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Evans Enolates: Solution Structures of Lithiated Oxazolidinone-Derived Enolates

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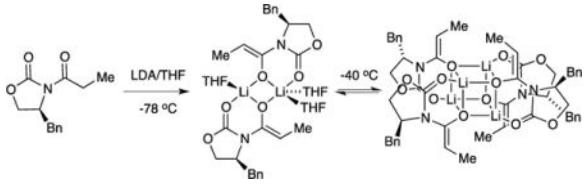
Abstract

The results of a combination of ^{6}Li and ^{13}C NMR spectroscopic and computational studies of oxazolidinone-based lithium enolates—Evans enolates—in tetrahydrofuran (THF) solution revealed a mixture of dimers, tetramers, and oligomers (possibly ladders). The distribution depended on the structure of the oxazolidinone auxiliary, substituent on the enolate, and THF concentration (in THF/toluene mixtures). The unsolvated tetrameric form contained a D_{2d}-symmetric core structure, whereas the dimers were determined experimentally and computationally to be trisolvates with several isomeric forms.

TOC image



Introduction

A seminal paper by Evans, Bartroli, and Shih in 1981 introduced oxazolidinone-based chiral auxiliaries (eq 1)[1] in which boron-based enolates offered spectacular selectivities for aldol additions central to the synthesis of polyketides. Although aldol additions via analogous lithium enolates were notably unselective, Evans and coworkers soon revealed their importance in highly selective alkylations.[2] What followed is now history: oxazolidinone-based chiral enolates—so-called Evans enolates—have appeared in more than 1600 patents and countless academic and industrial syntheses.[3] Variations of the auxiliaries[4] and extensions of oxazolidinones beyond the chemistry of enolates[5] attest to their importance.

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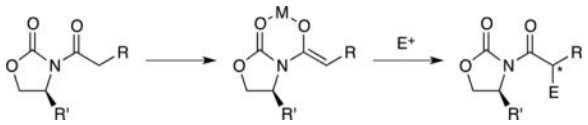
Supporting Information: Spectra, additional Job plots, and authors for reference 18. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interests.



(1)

Despite rapid and broad developments of Evans enolates in synthesis, structural and mechanistic studies of these compounds remain conspicuously rare.[6,7] Presumably the absence of crystal structures stems from limiting physical properties rather than a lack of interest; we have joined the ranks of those who have failed to grow diffractable crystals. Spectroscopic determination of the structures of enolates in solution is inherently difficult owing to the absence of usable O–M scalar coupling, and we have found only a single spectroscopic study of a boron-based Evans enolate.[6a,6b] The paucity of computational studies is most vexing,[6] but computations of the lithium enolates unsupported by experimental data would be of limited value regardless.[8,9]

We describe herein NMR spectroscopic and computational studies of a number of oxazolidinone-derived lithium enolates. The general structural types are illustrated in Scheme 1. The auxiliary- and solvent-dependent structural assignments are summarized in Table 1, and limited data on an additional 28 enolates are archived in the supporting information. We focus on the propionate enolate **5** (see Table 1) derived from phenylalanine owing to its importance in synthesis[3,4a], and structural tractability. In a subsequent paper we will offer insights into why aldol additions based on lithiated Evans enolates are so challenging[1,10,11,12] while possibly nudging them out of relative obscurity.

Results

Structure Determinations

General Strategies—Our structural studies required a variety of tactics and analytical methods, which centered on the method of continuous variations (MCV) delineated in a series of previous papers.[13,14] In short, the high symmetry of lithium enolate aggregates is broken by mixing two enolates, generically denoted as $\mathbf{A}_n$ and $\mathbf{B}_n$ in eq 2, to afford an ensemble containing heteroaggregates whose numbers, spectral symmetries, and concentration dependencies reveal the aggregation number, *n*. A plot of the relative concentrations of the aggregates versus measured[15] mole fraction of the enolate subunits (*X*) affords Job plots[14,16] (see Figure 2, for example) that confirm the aggregation number. If two homoaggregates coexist (dimers and tetramers, for example), assigning one with MCV allows us to assign the other by monitoring their proportions versus the total enolate titer.

$$\mathbf{A}_n + \mathbf{B}_n \text{âđľ} \mathbf{A}_n + \mathbf{A}_{n-1}\mathbf{B}_1 + \mathbf{A}_{n-2}\mathbf{B}_2 + \mathbf{A}_{n-3}\mathbf{B}_3 + \ldots \mathbf{B}_n \quad (2)$$

Solvation numbers were probed by using several methods. Pyridine is a ^{6}Li chemical shift reagent: solvated ^{6}Li nuclei shift markedly (0.5–1.5 ppm)[17] downfield, whereas unsolvated nuclei do not shift detectably. The relative tetrahydrofuran (THF) solvation numbers can be

quantitated by monitoring the homoaggregate dimer–tetramer proportions versus THF concentration (with a hydrocarbon cosolvent). When guided by detailed experimental data, density functional theory (DFT) computations[18] offer particularly compelling insights. A few computational results are salted throughout the text; extensive computations are archived in the supporting information. A summary of the auxiliary- and condition-dependent results is found in Table 1.

Enolization

The enolates were generated using [^{6}Li] lithium diisopropylamide ([^{6}Li]LDA) or [^{6}Li,^{15}N]LDA[19] in THF as illustrated in Scheme 2. At −80 °C the enolization proceeds through mixed dimer **20** (*d*, $J_{Li–N}$ = 5.2 Hz).[20] The single resonance indicates that the chelate in **20** is either nonexistent or the exchange is fast on NMR time scales. Broadening at lower temperatures suggested the latter. The enolization can be completed by either holding the temperature at −78 °C or warming to −40 °C. The results are *not* the same, however. Enolization at −78 °C affords exclusively dimer as the *kinetic* product, which is stable for hours. Warming to −40 °C equilibrates the homoaggregates, affording distributions of dimers and tetramers that are sensitive to enolate and THF concentrations. We focus exclusively on equilibrated mixtures in this report and reserve discussion of unequilibrated mixtures[21] for a subsequent treatise on the aldol addition.

