Structures of β-Amino Ester Enolates:

New Strategies Using the Method of Continuous Variation

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Abstract

The solution structures of four enolates derived from β-amino esters are investigated using ^{6}Li NMR spectroscopy in conjunction with the method of continuous variation (method of Job). Ensembles of homo- and heteroaggregated enolates are generated by mixing enantiomers of a single enolate (R/S mixtures), opposite antipodes of two different enolates (R/S' mixtures), and the same antipodes of two different enolates (R/R' mixtures). The numbers of observable aggregates and their dependence on the mole fraction of the two enolates confirm the hexamer assignments. Inherent symmetries observable in the ^{6}Li NMR spectra show the stereochemistry of chelation about the hexagonal drum.

Introduction

Very few reactive intermediates have captivated the attention of organic chemists more than lithium enolates.[1] It is not surprising, therefore, that the underlying physical organic chemistry of enolates has garnered attention as well.[2,3] Understanding structure-reactivity relationships of lithium enolates, however, requires knowing the structures of the aggregates.[4,5,6] From the early structural studies of Jackman[7] up to the more recent studies of Streitwieser,[8] and others, [9,10,11] progress has been made, but it is slow and, at times, contentious.[11] The challenge stems in large part from a combination of high aggregate symmetries (cf., **1**-**4**) and Li-O linkages that are opaque to NMR spectroscopy.[12]
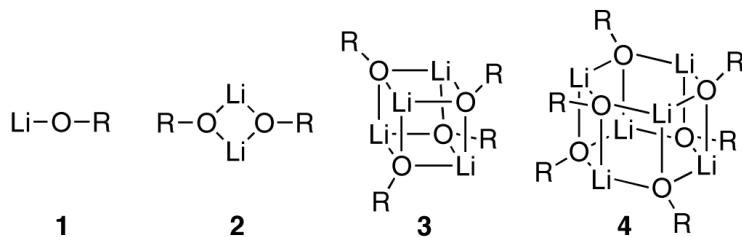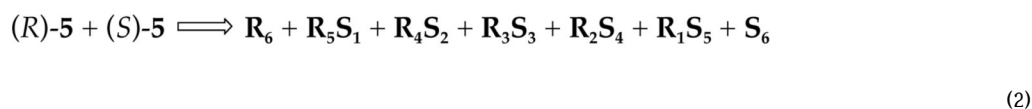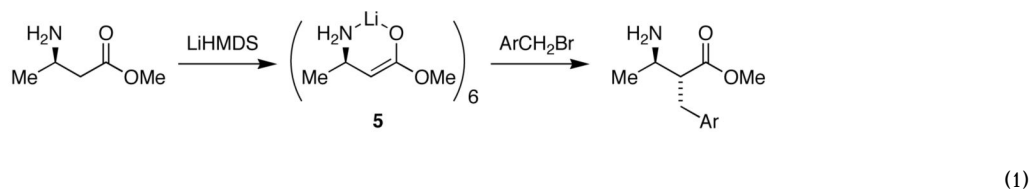

As part of a collaboration with Sanofi-Aventis to develop a plant-scale synthesis of Otamixaban,[13] we were charged with the task of studying the alkylation of β-amino esters (eq 1).[14] Although the mechanistic insights were interesting, it was the characterization of enolate **5** that proved acutely challenging. We solved the problem by generating an ensemble of

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aggregates from mixtures of antipodes (R)-**5** and (S)-**5** (eq 2). ^{6}Li NMR spectroscopy showed that the number and relative integrations of the aggregates were highly characteristic of hexamers and inconsistent with monomers, dimers, and tetramers. The protocol formally falls under the rubric of the method of continuous variation[15] (also called the method of Job[16]), which has found widespread application in chemistry and biochemistry.[17] This strategy has now been generalized to a range of enolates representing the aggregates (2-4) anticipated from crystallographic studies.[18, 19]

(1)

$$(R)\text{-}\mathbf{5} + (S)\text{-}\mathbf{5} \implies \mathbf{R_6} + \mathbf{R_5S_1} + \mathbf{R_4S_2} + \mathbf{R_3S_3} + \mathbf{R_2S_4} + \mathbf{R_1S_5} + \mathbf{S_6}$$

(2)

The study described herein focuses on the structures of β-amino ester enolates **6-8**. By analogy to **5**, enolates **6-8** were expected to form hexameric drums of general structure **9**, and, indeed, they do. We focused on hexamers because they offer unique opportunities to examine new strategies and tactics.

5; R = Me
6; R = i-Pr
7; R = CH$_2$Ph
8; R = Ph

9
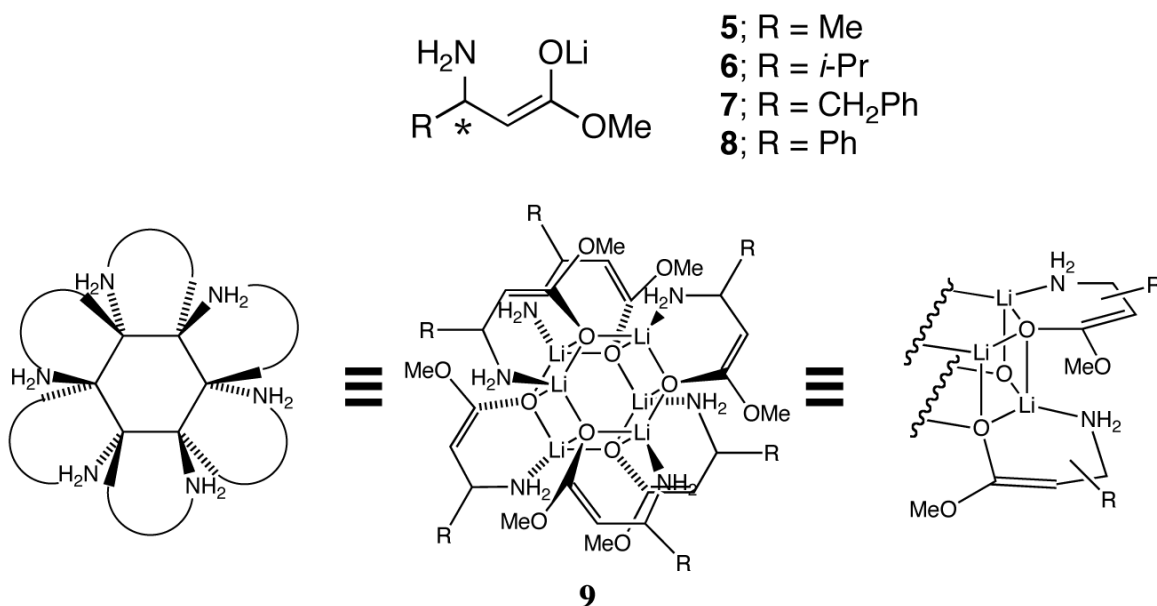
Background

Applying the method of continuous variation to large ensembles in general and enolates **5-8** in particular presents acute challenges. Merely resolving a large number of species

