

# Mechanistic Studies of the Lithium Enolate of 4-Fluoroacetophenone: Rapid-Injection NMR Study of Enolate Formation, Dynamics, and Aldol Reactivity

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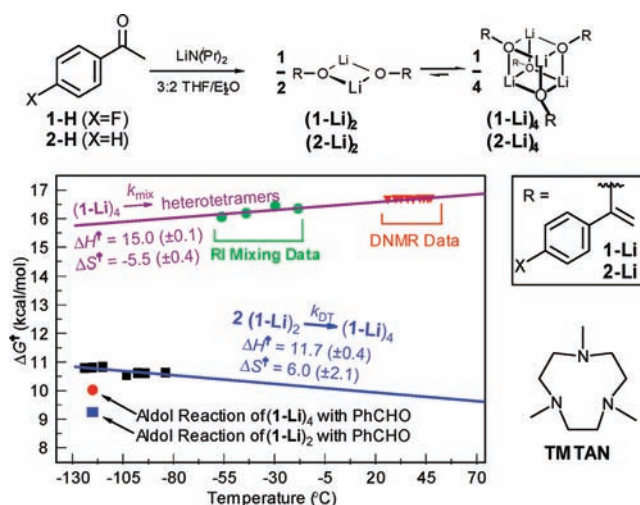
Supporting Information

**ABSTRACT:** Lithium enolates are widely used nucleophiles with a complicated and only partially understood solution chemistry. Deprotonation of 4-fluoroacetophenone in THF with lithium diisopropylamide occurs through direct reaction of the amide dimer to yield a mixed enolate-amide dimer (3), then an enolate homodimer (1-Li)<sub>2</sub>, and finally an enolate tetramer (1-Li)<sub>4</sub>, the equilibrium structure. Aldol reactions of both the metastable dimer and the stable tetramer of the enolate were investigated. Each reacted directly with the aldehyde to give a mixed enolate-aldolate aggregate, with the dimer only about 20 times as reactive as the tetramer at -120 °C.

Lithium enolates represent a class of powerful reagents for synthesis. Much is known about their solution structures and aggregation states,<sup>1a,2a,3,4a,b,5a,b</sup> but our understanding of the individual reactivity and rates of interconversion of the various homo and mixed aggregates known to be involved in their chemistry (of interest from Curtin–Hammett considerations) is in a more primitive state.<sup>3,5b</sup> We address here the dynamics and chemistry of several aggregates and mixed aggregates of the lithium enolate of 4-fluoroacetophenone (1-Li).

All techniques agree that the enolates of both 4-fluoroacetophenone (1-Li) and acetophenone (2-Li) form cubic tetramers in THF solution.<sup>2a,4a,b,5a</sup> Mixing solutions of 1-Li and 2-Li<sup>6</sup> gave three new <sup>19</sup>F and <sup>13</sup>C NMR signals (1:3, 2:2, 3:1 ratio of 1-Li to 2-Li), giving a 1:3:3:1 cluster of peaks as required for a tetramer. These species were in slow exchange on the NMR time scale from -120 to 25 °C.<sup>7</sup> Thus tetramers are the predominant form over this temperature range, and they have a high barrier to dissociation (>15.5 kcal/mol). Even with the addition of polydentate ligands (*N,N,N',N'*-tetramethylethylenediamine (TMEDA), *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA), trimethyltriazacyclononane (TMTAN)) or polar solvent additives (hexamethylphosphoric triamide (HMPA)) to solutions of (1-Li)<sub>4</sub> in THF, no lower aggregates were detected.<sup>5a</sup> Above 25 °C, the <sup>13</sup>C and <sup>19</sup>F NMR signals of the homo- and heterotetramers underwent a coalescence event.<sup>7</sup> Simulation of the DNMR line shapes<sup>5c,d,e</sup> assuming an exchange mechanism that involves reversible dissociation of the tetramer provided an estimate of the tetramer dissociation rates (Figure 1 shows the rate data).