Solvated Dimers

Neat THF solutions of hindered enolates **7** and **18** at −80 °C each display a single ^{6}Li resonance. Both also show marked (>0.6 ppm) downfield shifts with the addition of pyridine, which attests to the importance of solvation analyzed quantitatively below.[17,22] The ^{6}Li resonances of **7** and **18** are sufficiently well-resolved for the use of MCV (Figure 1). Thus, varying the proportions in mixtures of **7** and **18** at a constant total enolate titer revealed a single heteroaggregate consistent with enolate dimers. Plotting the relative integration versus the measured mole fraction of enolate subunit **18** ($X_{\mathbf{B}}$) afforded a Job plot (Figure 2) consistent with a nearly statistical $\mathbf{A_2}$–**AB**–$\mathbf{B_2}$ mixture of homo- and heterodimers (see Table 1). An alternative approach that we originally applied to hexameric β-amino ester enolates[13a] involves varying the mole fraction (optical purity) of two enantiomers (eq 3). The resulting Job plot obtained with *R*/*S* mixtures of **7** (Figure 3) was a bit unusual in showing only two curves because the homochiral dimers [(*R*)–**7**]$_2$ and [(*S*)–**7**]$_2$ ($\mathbf{A_2}$ and $\mathbf{B_2}$, respectively) were indistinguishable. In a perfectly statistical (1:2:1) distribution, the two curves in Figure 3 would intersect at a relative aggregate concentration of 0.50 (*y* axis) and *X* = 0.50 (*x* axis).

$$[(R)-\mathbf{7}]_2+[(S)-\mathbf{7}]_2 \rightleftharpoons 2[(R)-\mathbf{7}][(S)-\mathbf{7}] \quad (3)$$

We occasionally obtained glimpses of spectral complexity consistent with coexisting symmetric and unsymmetric dimers and tentatively assigned them as **2** and **3**, respectively. The ^{6}Li resonance attributed to dimers was often broad, decoalescing at temperatures below −80 °C to give two dimer-derived resonances (Figure 4) and occasionally as many as three in especially hindered cases such as **7**. The intensities of the various dimer resonances are

independent of enolate and solvent concentration, attesting to the common aggregation and solvation numbers. Two resonances manifested a 1:1 integration, which suggested a single unsymmetric dimer consistent with (but by no means definitively supporting) structure **3**. Facile coalescences of the putative dimer resonances *but not the tetramer resonance* between −80 and −95 °C were consistent with isomer exchanges. In general, however, dimer isomerism eluded detailed experimental scrutiny; all we know for certain is that symmetric and unsymmetric variants are observable in some samples.[23,24]

Computational studies at the B3LYP level of theory with the 6–31G(d) basis set and MP2 correction offered some insights.[8] The reported energies are free energies at −78 °C and do not account for translational entropy (Scheme 3).[25] Symmetric dimer **2a** derived from enolate **5** displayed favorable solvation up to the trisolvate, consistent with experiment. No tetrasolvates were found. Several spatial orientations (puckering) of **2** were detected; **2a** is the most favorable. Similar tendencies toward trisolvation were observed for spirocycle **3a** relative to the disolvated forms. Although the trisolvated spirocyclic **3a** displayed no stereoisomerism, the disolvated spirocyclic dimer can exist as energetically equivalent stereoisomers **3b** and **3c**. In general, dimers are promoted by high steric demands and high THF concentration. They are the sole observable form for only a handful of substrates, with valine-derived propionate **10** being the most notable.

Dimer–Tetramer Mixtures

Enolate **5** forms a mixture of dimers **2** and **3** and unsolvated tetramer **1** with a D_{2d}-symmetric core. Raising the enolate concentration or reducing the THF concentration (toluene cosolvent) favored tetramer **1**, with the tetramer becoming the exclusive form at concentrations of <3.0 M THF (see Figure 4). The concentration dependencies attest to the higher aggregation state and lower per-lithium solvation number of the tetramer relative to the dimer. Adding low concentrations of pyridine causes a marked shift of only the dimer-derived resonances (Figure 5), which shows that the tetramer is unsolvated. The merits of pyridine as a shift reagent and diagnostic probe of solvation are considerable.

Empirical studies of dozens of pairs of enolates in which we probed for adequate resolution of the complex tetramer ensemble led us to pairings of the substitutionally similar propionyl-derived enolate **5** and butyryl-derived enolate **6**. The ensembles generated from these mixtures were extraordinarily complex (Figure 6). Traces of pyridine were added to shift the dimer resonances downfield of the ensemble. The resonance count of 16 within the ensemble matched that predicted for tetramers assuming slow chelate exchange within tetramers bearing a D_{2d}-symmetric core (Chart 1). By contrast, the corresponding S_4 tetramers would produce 32 resonances in total. (We return to the distinction of S_4 and D_{2d} below.) No amount of tinkering provided sufficient resolution to produce a convincing Job plot, however.

We turned to more traditional strategies to assign the higher aggregate (*n*-mer) as a tetramer. A plot of the relative concentration of enolate dimer and *n*-mer versus total concentration (eqs 4 and 5 and Figure 7) afforded an aggregation number of $n = 4.1 \pm 0.1$, consistent with a tetramer. Moreover, given that the tetramer was unsolvated, a plot of dimer–tetramer

proportion versus THF concentration (eqs 6 and 7 and Figure 8) afforded a solvation number of *3* (*m* = 2.86 ± 0.04) for the dimer.[24] Computations support the trisolvation assignment (*vide infra*).

$$\mathrm{A}_n \overset{K_{\mathrm{eq}}}{\rightleftharpoons} n/2\ \mathrm{A}_2 \quad (4)$$

$$[\mathrm{A}_2]^{n/2}/[\mathrm{A}_n]=K_{\mathrm{eq}} \quad (5)$$

$$\mathrm{A}_4 \overset{K_{\mathrm{eq}}[\mathrm{S}]^{2m}}{\rightleftharpoons} 2\mathrm{A}_2\mathrm{S}_m \quad (6)$$

$$[\mathrm{A}_2\mathrm{S}_m]^2/[\mathrm{A}_4]=K_{\mathrm{eq}}[\mathrm{S}]^{2m} \quad (7)$$

Tetramers **1** and **4** can be distinguished spectroscopically in that *chiral* chelates of **1** display a single ^{6}Li resonance and a single set of ^{1}H and ^{13}C resonances, whereas tetramer **4** with an S_4-symmetric core should show duplication of all resonances.[13b] At −100 °C we saw neither duplication nor even hints of broadening, which provided strong, albeit indirect, evidence of **1**.

Computationally, we detected a modest preference for the D_{2d} tetramer (**1a**) relative to the experimentally unobserved S_4 isomer (**4a**; see Scheme 4). Although comparisons of dimers and tetramers are dubious (non-isodesmic),[26] we note that the computations showed that the deaggregation is nearly thermoneutral (without accounting for translational entropy affiliated with solvation[25]).