spectroscopically can be problematic given the relatively narrow (≈3 ppm) spectral range of [6]Li, constituting a major focus throughout this manuscript. In addition, enolates **5**-**8** present considerable complexities stemming from stereoisomerism within the chelates (cf., **10**-**12**) and positional isomerism (cf., **13** and **14**) characteristic of the hexagonal drum.[20] Indeed, [6]Li NMR spectra recorded at the lowest attainable NMR probe temperatures (< -100 °C) are often intractably complex. Warming the probe, however, elicits rapid chelate-chelate,[21] conformational exchange,[22] and intraaggregate lithium-lithium exchanges,[23] which cause the spectra to simplify.[24,25] Rapid intraaggregate exchange in conjunction with slow *inter*aggregate exchange causes each aggregate to appear as only a single [6]Li resonance and affords separate resonances only for aggregates differing by subunit composition (cf., 4:2 versus 3:3 mixed aggregates; **14** and **15**) or by virtue of their aggregation numbers (tetramers versus hexamers). Monitoring the relative [6]Li resonance integrations as a function of mole fraction of the enolate mixtures and subsequent parametric fits[3,14] afford multicomponent Job plots that prove highly diagnostic of aggregation state. Representative Job plots and new strategies for exploiting ensembles of β-amino ester enolates are described below.
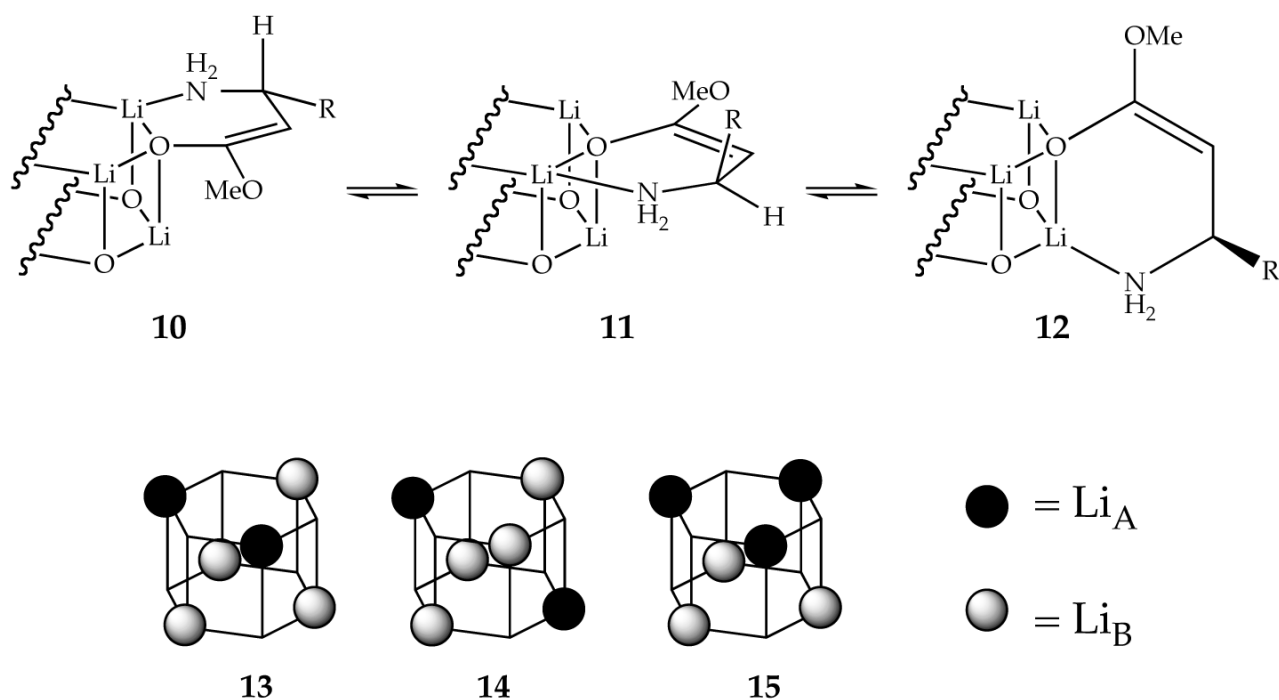
Results

We examined three strategies for characterizing enolates **6**-**8**. Table 1 summarizes the predicted number of spectroscopically distinct structural forms observed for hexamers.[26] In the first section, we describe mixtures of *R* and *S* enantiomers (so-called R/S mixtures) derived from a single β-amino ester enolate. This approach used to characterize enolate **5**[14] is extended to enolates **6**-**8**. A stereochemical degeneracy simplifies the [6]Li NMR spectra. In the subsequent two sections, ensembles were generated from two structurally distinct enolates derived from opposite stereochemical series (R/S' mixtures) and from the same stereochemical series (R/R' mixtures). R/S' and R/R' mixtures lift the stereochemical degeneracy (Table 1). The three

strategies present different technical challenges and offer complementary views of the hexameric aggregation state.[27]

R/S Mixtures

We first examined the structures of enolates **6**-**8** using R/S mixtures derived from a single enolate following the protocol established previously.[14] Enantiomeric pairs of aggregates-- **R₆**/**S₆**, **R₅S₁**/**R₁S₅** and **R₄S₂**/**R₂S₄**.-are degenerate, resulting in ensembles comprising four rather than seven observable aggregates (Table 1). (Note: **RₘSₙ**/**RₙSₘ** refers to spectroscopically indistinguishable pairs of enantiomerically related aggregates.) Characterization of the isopropyl derivative **6** is illustrated emblematically as follows. [6]Li NMR spectra recorded on R/S mixtures of enolate **6** under conditions optimized for fast *intra*aggregate exchange and slow *inter*aggregate exchange (9.0 M THF in toluene, -20 °C) reveal four distinct resonances consistent with an ensemble of hexamers and inconsistent with monomers, dimers, and tetramers (Table 1).[3] Serial dilution at fixed R/S proportions showed that the integrations are concentration independent, confirming a common aggregation number.

The integrations of the resonances corresponding to the **RₘSₙ** aggregates of **6** were monitored as a function of mole fraction of the R and S antipodes. The equilibria are described according to eqs 3-5. A parametric fit affords the Job plot shown in Figure 1. The fit to the hexamer model is excellent. The **R₃S₃** form is inordinately stable. Figure 2 displays the curves predicted from a purely statistical model.

$$2\mathbf{R_3S_3} \overset{K_1}{\rightleftharpoons} \mathbf{R_6} + \mathbf{S_6} \tag{3}$$

$$2\mathbf{R_3S_3} \overset{K_2}{\rightleftharpoons} \mathbf{R_5S_1} + \mathbf{R_1S_5} \tag{4}$$

$$2\mathbf{R_3S_3} \overset{K_3}{\rightleftharpoons} \mathbf{R_4S_2} + \mathbf{R_2S_4} \tag{5}$$
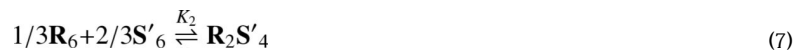
The corresponding analysis of benzyl-substituted enolate **7** in 9.0 M THF at -25 °C revealed only three resonances, consistent with either an ensemble of tetramers (**R₄**/**S₄**, **R₃S₁**/**R₁S₃**, and **R₂S₂**) or an ensemble of hexamers in which two resonances are unresolved. Failure of the tetramer-based model was suggested by a poor parametric fit (Figure 3). By contrast, the fit to a hexamer model assuming the two resonances corresponding to the **R₃**/**S₃** and **R₄S₂**/**R₂S₄** hexamers are superimposed afforded a distinct improvement (Figure 4). The latter fit is further justified by the sporadic appearance of the fourth resonance as a shoulder. A similar problem surfaced during the analysis of R/S mixtures of phenyl-substituted enolate **8** in which resonances corresponding to **R₆** and **R₅S₁**/**R₁S₅** do not resolve in 9.0 M THF. In the case of **8**, however, all four [6]Li resonances fully resolve in 3.0 M THF/toluene, affording a Job plot of comparable quality to that in Figure 1 consistent with hexamers (Supporting Information).