Another estimate of the tetramer dissociation rate at lower temperatures was provided by dynamic mixing experiments

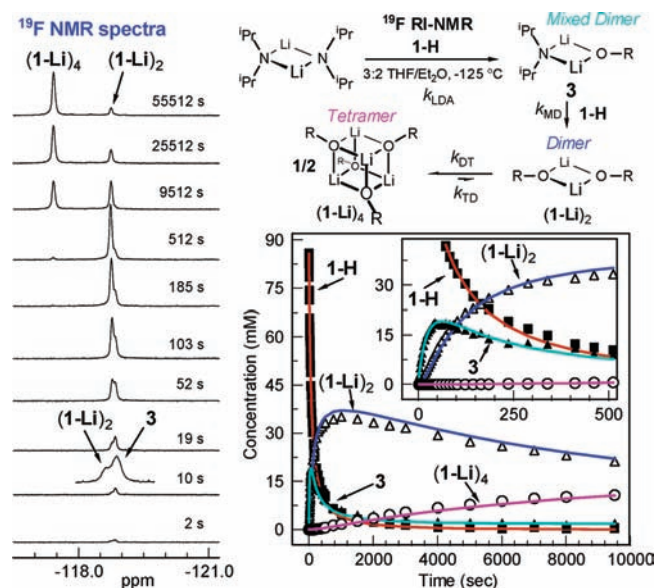


**Figure 1.** Interaggregate exchange rates for 1-Li dimer and tetramer in 3:2 THF/ether solution. The rate constant  $k_{DT}$  is the rate of dimerization of (1-Li)<sub>2</sub>,  $k_{mix}$  is the rate of tetramer heteroaggregate interchange, measured either by DNMR line broadening of the mixtures of 1-Li and 2-Li homo- and heterotetramers or by a RI-NMR mixing experiment in which (2-Li)<sub>4</sub> was injected into (1-Li)<sub>4</sub>. The free energies of activation for the aldol reactions of dimer and tetramer with benzaldehyde are also shown.

utilizing Rapid Injection NMR (RI-NMR).<sup>5f</sup> Solutions of (2-Li)<sub>4</sub> were injected into solutions of (1-Li)<sub>4</sub> at several temperatures (-56 to -18 °C), and the formation of heterotetramers was followed.<sup>8</sup> The initial rate of dissociation of (1-Li)<sub>4</sub> was determined by fitting the first 5% loss of the <sup>19</sup>F NMR signal to a first-order decrease line at each temperature. These data fall on the same line in an Eyring plot as did rates measured by the DNMR experiment (Figure 1). The mechanism of these mixing reactions was not firmly established. Bimolecular exchange through octamers was ruled out, since the rate was independent of the concentration of the enolate solutions. Exchange via rate-limiting dissociation to dimers is questionable, because this would require that the 2:2 heterotetramer be the first-formed exchange product. Although this would be a subtle effect, the 2:2 actually lags behind the 3:1 heterotetramer.<sup>7</sup> A third mechanistic possibility is slow dissociation to dimers followed by a chain of exchanges via hexamers. Attempts to find an electrophile which showed saturation kinetics

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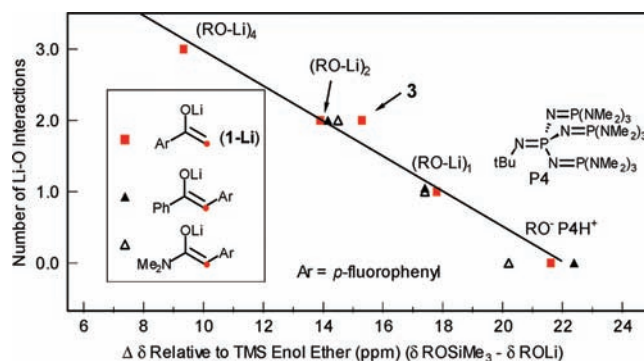
**Figure 2.**  $^{19}\text{F}$  RI-NMR spectra of the enolization of **1-H** (0.085 M) by  $\text{LiN}(\text{iPr})_2$  ( $(\text{LDA})_2$ , 0.049 M) in 3:2 THF/ $\text{Et}_2\text{O}$  at  $-125^\circ\text{C}$ . The lines are simulations with  $k_{\text{LDA}} = 2.9 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{MD}} = 2.2 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{DT}} = 0.013 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ .

(i.e., for which dissociation of the tetramer to more reactive dimers became rate determining) were not successful. Depending on the contributions from the hexamer, octamer, and other processes, the dissociation to the dimer could be close to, or substantially slower than, the measured exchange rates, i.e.  $k_{\text{TD}} \leq k_{\text{mix}}$  (Figure 1).

With the structural identity of the thermodynamic aggregate of **1-Li** characterized and its dynamic behavior explored, attempts were made to generate kinetically stable lower aggregates of **1-Li**. Previous work has shown that lithium diisopropylamide (LDA)-mediated enolizations in ethereal solvents tend to proceed via monomeric pathways (LDA is a dimer in THF<sup>4g,h</sup>) that should yield, at least transiently, a less associated enolate. These studies were performed on hindered esters whose rate of deprotonation is slow enough for careful kinetic studies.<sup>4c</sup> Very little is known about lithium amide enolization of unhindered ketones like **1-H**.<sup>5g</sup> Isotope effects<sup>9</sup> and *Z/E* ratios<sup>4e,9b</sup> based on product studies have provided only an indirect understanding of the role of aggregates.

The LDA mediated enolization of **1-H** could be followed by  $^7\text{Li}$  or  $^{19}\text{F}$  RI-NMR spectroscopy (Figure 2). Deprotonation occurred rapidly ( $t_{1/2} = 35 \text{ s}$ ) at  $-125^\circ\text{C}$  in 3:2 THF/ $\text{Et}_2\text{O}$ . The initial  $^{19}\text{F}$  NMR spectra revealed no detectable  $(\text{1-Li})_4$ , but two new signals at  $\delta = -118.82$  and  $-118.76$ , upfield from those of the tetramer at  $\delta = -117.43$ , were observed (Figure 2). The first dominated for several seconds, after which the second grew in at the expense of the first and ketone. After several minutes, a signal corresponding to  $(\text{1-Li})_4$  was detectable, but full conversion occurred slowly ( $t_{1/2} = 8000 \text{ s}$ ).

The  $^7\text{Li}$ ,  $^{19}\text{F}$ , and  $^{13}\text{C}$  NMR shifts for the two initially formed intermediates are consistent with enolate species of increased charge density (lower aggregation) than  $(\text{1-Li})_4$ . Both show very similar  $^{13}\text{C}$  NMR signals for the  $\alpha$ -carbon ( $\text{Li-O-C}$ ) and the  $\beta$ -carbon ( $\text{O-C=C}$ ) which are downfield and upfield, respectively, from those of the tetramer ( $\delta_{\text{C}} 165.8, 75.8$  vs  $164.4, 80.4$  for tetramer).<sup>10</sup> Based on their NMR properties and reaction behavior,