Monomers

Monomers have not been observed in THF solution. Computations show that the deaggregation of disolvated dimers to give trisolvated monomers costs 1.7 kcal/mol/lithium. As an aside, the most hindered substrates, such as **7** and **18** (see Table 1), afford monomers with added *N,N,N′,N′*–tetramethylcyclohexanediamine, a chelating diamine with a high capacity to deaggregate organolithium aggregates.[20]

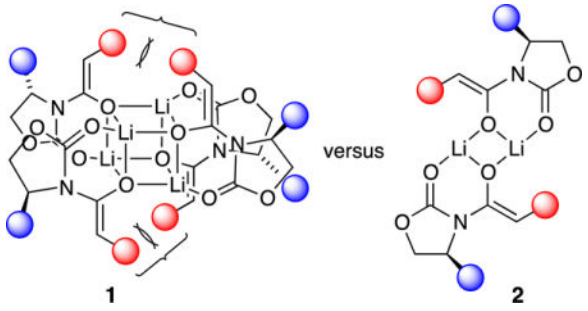
Discussion

The lithiation of acylated oxazolidinones is fast relative to the rates at which the resulting lithium enolate aggregates equilibrate (see Scheme 2). Although evidence is mounting that aging effects are consequential to reactivity,[9b,21] such aggregate dynamics are *not* the topic of this paper. All assignments stem from fully equilibrated mixtures of homoaggregates obtained using the combination of tactics outlined at the beginning of the results section. The use of MCV (Job plots) is only a portion of the strategy, but it is the lynchpin for providing clear assignments for the dimers. Monitoring the THF- and enolate-concentration-dependent equilibria provided the additional data needed to finish assigning the aggregation and solvation states, with computational chemistry adding some nuance. In summary,

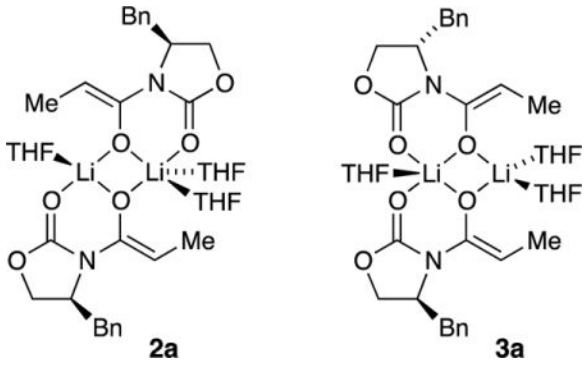
lithiated Evans enolates can reside as exclusively dimers, dimer–tetramer mixtures, exclusively tetramers, or even mixtures of oligomers (possibly ladders of variable lengths[27]) depending on the choice of auxiliary, enolate substituent, and THF concentration (see Scheme 1 and Table 1).

Dimers

Deaggregation is driven by several forces. High steric demands can *destabilize* higher aggregates, as illustrated below with color-coded depictions of tetramer **1** and dimer **2**. Thus, exceedingly hindered enolates bearing substituted oxazolidinones *and tert*-butyl groups on the enolate moieties afford exclusively dimers. Although the dominant dimeric forms are symmetric dimer **2**, we observed fleeting glimpses of less symmetric, demonstrably isomeric (equivalently solvated and aggregated) forms suggested by computational studies to be spirocyclic dimer **3**.



Dimers are also *stabilized* relative to tetramers by solvation. Incremental additions of pyridine—a form of NMR shift reagent that markedly shifts *solvated* ^{6}Li nuclei downfield[17]—qualitatively confirmed the presence of ligated solvents on the dimers (see Figure 5). Quantifying the dimer–tetramer ratio benchmarked to unsolvated tetramers showed that **2a** and **3a** are trisolvated. DFT computations concurred (see Scheme 3).



Tetramers

Intermediate steric demands—steric demands akin to the standard propionate-based Evans enolate **5** used in synthesis—and reduced THF concentrations promote tetramer formation. Although the ensembles used to assign tetramers with MCV (see Figure 6) showed a peak

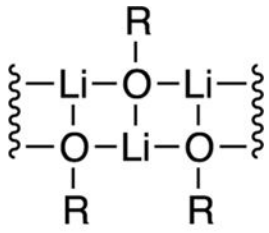
count (see Chart 1) consistent with tetramers bearing D_{2d}-symmetric cubic cores (**1**), the resolution thwarted Job plot analysis. Nonetheless, quantitation of the dimer–tetramer equilibrium confirmed the tetramer aggregation state, and the use of pyridine as a shift reagent confirmed that the tetramers are unsolvated (see Figure 5).

The two tetrameric forms, **1** and **4**, bearing D_{2d} and S_4 core symmetries (respectively) are both precedented in the crystallographic literature of chelated lithium salts.[28,29] Even knowing the enolates were tetrameric, it would have been difficult to predict the stereochemistry. The ^{6}Li and ^{13}C resonance counts for the homotetrameric aggregates as well as within the ensemble of heterotetramers (see Figure 6), however, strongly support the D_{2d} form (**1**). Although absence of evidence is not *necessarily* evidence of absence, we are satisfied with the assignment. Moreover, the DFT computations in Scheme 4 support the D_{2d} tetramer, albeit by a narrow margin.

Bolstered by casual inspection of reported crystal structures of chelating lithium salts showing both S_4 and D_{2d} forms,[28,29] we suspect that steric congestion promotes the S_4 forms. We explored this putative preference for **1** computationally by focusing on a variety of unsubstituted and substituted oxazolidinones and found that all prefer the D_{2d} tetramer **1** over the S_4 tetramer **4** but without any obvious sterically determined trends. Thus, the oxazolidinone substituent does not appear to be a strong determinant of the tetramer stereochemistry. The oxazolidinone substituents do, however, seem to be important in precluding oligomerization.

Oligomers

Low steric demands exemplified by unsubstituted oxazolidinones (see Table 1, **10–14**) afford intractable broad mounds in the ^{6}Li NMR spectra irrespective of temperature. Additional examples are described in the supporting information. We suspect that some minimum level of substitution is required to preclude laddering (**21**). The popular valine-derived propionate enolate **10** (see Table 1) sits on the cusp: it is dimeric in neat THF solution **10** but oligomeric at low THF concentrations. A delicate balance appears to be required to differentiate tetramers and oligomers.



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Conclusions

Organolithium chemists have enjoyed the huge advantages offered by ^{6}Li-X scalar coupling (X = ^{13}C and ^{15}N) for characterizing complex aggregates. There are, however, a host of organolithium salts and other organometallic aggregates for which no such scalar coupling

can be observed. The results herein underscore the importance of some of the tricks we can use—MCV, concentration dependencies, pyridine as a chemical shift reagent, and computations—to study the solution structures of lithium enolates. We are optimistic that these strategies will continue to evolve.[9]

Characterization of the iconic Evans enolates is also a key to understanding the structure–reactivity relationships of *synthetically* important enolates. The various enolate aggregates described herein have likely been impacting yields and selectivities even without the full appreciation of their consequences by practitioners. The epic struggle by Singer et al.[12a] at Pfizer to develop a plant-scale aldol addition featured a lithiated Evans enolate. This story is remarkable given the paucity of lithium-based aldol condensations with Evans enolates.[11,12]

One topic mentioned only in passing is that warming is required for full equilibration of homoaggregated Evans enolates. Slow aggregate exchange in enolates has been noted previously,[21] most notably in seminal studies of enolates at very low temperature by Reich.[9b,f] One could imagine, therefore, that exceedingly fast reactions such as aldol additions might be *very* different under non-equilibrium and equilibrium conditions. By contrast, slow reactions such as alkylations[2,3] may be impervious to the observable forms, simply funneling through whatever fleeting form offers the route of least resistance to product. We have little doubt that a multitude of mechanisms exist for the various reactions of Evans enolates. Of course, we are merely foreshadowing forthcoming mechanistic studies already in progress.