R/S' Mixtures

We examined mixtures of structurally distinct enolates derived from opposite absolute configuration (R/S' mixtures).[27] The R/S' mixtures should be similar to the R/S mixtures except that the enantiomeric degeneracy has been removed: An ensemble of **RₘS'ₙ** hexamers would appear as *seven* discrete aggregates (Table 1). Resolution of *seven* [6]Li resonances was, at times, more difficult because intraaggregate exchange rates varied slightly among aggregates

of different stoichiometries. Parametric fits[3,14] to equilibria in eqs 6-10 were carried out in each case. The studies were arbitrarily restricted to mixtures of enolates **6**-**8** with enolate **5**. (No such restriction would exist in the event that an enolate resists characterization.)

$$1/6\mathbf{R}_6 + 5/6\mathbf{S'}_6 \overset{K_1}{\rightleftharpoons} \mathbf{R}_1\mathbf{S'}_5 \tag{6}$$

$$1/3\mathbf{R}_6 + 2/3\mathbf{S'}_6 \overset{K_2}{\rightleftharpoons} \mathbf{R}_2\mathbf{S'}_4 \tag{7}$$

$$1/2\mathbf{R}_6 + 1/2\mathbf{S'}_6 \overset{K_3}{\rightleftharpoons} \mathbf{R}_3\mathbf{S'}_3 \tag{8}$$

$$2/3\mathbf{R}_6 + 1/3\mathbf{S'}_6 \overset{K_4}{\rightleftharpoons} \mathbf{R}_4\mathbf{S'}_2 \tag{9}$$

$$5/6\mathbf{R}_6 + 1/6\mathbf{S'}_6 \overset{K_5}{\rightleftharpoons} \mathbf{R}_5\mathbf{S'}_1 \tag{10}$$

Analysis of R/S' mixtures of enolates **5** and **6** was reasonably successful. All seven resonances were readily observed. At nearly equimolar concentrations ($X_{(R)-5} = 0.4$-0.6), the resonances corresponding to $\mathbf{R_4S'_2}$ and $\mathbf{R_2S'_4}$ were readily observed but difficult to accurately integrate separately. Accordingly, the two resonances were summed, affording the Job plot illustrated in Figure 5. The increased stability of $\mathbf{R_3S'_3}$ was anticipated from results for the R/S mixtures (vide supra).

R/S' mixtures derived from enolates **5** and **7** also successfully afforded a Job plot, albeit with the requisite summation of the resonances corresponding to $\mathbf{R_4S'_2}$ and $\mathbf{R_2S'_4}$ (Supporting Information). By contrast, R/S' mixtures of **5** and **8** afford ensembles of aggregates that are qualitatively familiar, but poor resolution precludes a detailed analysis.

R/R' Mixtures

Mixtures of structurally distinct enolates derived from the same stereochemical series (R/R' mixtures) afford an ensemble of seven spectroscopically distinct hexamers. Each of the $\mathbf{R_mR'_n}$ hexamers should mimic the optically pure ($\mathbf{R_6}$) forms. Success depended critically on the choice of enolates.

[6]Li spectra of R/R' mixtures derived from enolates **5** and **8** in the limit of rapid intraaggregate exchange (-10 °C) display seven well-resolved resonances bracketed by the resonances of homoaggregates of **5** and **8** (Figure 6). The resulting Job plot (Figure 7) is both instructive and aesthetically pleasing. (Figure 7 represents a single parametric fit displayed in two parts for visual clarity.) Superposition of the curves from the parametric fit in Figure 7 with the analogous curves anticipated from a purely statistical distribution shows a striking similarity (Figure 8).

R/R' mixtures derived from methyl- and isopropyl-substituted enolates **5** and **6** (respectively) presented minor resolution problems. The [6]Li signals of $\mathbf{R_6}$ and $\mathbf{R_5R'_1}$ (R = **5**; R' = **6**) were

observable as discrete resonances but were poorly resolved, requiring summation of their integrations when fitting the data (Supporting Information). Mixtures of the methyl- and benzyl-substituted enolates **5** and **7** afforded a poorly-resolved ensemble of aggregates due to a small chemical shift dispersion.

Stereochemistry of Chelation

With the hexameric aggregation state established, it is instructive to examine the ^{6}Li NMR spectra recorded in the low temperature limit in which all *intra*aggregate exchanges are slow. We discuss the results in the context of the possible structural forms shown in Chart 1. Spectra are archived in Supporting Information.

Let us first consider the structures of the **R$_3$S$_3$** hexamer available as the predominant species in equimolar R/S mixtures (racemates). **R$_3$S$_3$** hexamers derived from racemates of **5-8** display an inordinate stability relative to less symmetric counterparts of unequal stoichiometry. Of the three high-symmetry structural types represented by **A**, **B**, and **C**, isomers **A** and **C** should each display a single ^{6}Li resonance, whereas **B** should display a pair of resonances in a 1:1 ratio. Isomer **B** appears to be excluded. In light of the crystal structure of **5** showing a hexamer of type **A**,[14] we deem **A** as the probable form in solution. The orientation in the alkyl substituents away from the perimeter of **A** also logically accounts for the unusual stability.

The **R$_3$S'$_3$** hexamers formed from the R/S' mixtures (pseudo racemates) display the same unusual stability as the **R$_3$S$_3$** aggregates. The reduced symmetry of **R$_3$S'$_3$** hexamers causes the R antipodes to reside on one hexagonal face and the S' antipodes on the other, resulting in two ^{6}Li resonances (1:1). Warming causes the two resonances to coalesce, which we attribute to intraaggregate exchange of the lithium nuclei. Although this experiment does not distinguish **A** and **C**, the consistency with **A** is satisfying.

The homochiral (**R$_6$** and **S$_6$**) aggregates appear to be hexagonal drum **D**. The R$_6$ and S$_6$ homoaggregates of **6-8** each showed two resonances (1:1) at ≤-90 °C, consistent with **D** and inconsistent with **E** and **F**. Wrapping the six chelates of **E** in the opposite direction affords a second isomer in which both alkyl groups are in the equatorial positions around the perimeter, but it seems unlikely that the two stereoisomers would be of equal stability. The homoaggregates of **5**, however, initially presented a minor conundrum. Previously reported[14] spectra recorded on solutions of optically pure **5** revealed a single ^{6}Li resonance, suggesting that the R$_6$ and S$_6$ forms of **5** are *not* type **D**. Results from enolates **6-8** suggested that the rates of chelate exchange may be high for the relatively small methyl-substituted enolate. Indeed, reinvestigation of optically pure enolate **5** showed that the **R$_6$** and **S$_6$** forms display two resonances albeit at <-120 °C and low THF concentration. Therefore, enolates **5**-**8** are all assigned as hexamer type **D**.

In the case of the R/S and R/S' mixtures, the **R$_3$S$_3$** and **R$_3$S'$_3$** are inordinately stable and show distinct preferences for a single positional isomer, resulting in relatively clean spectra with minor mounds in the baseline in equimolar mixtures. By contrast, the R/R' mixtures should afford the statistically distributed **R$_m$R'$_n$** aggregates and nearly isoenergetic positional isomers (see **13** and **14**). Each positional isomer could display multiple inequivalent lithium sites (as many as six per isomer). Indeed, the R/R' mixtures afforded only broad mounds regardless of stoichiometry.

Discussion

We are currently developing methods for characterizing a wide range of lithium enolates, all of which are based on the method of continuous variation.[3,14] Recent studies, for example, show that standard enolates unadorned with further functionality are either dimers or tetramers,

depending on the choice coordinating solvent.[14] A primary goal of the study described herein was to exploit enolates **5**-**8** derived from β-amino esters to examine methods and strategies for characterizing highly aggregated enolates. We open the discussion by summarizing the structural assignments. This is followed by a more detailed analysis of *how* [6]Li NMR spectroscopy in conjunction with the method of continuous variation (Job plots) afforded the critical aggregation numbers.

Enolate structures

Job plots salted throughout the results section and discussed below show that enolates **5**-**8** are hexameric. We believe that *all* of the homo- and heteroaggregated hexamers are of general structure **9** bearing chelates wrapped around the hexagonal drum in the same direction. Direct support for this assertion is based on [6]Li NMR spectroscopic studies of a smaller subset that includes: (1) $\mathbf{R_6}$ and $\mathbf{S_6}$ homochiral hexamers derived from optically pure samples (denoted by **R** and **S**), (2) $\mathbf{R_3S_3}$ heterochiral hexamers prevalent in racemic samples, (3) $\mathbf{R_3S'_3}$ hexamers prevalent in equimolar mixtures of structurally distinct enolates of opposite absolute configuration, and (4) all $\mathbf{R_mR'_n}$ (and $\mathbf{S_mS'_n}$) hexamers prepared from mixtures of structurally distinct enolates of the same absolute configuration. The structures of the $\mathbf{R_mS_n}$ and $\mathbf{R_mS'_n}$ hexamers in which $m \neq n \neq 0$ (e.g., 5:1 and 4:2) are assigned as general structure **9** only by analogy.

