When comparing (−)-sparteine's basicity to the previously mentioned catalysts all show comparable values.[28,31] To test whether or not a prospective catalyst promoted chain transfer, they were all individually stirred with a polylactide standard (M_n = 28 kDa; PDI, 1.06) under analogous polymerization conditions.[32] After 4 h little if any experimentally discernible changes to polymer size and PDI were observed via refractive index or UV−vis detection for all catalysts except TACN. The cyclic triamine

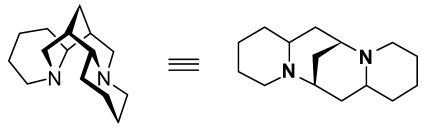

Figure 1. Molecular structure of (−)-sparteine.

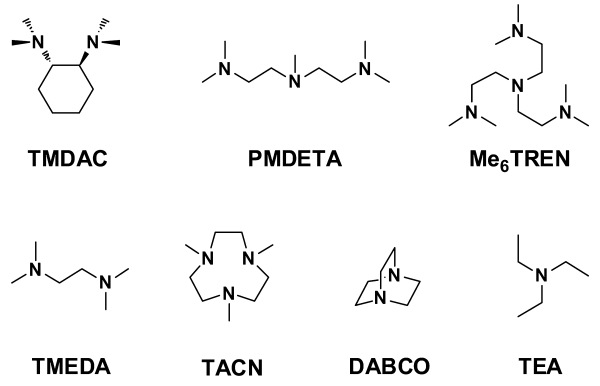

Figure 3. Various nitrogenous catalysts.

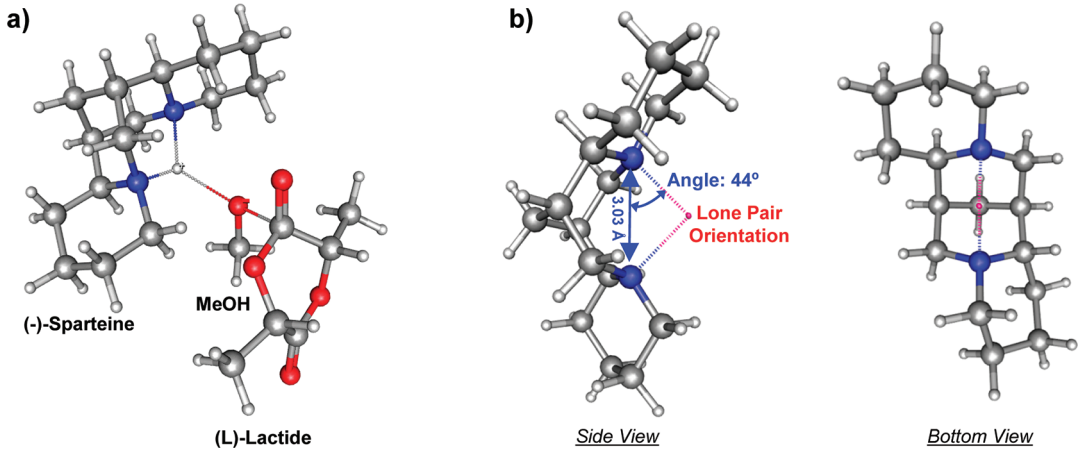

Figure 2. (a) Approximate geometry of the rate limiting step of (−)-sparteine catalyzed ROP of L-lactide with methanol[27] showing no dependence on catalyst chirality and (b) the calculated distance between N atoms along with the lone pair angle extending from the *N*−*N* plane.

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Table 1. Experimental and Calculated Data for the Various Organocatalysts Tested

compound	spacing[a] (Å)	angle[b] (deg.)	rxn time[c] (min)	conv. (%)	M_n (kDa)	PDI	ΔPDI[d]
sparteine	3.02	44	<10	>99	25	1.06	0.01
TMEDA	3.07	60	24 h[f]	85	24	1.06	0.01
TMDAC	2.90	54	120	>99	27	1.05	0.01
PMDETA	3.18	58	90	>99	26	1.06	0.00
Me_6TREN	3.25	60	15	>99	23	1.07	0.02
TACN	3.03	53[e]	<10	>99	27	1.06	0.25
TEA	N/A	N/A	24 h[f]	78	19	1.05	0.00
DABCO	2.58	180	24 h[f]	85	21	1.05	0.01

[a]Distance calculated between two nitrogen centers for its reactive conformation. [b]Determined by calculating the angle between the N−N plane and the N lone pair orientation. [c]Polymerizations were run in 2.3 M DCM using 1-pyrenebutanol as an initiator. The ratio of monomer/catalyst/initiator was 100:5:1 with an additional 5 equiv of thiourea. [d]This value was obtained by taking the difference between the original poly(lactide) standard PDI (1.06) and the PDI after 4 h of catalyst exposure. [e]TACN has two different angles, 56 and 51°, which were averaged. [f]The reaction was stopped after 24 h, regardless of conversion.

proved to readily digest the resultant polymer upon full conversion. Any catalyst instigated epimerization on the resultant polymers was evaluated using differential scanning calorimetry. Isotactic poly(lactide) was found to have a melting temperature (T_m) of 153 °C, whereas atactic poly(lactide) was 117 °C.[33] Polymers formed using the catalysts found in Table 1 all showed very little change in T_m and were found to range from 147 to 155 °C, signifying monomer chirality was minimally effected during the polymerization.

Catalyst hybridization was also found to be a key component in determining activity. It is well-known that as *s*-character increases ($sp^3 \rightarrow sp^2$) basicity decreases; to evaluate this effect on L-lactide ROP *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamine (TMNDA), tris(2-pyridylmethyl)amine (TPMA), and 1,8-bis-(tetramethylguanidino)naphthalene (BTMGN) were also evaluated. All three were found to adopt appropriate *N*−*N* spacings and lone pair orientations (SI Figures 8−10), but as expected, both TMDNA and TPMA showed almost no activity after 24 h presumably due to their weakened proton affinity. Conversely, the increased basicity imparted by the guanidino moieties of BTMGN did show polymerization activity. However, the mechanism of this activity was found to be different than that of the previously mentioned organocatalysts and will be the subject of a future report.

In conclusion, commercially available (−)-sparteine alternatives for the ROP of (−)-lactide have been investigated. Using molecular modeling the activity of (−)-sparteine was found to stem from the rigid distance between nitrogens (3.02 Å) and the orientation angle of their respective lone pairs (44°). These two factors facilitated chelative association of hydroxyl protons rendering propagating alcohols more nucleophilic. Subsequent identification of compounds that achieve similar conformations yielded new catalyst candidates. Catalyst activity was found to continually increase through the addition of active conformations and restriction of molecular mobility. Both paradigms allowed for a greater catalyst population within the respective active state providing augmented reaction kinetics. Of the commercially available catalysts investigated, Me_6TREN showed the most similar performance to (−)-sparteine with respect to the polymerization rate, low PDI, and absence of any observable transesterification. These findings show that new catalysts can be readily developed by three factors: (1) basicity, (2) chelative spacing, and (3) appropriate orientation of basic lone pairs.

■ ASSOCIATED CONTENT

Supporting Information

Molecular modeling experiments and GPC results for all compounds tested. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

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(33) The isotactic and atactic polylactide T_m values were obtained by polymerizing pure L-lactide and (*rac*)-lactide, respectively, using (−)-sparteine/thiourea as the reaction catalyst. All polymers were initiated from 1-pyrenebutanol with a targeted DP of 100.