Experimental

Reagents and Solvents

THF and toluene were distilled from solutions containing sodium benzophenone ketyl. The toluene stills contained approximately 1% tetraglyme to dissolve the ketyl. LDA, [^{6}Li]LDA, and [^{6}Li,^{15}N]LDA were prepared as described previously.[19] Solutions of LDA were titrated for active base by using a literature method.[30] Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques. The Evans enolate precursors were either purchased or prepared as described previously.[4] Several previously unreported precursors were prepared by acylating[1] the oxazolidinones, which were prepared from the amino alcohol and diethylcarbonate[31] as described in the supporting information.

NMR Spectroscopy

Individual stock solutions of substrates and LDA were prepared at room temperature. An NMR tube under vacuum was flame-dried on a Schlenk line and allowed to return to room temperature. It was then backfilled with argon and placed in a −78 °C dry ice/acetone bath. The appropriate amounts of oxazolidinone and LDA (1.1 equiv) were added sequentially via syringe. The tube was sealed under partial vacuum, vortexed three times on a vortex mixer for 5 s with cooling between each vortexing, and stored in a freezer at −20 °C. Samples were stored for days at −86 °C. Each sample routinely contained 0.10 M total enolate with a 0.005 M excess of LDA. (The excess base forms mixed dimers **20** with the resulting enolates, which were characterized with ^{6}Li and ^{15}N NMR spectroscopy.) Standard ^{6}Li and ^{13}C NMR

spectra were recorded on a 500 MHz spectrometer at 73.57 and 125.79 MHz, respectively. The ^{6}Li and ^{13}C resonances are referenced to 0.30 M [^{6}Li]LiCl/MeOH at −90 °C (0.0 ppm) and the CH_2O resonance of THF at −90 °C (67.57 ppm).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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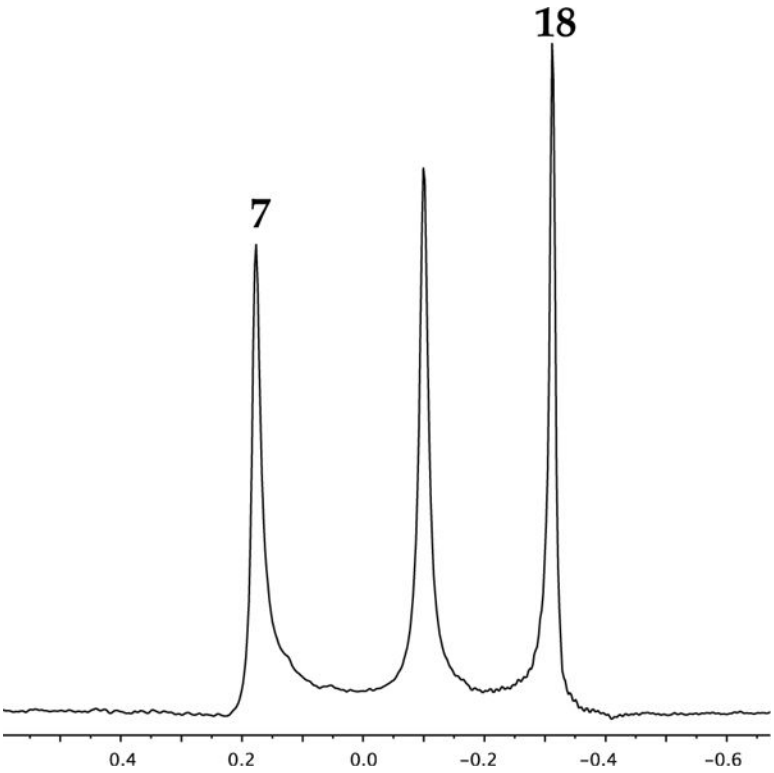


Figure 1.

Equimolar mixture of dimeric **7** and **18** (0.10 total enolate concentration) in neat tetrahydrofuran (THF) at −80 °C showing a single heterodimer resonance.

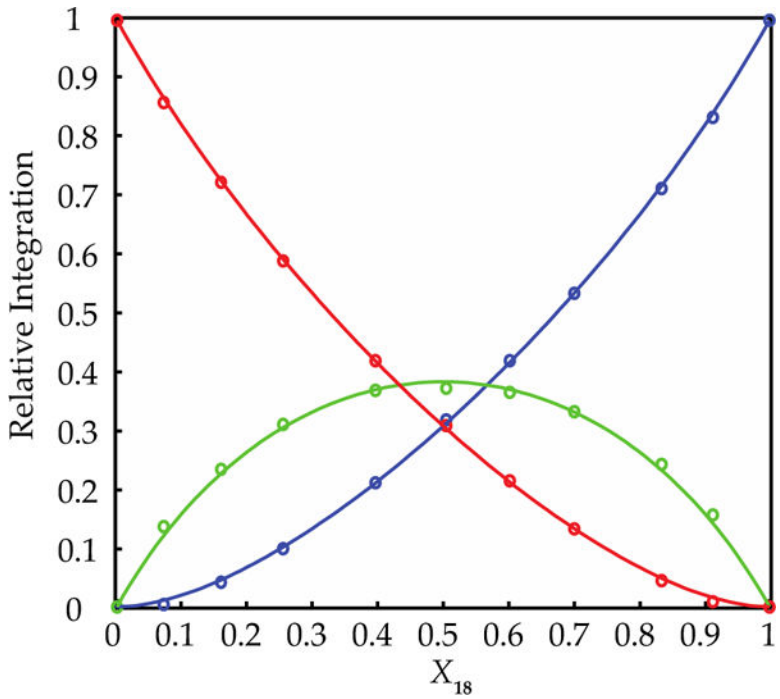


Figure 2.

Job plot of dimeric **7** and **18** at fixed (0.10 M) total enolate concentration in neat THF at −80 °C. The relative integrations are plotted as a function of the mole fraction of **18**.