One consequence of the hexagonal drum **9** is that subunits of opposite absolute configuration exemplified by $\mathbf{R_3S_3}$ and $\mathbf{R_3S'_3}$ mixed hexamers allow optimal disposition of the alkyl side chains as shown in hexamer **A** (Chart 1). Type **A** hexamers are reflected in the x-ray structure of *rac*-**5**[14] and display inordinate stability in solution (vide infra). Conversely, the homochiral aggregates $\mathbf{R_6}$ and $\mathbf{S_6}$ as well as the $\mathbf{R_mR'_n}$ hexamers derived from pairs of enolates within the same enantiomeric series appear to be type **D** hexagonal drums in which the β-alkyl substituents point away from the perimeter on one hexagonal face and toward the perimeter on the other.

Method of Job

The most probable forms of lithium enolates--monomers, dimers, tetramers, and hexamers (**1**-**4**)--are indistinguishable by standard NMR spectroscopic methods due to the high symmetry and opaque Li-O linkages. The aggregate structures emerge when mixtures of structurally related enolates afford ensembles of mixed aggregates. The number of possible aggregates in the ensemble increases with aggregate size and is highly diagnostic (Table 1).[29] Thus the total number of aggregates observed is revealing. The *quantitative* dependence of these ensembles on the mole fraction of the enolate subunits completes a compelling picture.

Chemical shifts and resolution

Success of the strategy for determining the aggregation state depends critically on the resolution of the discrete aggregates by [6]Li NMR spectroscopy. Although some problems presented by enolates **5**-**8** may be specific to the β-amino ester enolates, the lessons are proving useful as the method is extended to other classes of enolates.

Let us first consider the chemical shift dispersion resulting from pairs of enantiomers in R/S mixtures (Figure 9A). A relatively small number of resonances (four) arise because there are three degenerate pairs. The [6]Li resonances are bracketed upfield by the homochiral $\mathbf{R_6}/\mathbf{S_6}$ aggregates and downfield by the heterochiral $\mathbf{R_3S_3}$ aggregate. The chemical shifts of the aggregates reflect the degree of heterochirality. The nature of the hydrocarbon does *not* significantly influence the resolution,[30] but the proportion of THF in THF/hydrocarbon mixtures is important. Although one has limited *control* over the resolution, the resolution was adequate in most cases.

R/S' mixtures present a different scenario (Figure 9B). Because the R and S' enantiomers come from structurally different enolates, the degeneracy caused by enantiomerism is eliminated: All seven $R_mS'_n$ hexamers are spectroscopically distinct (Table 1). The resonances are bracketed by the homochiral R_6 and S'_6 forms upfield and the $R_3S'_3$ heterochiral form downfield. Clustering of resonances within the $R_4S'_2/R_2S'_4$ and $R_5S'_1/R_1S'_5$ pairs causes some resolution problems that are often alleviated by adjusting the THF concentration. The chemical shift dispersion can be controlled by judicious pairing of enolates based on the chemical shifts of the R_6 and S'_6 homoaggregates. At the outset, we had the simple notion that maximally resolved R_6 and S'_6 pairs would afford maximally resolved ensembles of mixed aggregates. This was wrong. Widely separated resonances for the R_6 and S'_6 cause the resonances of the mixed aggregates to merge unpredictably. The best resolution is observed by pairing R_6 and S'_6 aggregates with *minimum* chemical shift separation (as shown in Figure 9B), conditions causing the R/S' mixtures to mimic the R/S mixtures.

The R/R' mixtures afford seven [6]Li resonances bracketed by the resonances of the two homoaggregates (Figure 9C). The chemical shifts of the $R_mR'_n$ mixed aggregates correlate predictably with stoichiometry. Resolution is maximized by pairing R_6 and R'_6 homoaggregates with the largest chemical shift separation. Tactically, this allows one homoaggregate with an unusual chemical shift--the phenyl substituted enolate **8**--to be paired with the others. Faced with a particularly difficult resolution problem one might explicitly design a derivative with a β substituent (such as a naphthyl or phenanthryl group) to impart an especially wide chemical shift dispersion. Additional importance of the R/R' mixtures is underscored by the parametric fits.

Parametric Fits

The Job plots and affiliated parametric fits[3,14] are fully consistent with hexamers. Although in several instances, limited resolution demands that resonances corresponding to two aggregates are summed (see Figures 4 and 5), the underlying math is flexible, and the conclusions appear robust. We remind the reader, however, that the primary goal is to exploit an ensemble of *heteroaggregates* to provide insights into the structures of the *homoaggregates*. To that end, control experiments showing that the proportion of all aggregates are independent of the concentration provide important support to the assignments. The parametric fits resulting from the three protocols offer complementary perspectives of the aggregates.

Using R/S mixtures of a single enolate is the simplest of the three protocols in that only four curves must be fit (Table 1). Enolates **6** and **8** afforded excellent results (Figure 1). Unusual stabilities of the R_3S_3 aggregates afford distributions that deviate markedly from statistical (Figure 2). Poor resolution for R/S mixtures of enolate **7** afforded a resonance count consistent with tetramers rather than hexamers. Fortunately, the parametric fit to a tetramer model (Figure 3) was decidedly worse than the fit to the hexamer model (Figure 4), and subsequent prodding revealed the missing resonance. Both the number and mole-fraction dependencies and absolute-concentration independencies of the aggregates are consistent with hexamers and argue strongly that the R_n and S_n homoaggregates are necessarily R_6 and S_6.

The R/S' mixtures afford ensembles containing seven potentially distinguishable aggregates (no degenerate pairs). Although we were forced to sum two resonances in some cases, the fits are excellent. One might ask what would happen if an R_6 hexamer and S'_4 tetramer were mixed. It seems most probable that an intractable mess would result, but that begs the question: Would an ensemble containing six hexamers and a tetramer be distinguishable from an ensemble of seven hexamers? Probably not from the parametric fit alone. The independence of the ensemble on the absolute enolate concentration provides support.

Job plots based on R/R' mixtures offer the most convincing view. The seven observable aggregates are nearly statistically distributed type **D** hexamers differing only in the β-alkyl group (Figure 8). This is highly consistent with a type **D** hexamer in which the various alkyl substituents are interchangeable isoenergetically.

Conclusion

The studies described above can be distilled to a single concept: Formation of mixed aggregates from mixtures of closely related organolithium species provides insight into the spectroscopically opaque homoaggregates.[29] The method is an unusually complex application of the method of continuous variation.[15,16,17] The strategy relies on high resolution NMR spectroscopy ([6Li] in this instance) and powerful curve fitting algorithms. We focused this portion of a more broadly-based study on β-aminoester enolates **5**-**8** because previous studies strongly suggested that they would form hexagonal drums. Such hexamers present challenges that are unique in both detail and severity when compared with dimer- and tetramer-based ensembles.[3] Nonetheless, the underlying issues are likely to surface again during studies of other highly functionalized enolates, and strategies developed herein should prove instructive.

Experimental Section

Reagents and Solvents

Substrates were prepared using literature procedures described in Supporting Information. THF was distilled from solutions containing sodium benzophenone ketyl. Hydrocarbon solvents were distilled from blue solutions containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. The diphenylacetic acid used to check *n*-BuLi solution titers was recrystallized from methanol and sublimed at 120 °C under full vacuum.[31] [6Li] LiHMDS used to prepare the enolates was recrystallized.[32] Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques.

Preparation of compounds

The precursors to **5**-**7** are literature compounds prepared using an Arndt-Eistert homologation of the corresponding α-amino acids.[33] The precursor to **8** was prepared according to a literature procedure.[34] Detailed procedures can be found in supporting information.

Enolization

The enolates were prepared in situ for NMR spectroscopy. After flame drying the NMR tube, the appropriate stock solutions were added, and the tube was sealed. Samples were warmed to 0 °C for 15-30 minutes and were thoroughly mixed prior to collecting the spectrum. Integrations were preformed using the deconvolution macro included with VNMR software.