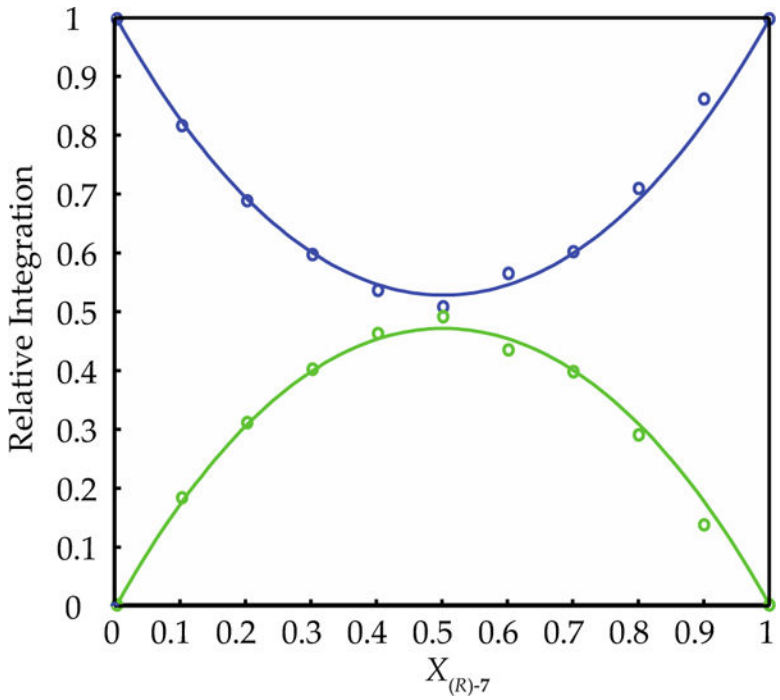


Figure 3.

Job plot of (*S*)-**7** and (*R*)-**7** dimers (0.10 M total enolate concentration) in neat THF at −80 °C. The relative integrations of the homoaggregates and the heteroaggregate are plotted as a function of the mole fraction of (*R*)-**7**.

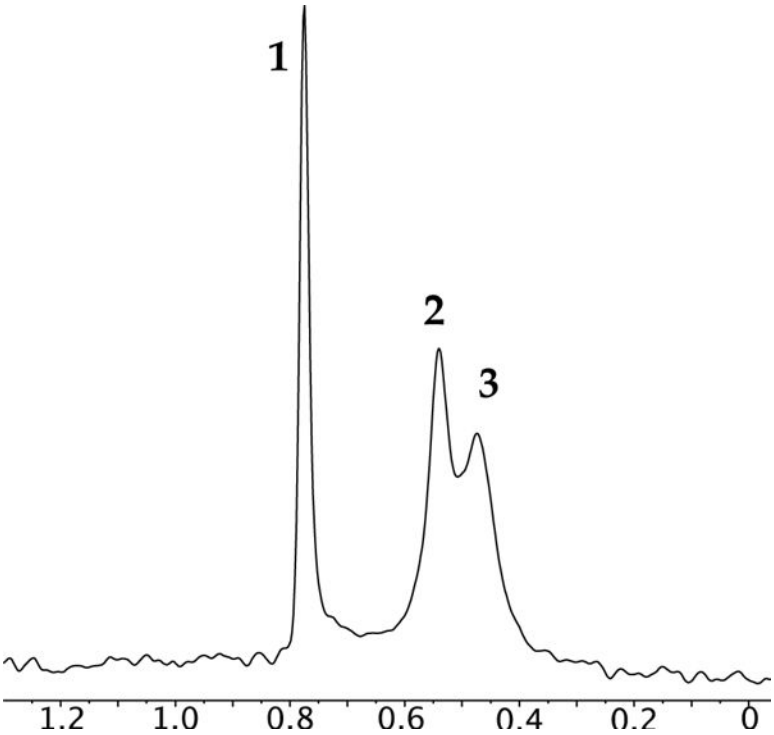


Figure 4.

^{6}Li NMR spectrum of **5** (0.10 M total concentration) in neat THF at −80 °C showing equilibrium populations of tetramer **1** and isomeric dimers **2** and **3**.

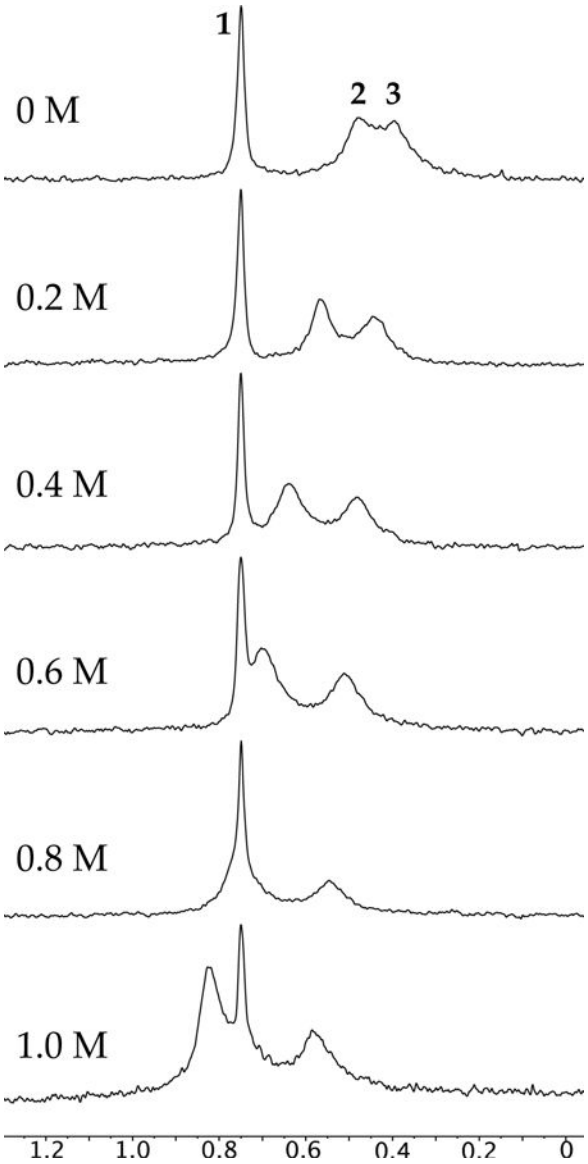


Figure 5.

^{6}Li spectra of **5** (0.10 M) with various pyridine concentrations (as labeled) in neat THF at −80 °C.

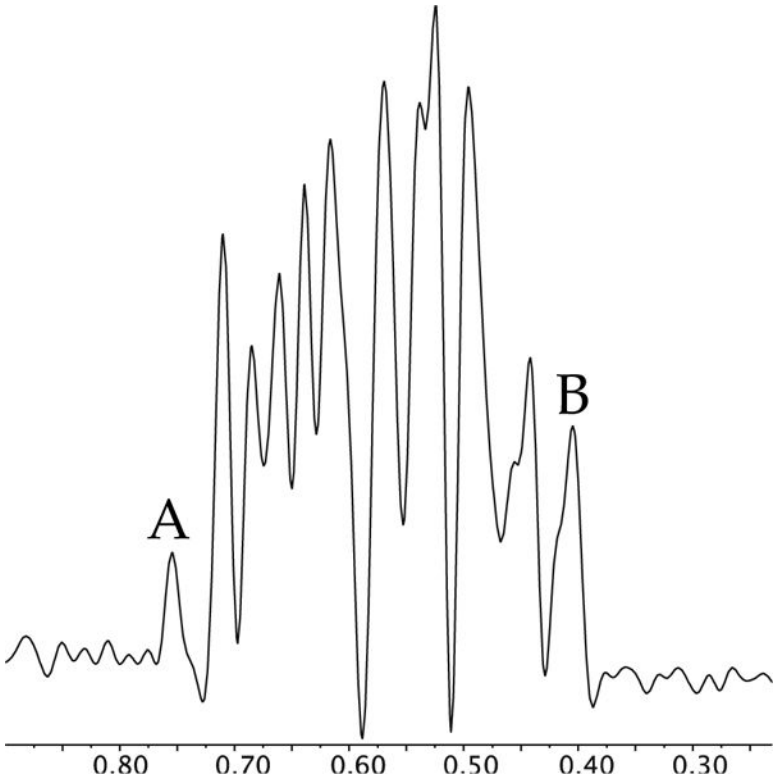


Figure 6.

Equimolar mixture of tetramers derived from enolates **5** and **6** (0.050 M **5**, 0.050 M **6**) with 0.20 M THF and 1.0 M pyridine in toluene at −60 °C. A and B correspond to the homotetramers of **5** and **6**, respectively.

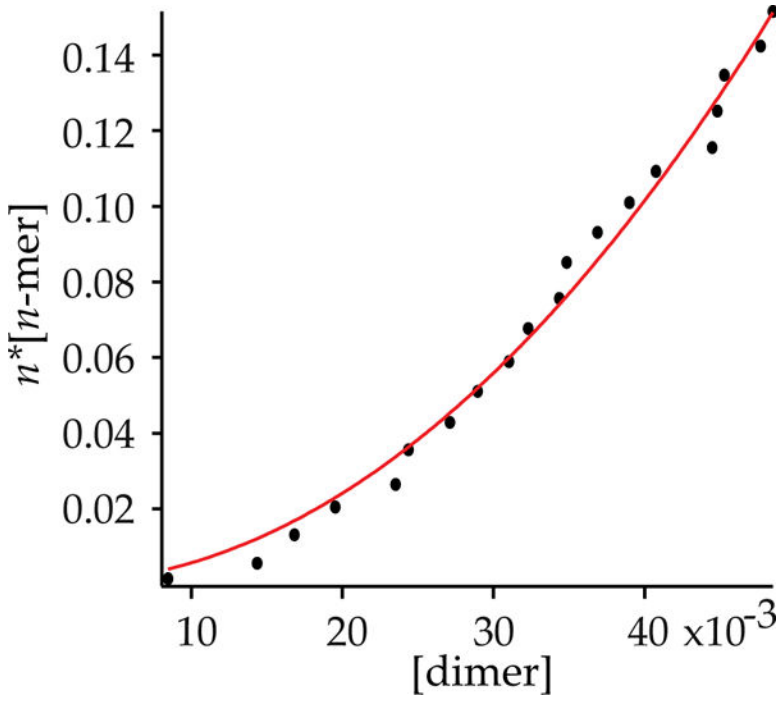


Figure 7.

Plot of concentration of dimeric **5** versus enolate normality to determine the tetramer aggregation state in neat THF at −60 °C. The curve corresponds to a best fit of $y = n^*K_{eq}^{1/2}(x^{n/2})$, such that $y = n^*[n\text{-mer}]$, x = [dimer], and n = aggregation number of the n-mer. The fit shows that n is 4.1 ± 0.2.