Parametric Fit

Data was fit parametrically to mathematical models described previously.[3]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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26. Ensembles of dimers and tetramers would afford three and five aggregates, respectively, which would afford two and three spectroscopically distinct resonances, respectively. Dimeric and tetrameric ensembles have been discussed in detail previously.[ref 3]

27. We refer to the enolates as R or S according to the structures as follows:In the case of a phenyl moiety (R = Ph), however, the Cahn-Ingold-Prelog (CIP) rules would formally reverse the stereochemical designation. We have taken the liberty ignoring the reversal to minimize confusion within the text.

28. The relative integration (I_n) was previously referred as aggregate mole fraction ($X_{n'}$, ref 14). We have changed it to avoid using two, distinctly different mole fraction terms and to include provisions for mixtures of aggregates which are not of the same aggregation number.

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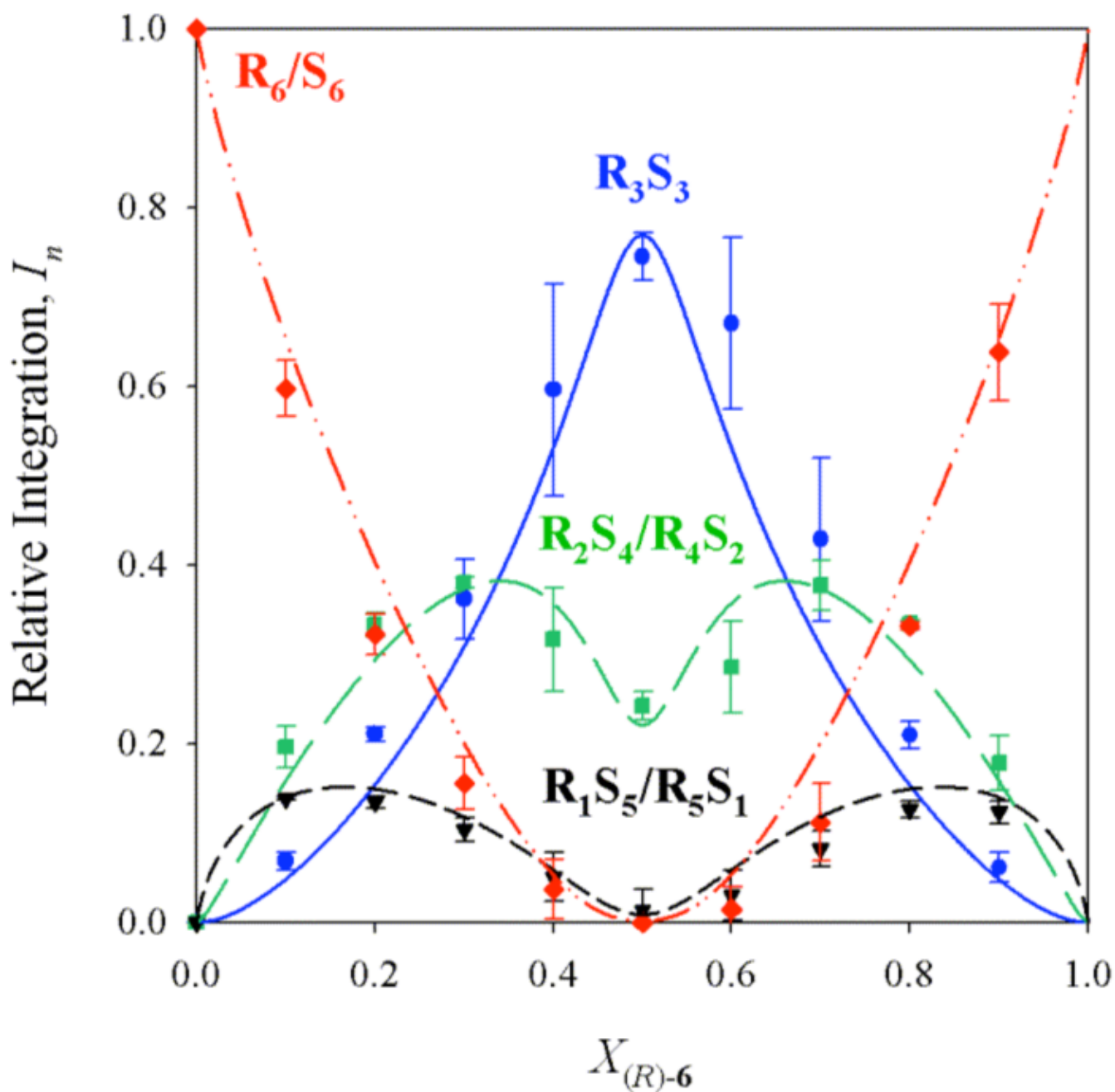
Figure 1.
Job plot showing relative integrations (I_n)[28] of $\mathbf{R_nS_{6-n}}$ hexamers as a function of the mole fraction of the *R* enantiomer ($X_{(R)\text{-}6}$) for enolate **6**. Samples were 0.10 M total enolate in 9.0 M THF/toluene, and spectra were recorded at -20 °C.
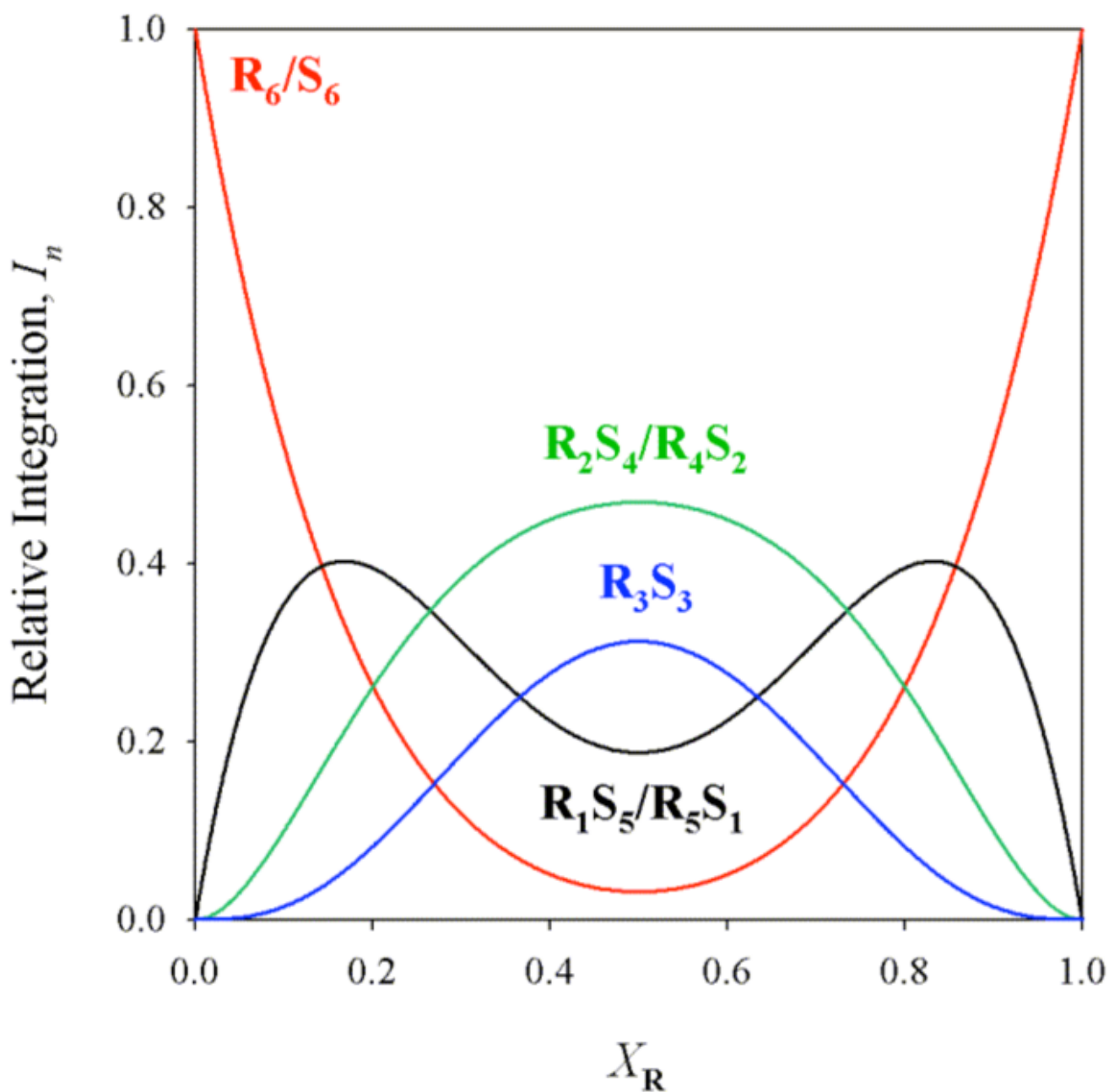
Figure 2.
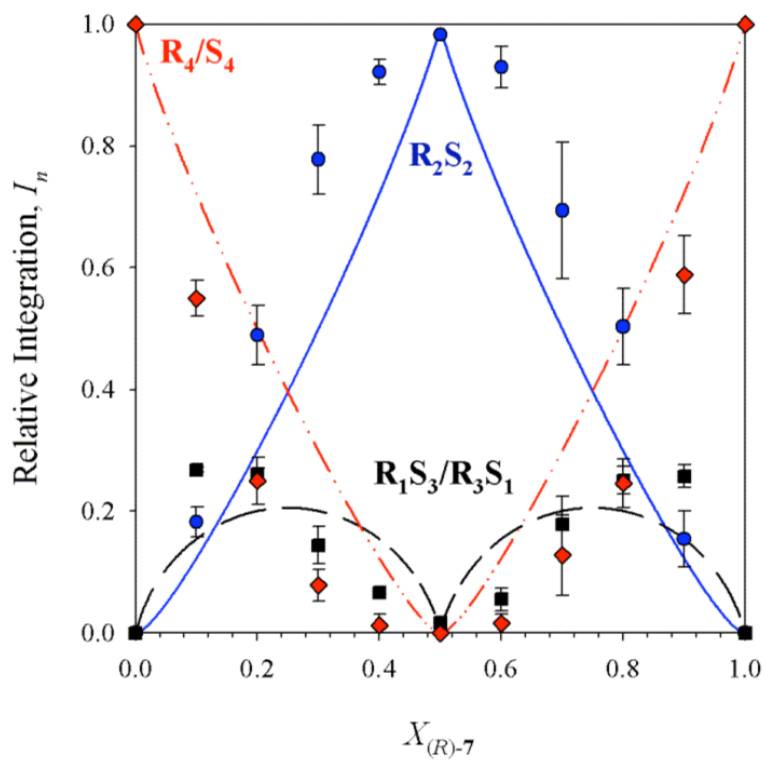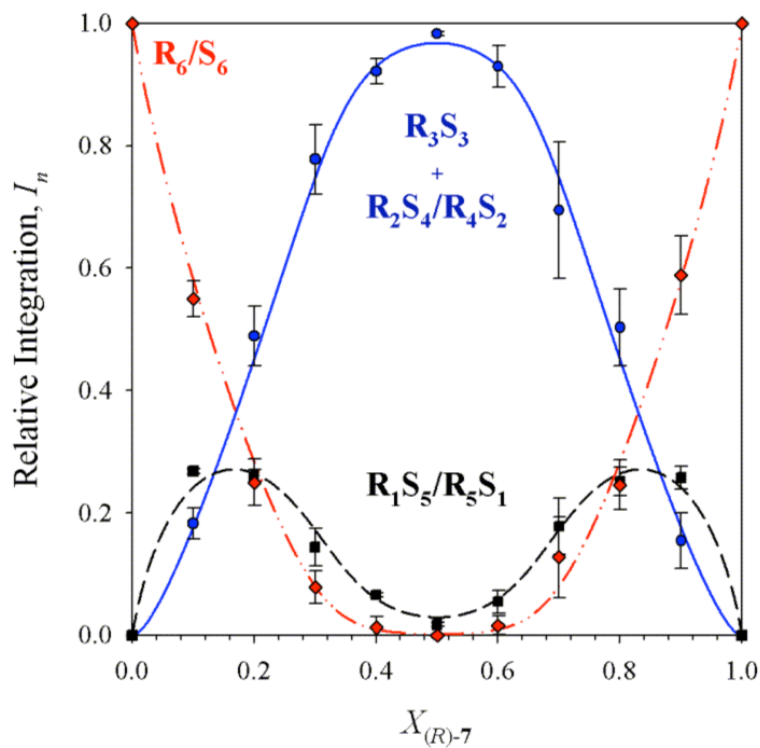Statistical distribution of **R**/**S** mixtures of enolates.