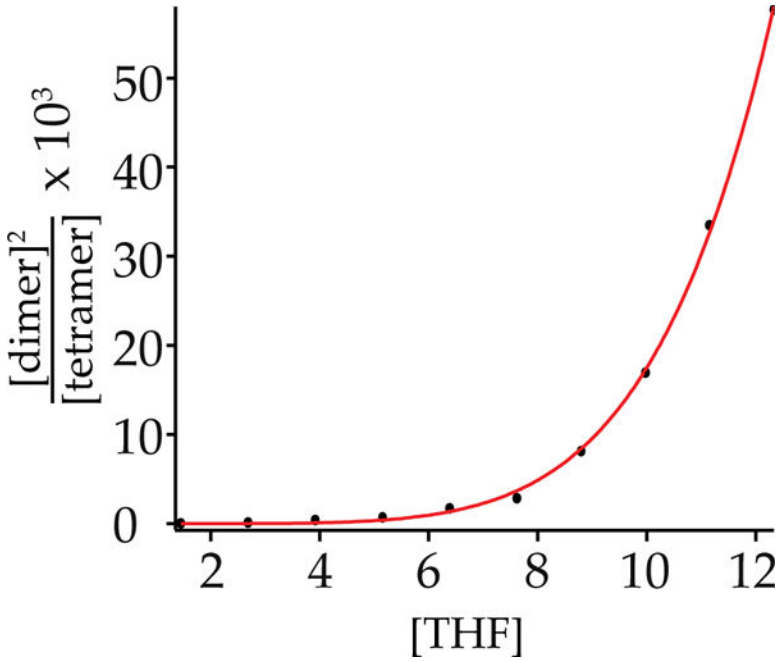
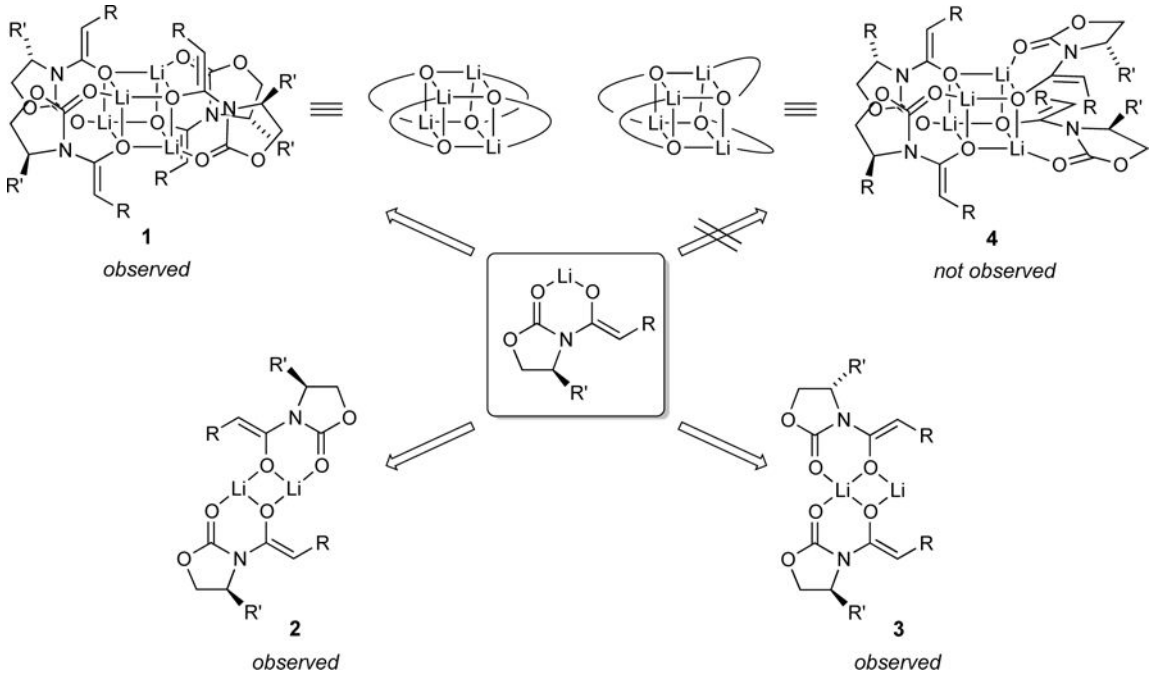
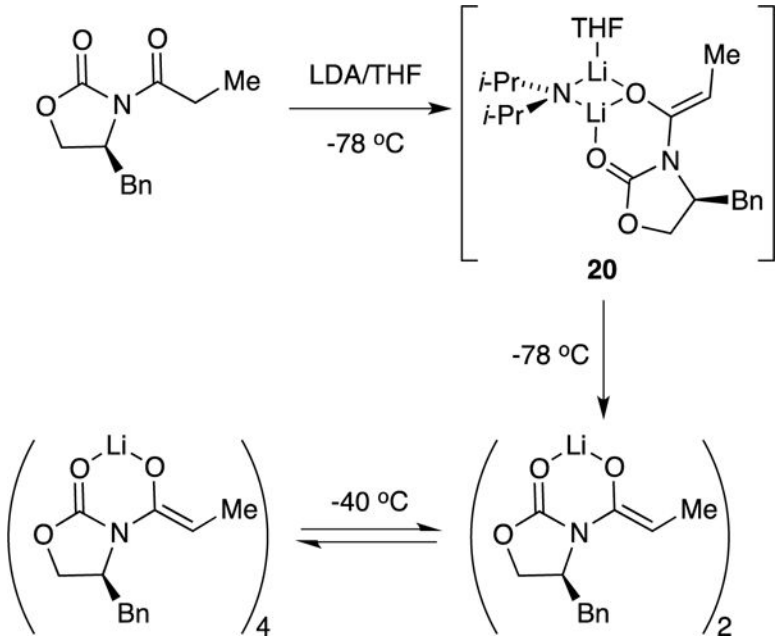


Figure 8.

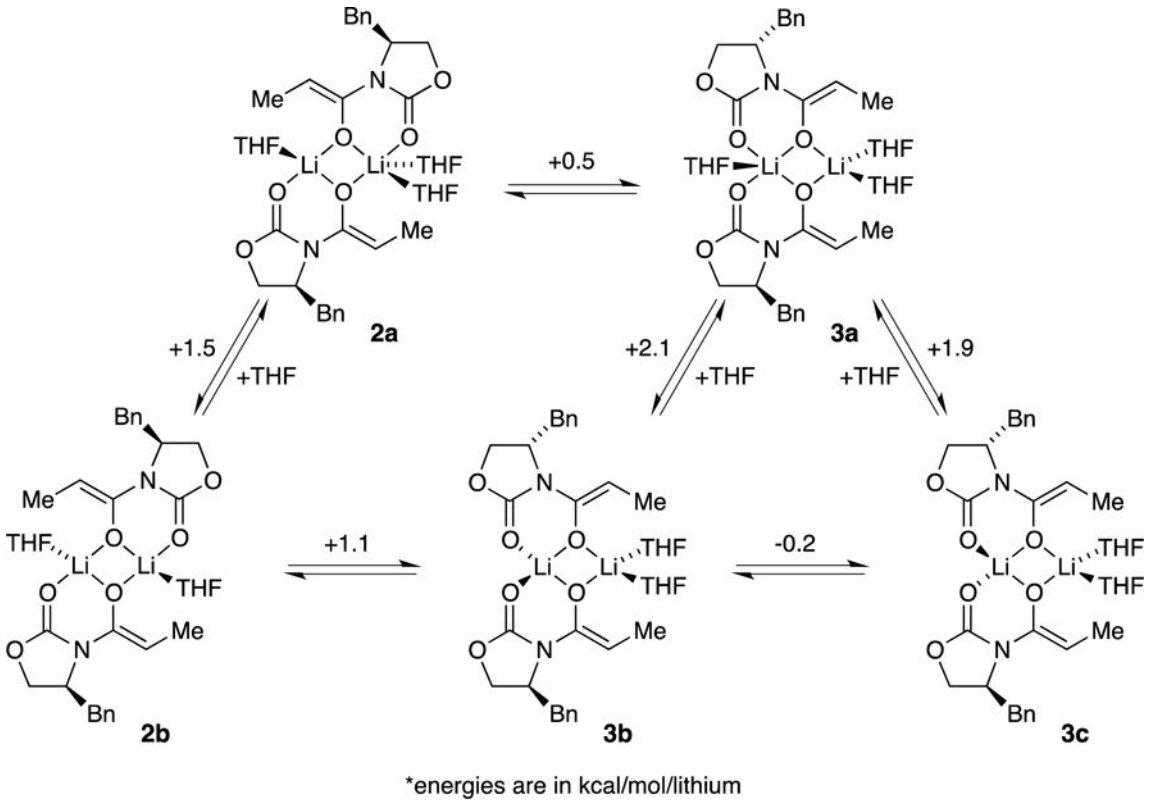
Fit of aggregate concentration versus THF concentration for enolate **5** at −60 °C. The curve corresponds to a best fit of eq 7 (m = 2.86 ± 0.04).



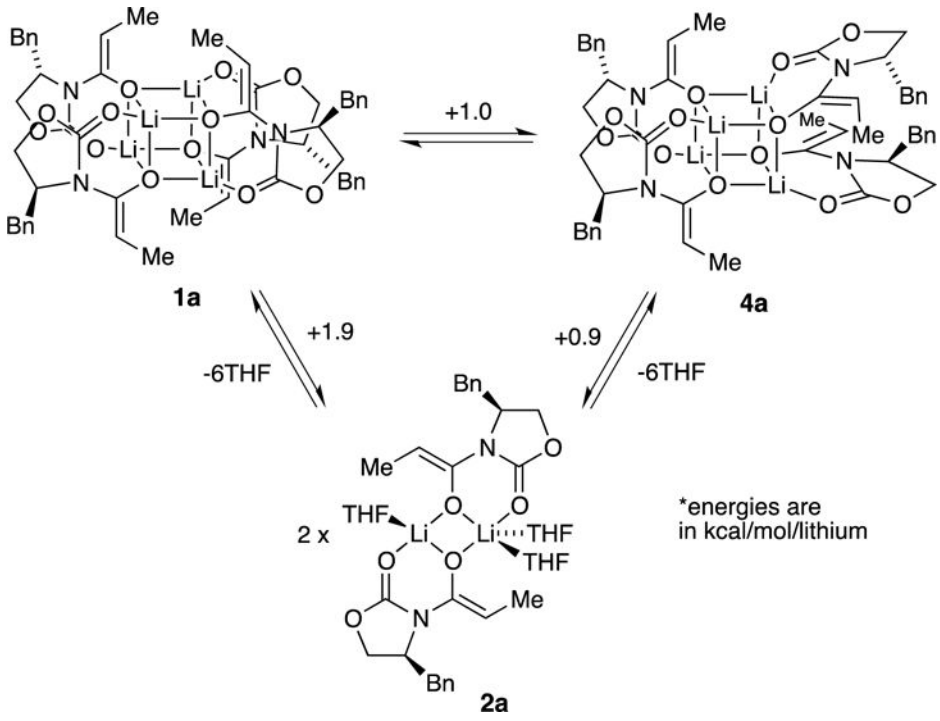
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

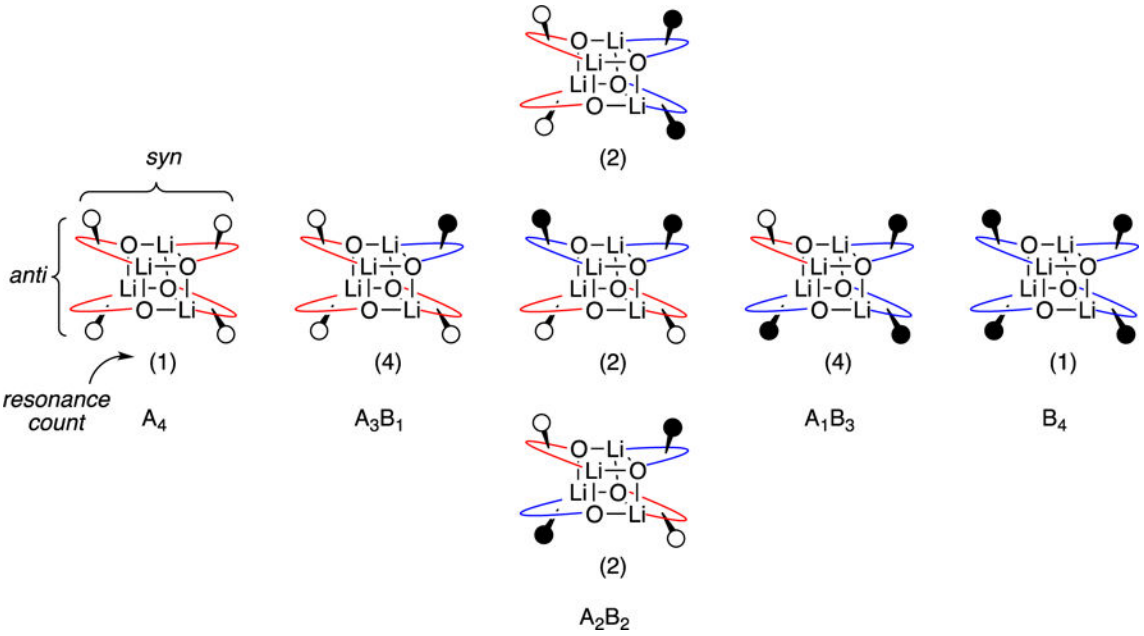
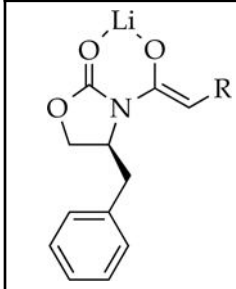
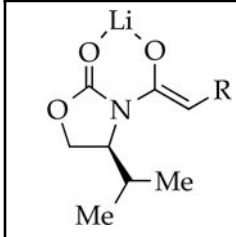
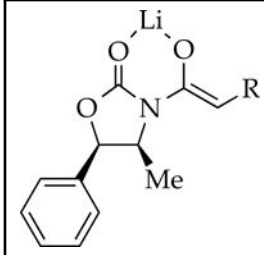
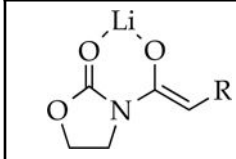
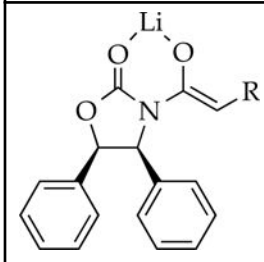
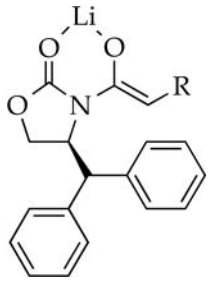
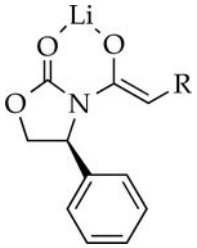
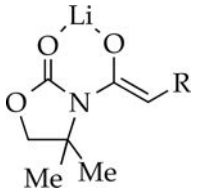


Chart 1.

Table 1

Structures of oxazolidine-derived enolates (0.10 M) in tetrahydrofuran (THF)/toluene and THF solutions at −80 °C corresponding to tetramers (**1**) and dimers (**2** and **3**).

enolate	R	cmpd	0.20 M THF	neat THF
	Me	**5**	tetramer	dimer/tetramer
	Et	**6**	tetramer	dimer/tetramer
	t-Bu	**7**	dimer	dimer
	Bn	**8**	dimer	dimer
	Ph	**9**	oligomers	oligomers
	Me	**10**	oligomers	dimer
	Ph	**11**	oligomers	oligomers
	Bn	**12**	oligomers	dimer
	Me	**13**	oligomers	oligomers
	Me	**14**	oligomers	oligomers
	Me	**15**	dimer	dimer

enolate	R	cmpd	0.20 M THF	neat THF
	Me	**16**	dimer	dimer
	Bn	**17**	dimer	dimer
	*t*-Bu	**18**	dimer	dimer
	Me	**19**	oligomers	oligomers