Figure 3.
Job plot showing the relative integrations (I_n)[28] of $\mathbf{R_n S_{4-n}}$ tetramers as a function of the mole fraction of the *R* enantiomer ($X_{(R)\text{-}7}$) for enolate **7**. The curves correspond to the parametric fit as described in the text. Samples were 0.10 M total enolate in 9.0 M THF/toluene, and spectra were recorded at -25 °C.
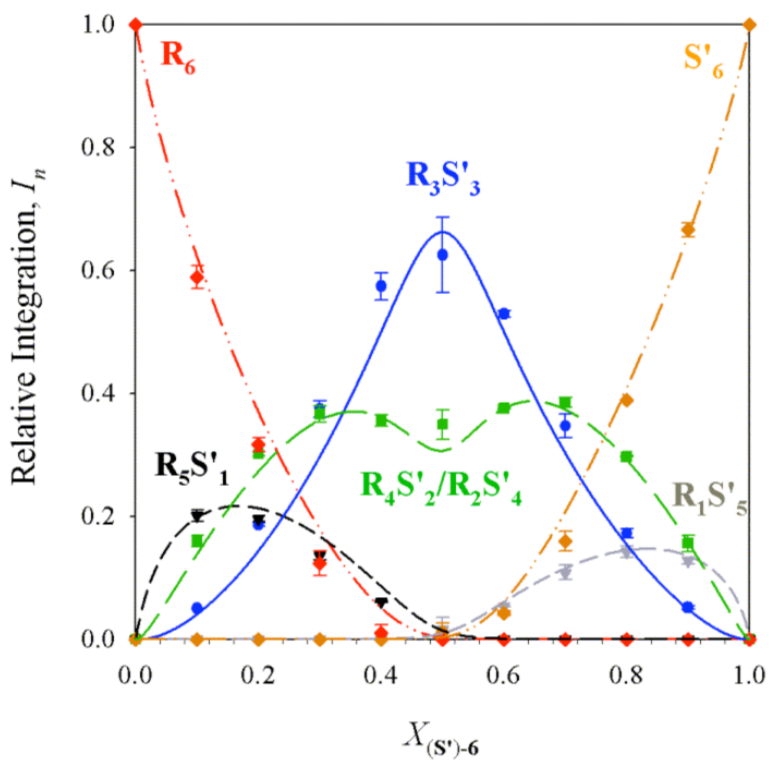
Figure 4.
Job plot showing the relative integrations (I_n)[28] of R_nS_{6-n} hexamers as a function of the mole fraction of the *R* enantiomer ($X_{(R)-7}$) for enolate **7**. The curves correspond to the parametric fit as described in the text. Samples were 0.10 M total enolate in 9.0 M THF/toluene, and spectra were recorded at -25 °C.
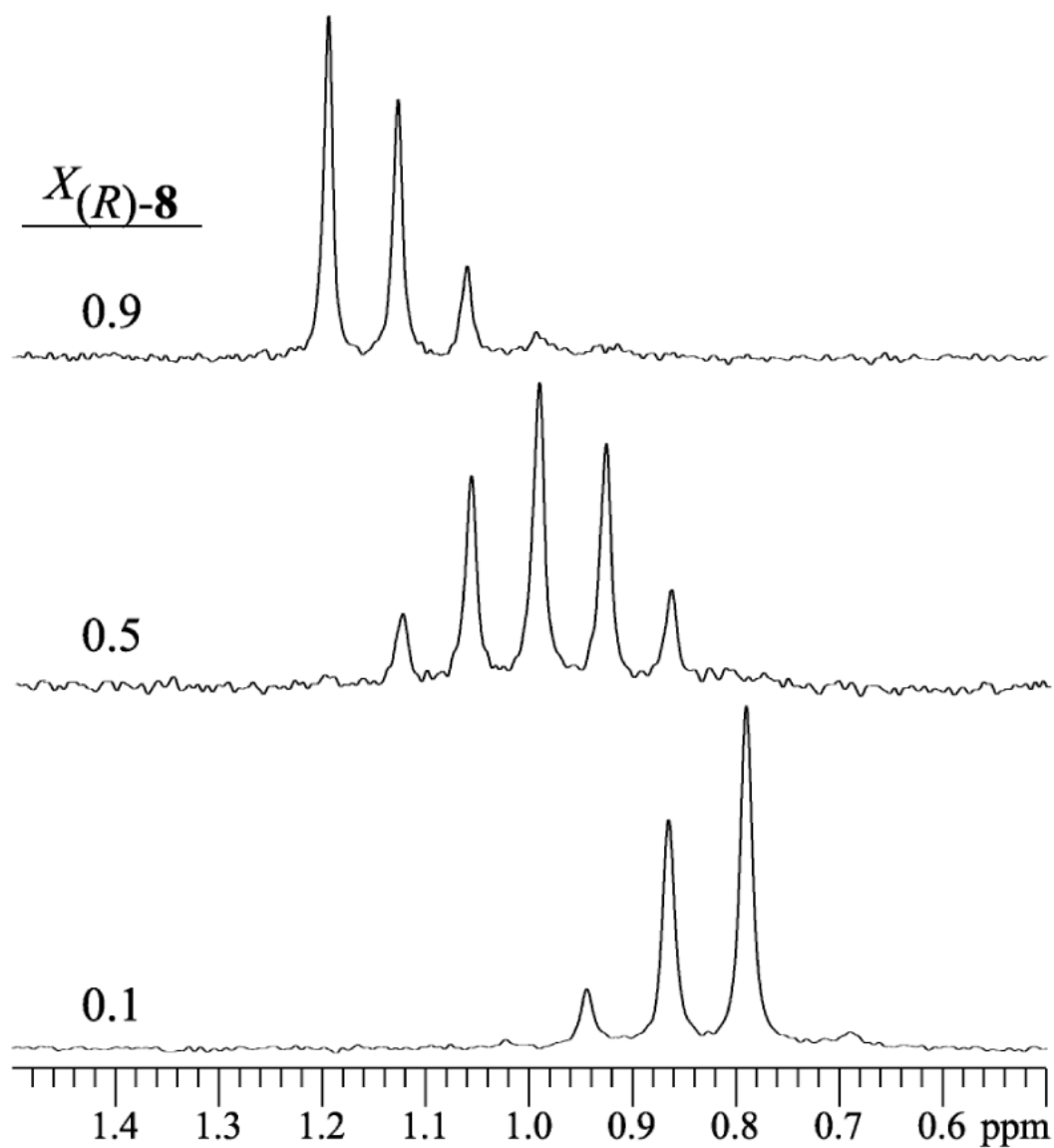
Figure 5.
Job plot showing relative integrations (I_n)[28] of $\mathbf{R_nS_{6-n}}$ hexamers as a function of the mole fraction of the *S* enantiomer ($X_{(S')\text{-}\mathbf{6}}$) for enolate **6**. The curves correspond to the parametric fit as described in the text. Samples were 0.10 M total enolate in 3.0 M THF/toluene, and spectra were recorded at -30 °C.

Figure 6.
[6]Li NMR spectra recorded on R/R' mixtures (the same stereochemical series) derived from enolates **5** and **8**. Samples were 0.10 M total enolate in 3.0 M THF/toluene, and spectra were recorded at -40 °C.
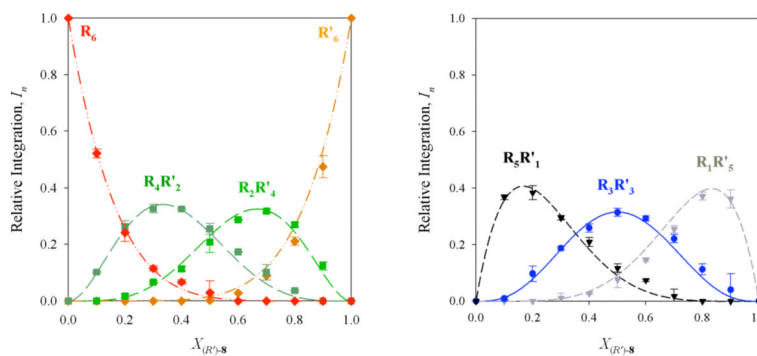
Figure 7.
Job plot showing the relative integrations (I_n)[28] of $\mathbf{R_nR'_{6-n}}$ hexamers of enolates **5** and **8** as a function of the mole fraction of the R enantiomer of enolate analogous curves anticipated from a purely statistical distribution shows a striking similarity (Figure 8). **8** ($X_{(R)\text{-}\mathbf{8}}$). The curves correspond to parametric fits as described. Samples were 0.10 M total enolate in 3.0 M THF/toluene, and spectra were recorded at -40 °C.
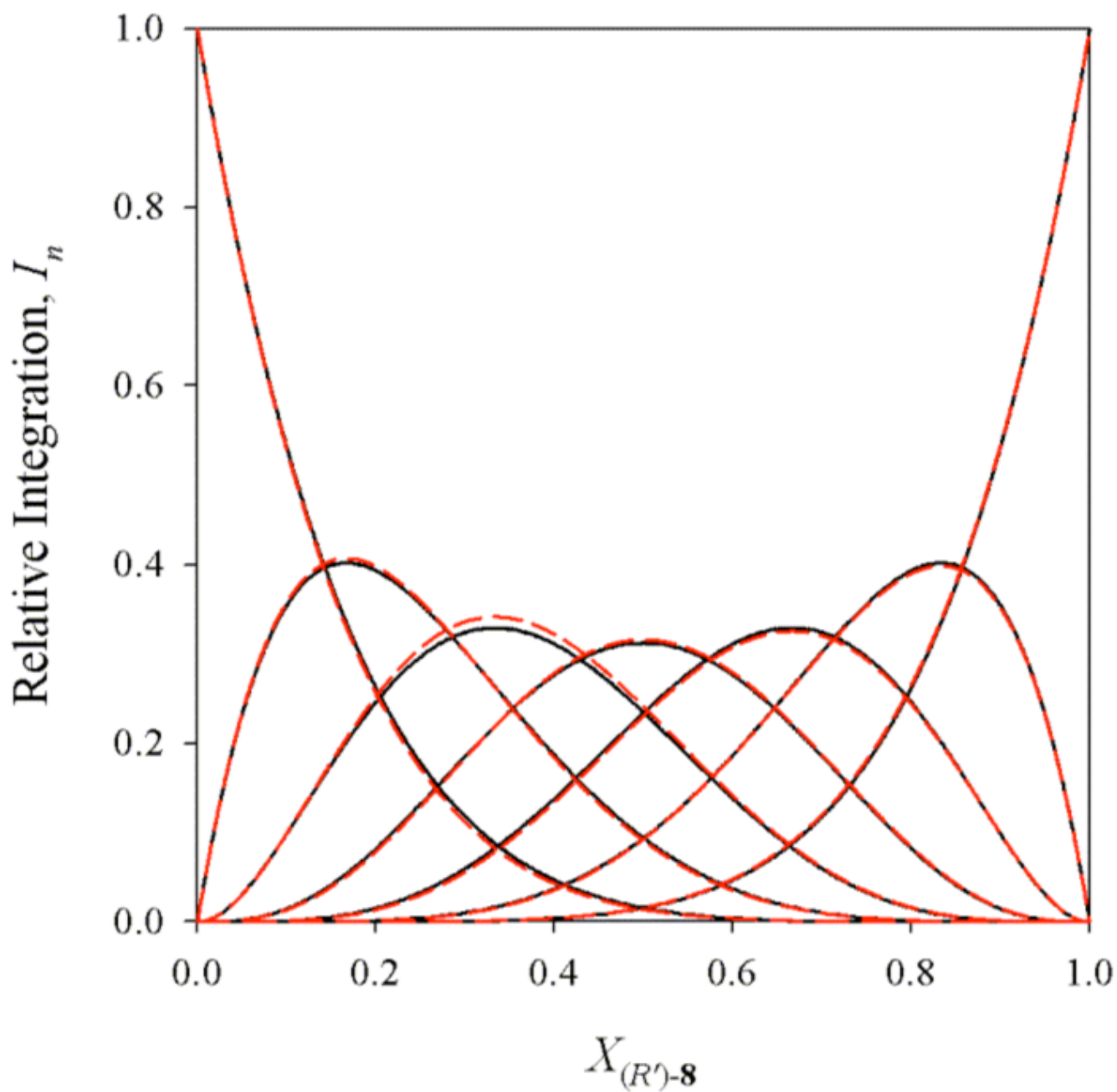
Figure 8.
Superposition of the parametric fit from Figure 7 (red) with the results anticipated from a statistical distribution (black).
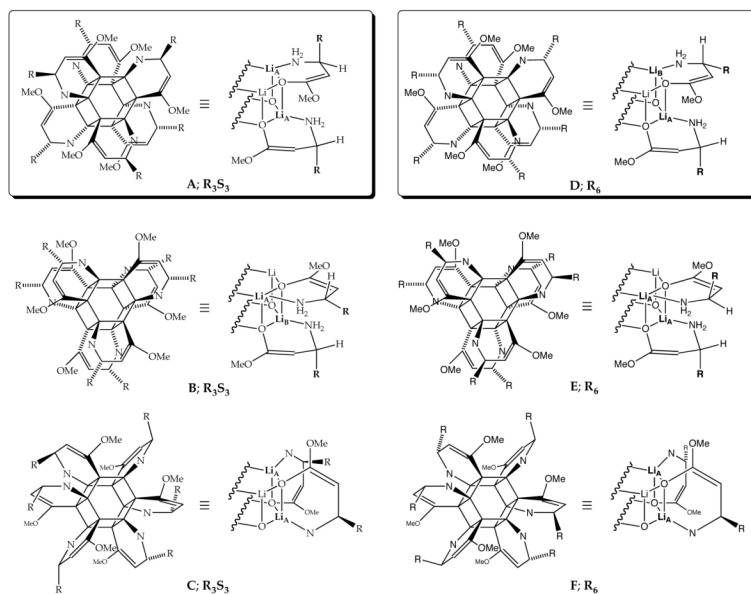
Chart 1.
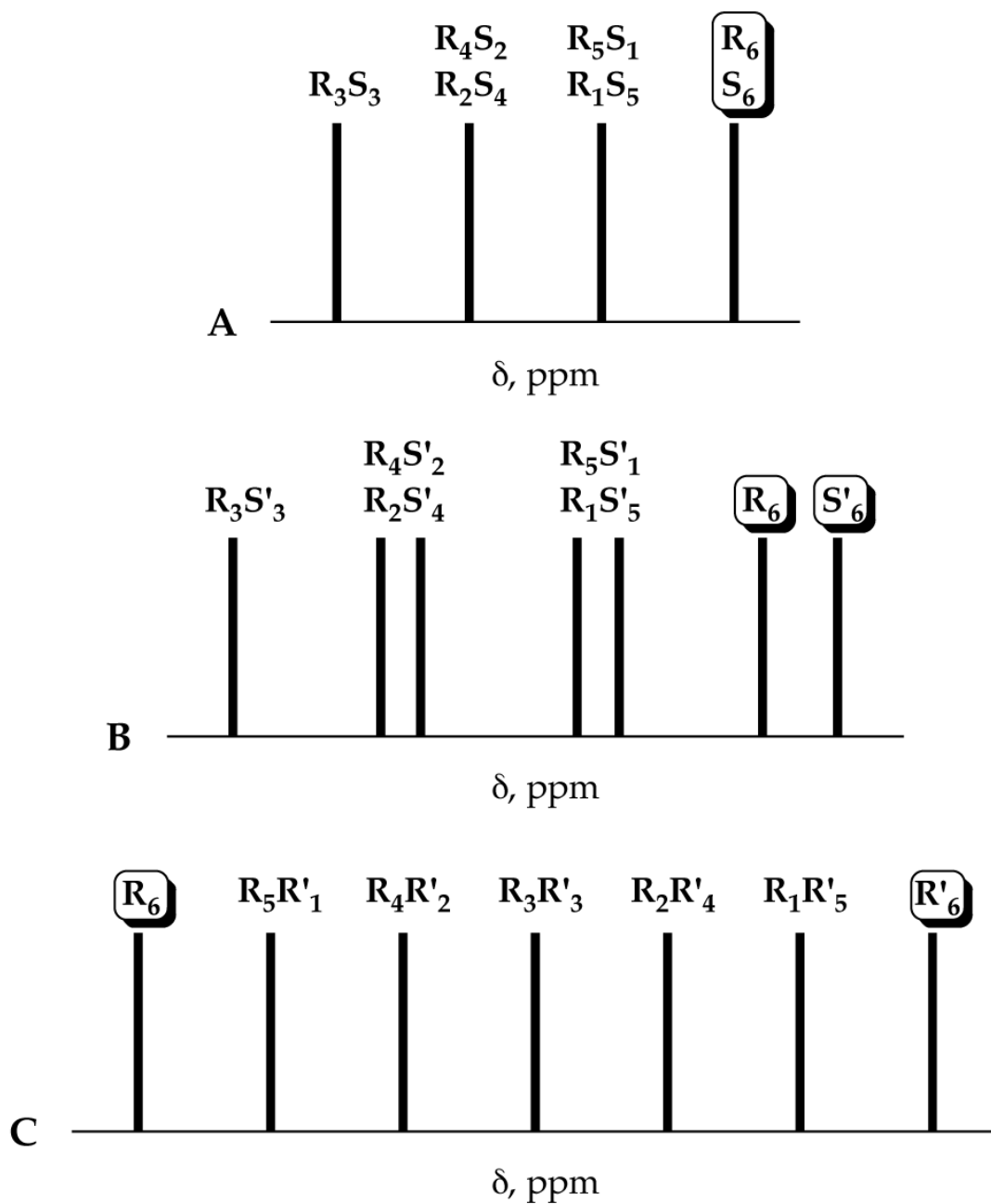Li and O have been omitted for clarity and N = NH$_2$.

Figure 9.
Chemical shift dispersion of enolate aggregates derived from (A) R/S mixtures, (B) R/S'
mixtures, and (C) R/R' mixtures.

Table 1

Spectroscopically distinguishable aggregates in binary mixtures of enolates.[a]

R/S mixtures	R/S' mixtures	R/R' mixtures
R_6/S_6	R_6	R_6
R_5S_1/R_1S_5	$R_5S'_1$	$R_5R'_1$
R_4S_2/R_2S_4	$R_4S'_2$	$R_4R'_2$
R_3S_3	$R_3S'_3$	$R_3R'_3$
	$R_2S'_4$	$R_2R'_4$
	$R_1S'_5$	$R_1R'_5$
	S'_6	R'_6

[a] The R and S notations refer to enantiomers of a single enolate.[27] The prime refers to subunits from a structurally distinct enolate. RmSn/RnSm refers to as.pectroscopically indistinguishable pair of enantiomers.