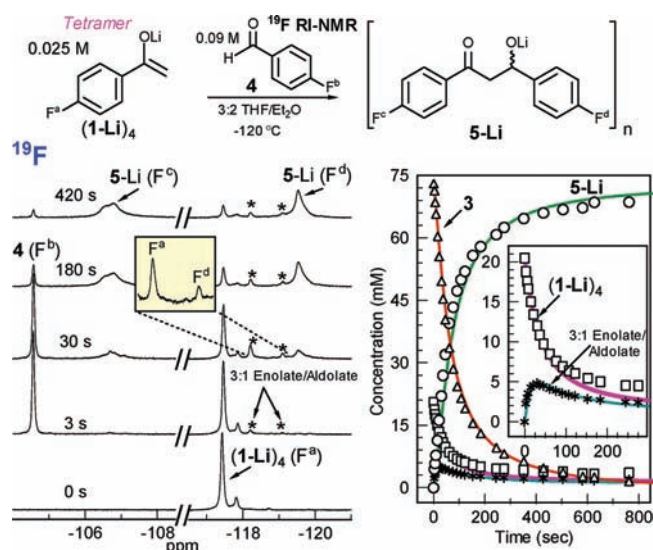


**Figure 3.** Aggregation effects on  $^{13}\text{C}$  chemical shifts of several enolates (difference between  $\delta$  of the  $\text{OC}=\text{C}$  carbon of  $\text{ROLi}$  and  $\text{ROSiMe}_3$ ).<sup>5a</sup> The monomers are TMTAN complexes.<sup>5b</sup> The salt-free enolate formed by deprotonation of **1-H** with the phosphazene base **P4** was used as a model for a separated ion pair (no  $\text{Li-O}$  contacts). Remarkably, the points for **1-Li** fall on a straight line.

they were assigned to a mixed LDA-enolate dimer **3** ( $\delta_{\text{F}} = -118.82$ )<sup>11</sup> and dimer  $(\text{1-Li})_2$  ( $\delta_{\text{F}} = -118.76$ ). Figure 3 shows the very consistent aggregate  $^{13}\text{C}$  chemical shift effects when several lithium enolates were compared to enol silyl ethers.<sup>5a,b</sup> The dimer assignment was supported by an experiment where a 1:1 mixture of **1-H** and **2-H** was injected into a solution of LDA. The  $^{19}\text{F}$  NMR spectra showed, in addition to  $(\text{1-Li})_2$ , only one additional signal assigned to the mixed dimer aggregate  $(\text{1-Li})(\text{2-Li})$ .<sup>4a,b</sup> A monomer would give no new signals; higher aggregates would give more.

Having established the identity of the species involved in the reaction, the kinetics of this system were explored. A first-order dependence on LDA was observed when a constant concentration of **1-H** (0.015 M) reacted with a range of concentrations of LDA (0.06–0.24 M). In these experiments the ratio of mixed-LDA-dimer to homodimer increased as the concentration of LDA was raised, supporting the mixed dimer assignment.<sup>11</sup> The reaction was also first order in **1-H**. Since LDA is primarily dimeric in these solutions,<sup>4g,h</sup> the enolization must involve direct reaction of the LDA dimer. This is reasonable, because the dissociation of LDA dimers to monomers is much slower than the deprotonation rates.<sup>15</sup>

The concentration vs time curves of these experiments were simulated with the COPASI program<sup>16</sup> using the reactions shown in Figure 2 as the kinetic model. Consistent replication of the experimental concentrations over a range of temperatures ( $-124$  to  $-84^\circ\text{C}$ ) as well as LDA dimer (0.025–0.05 M) and ketone (0.05–0.2 M) concentrations could be achieved for the deprotonations by LDA dimer and mixed dimer, as well as for the much slower dimerization to form the tetramer (lines in the rate plot of Figure 2). Thus, both the LDA dimer and the mixed dimer **3** are kinetically active.<sup>17</sup> Direct involvement of **3** was also demonstrated by the observation of primary kinetic isotope effects for the reaction of  $\alpha,\alpha,\alpha$ -trideuterio-**1-H** with the LDA dimer ( $k_{\text{H}}/k_{\text{D}} = 1.7$ ) and **3** ( $k_{\text{H}}/k_{\text{D}} = 6.3$ ). The much larger isotope effect for **3** suggests a difference in mechanism, in spite of the near identity of the rates. It is interesting that the mixed and homodimer have similar reactivities. In ester deprotonations the mixed dimer intermediates were much less reactive.<sup>4f</sup> From these simulations the free energies of activation for the dimerization of  $(\text{1-Li})_2$  to  $(\text{1-Li})_4$  were obtained and are plotted in Figure 1. With  $k_{\text{DT}}$  known and an upper limit on  $k_{\text{TD}}$  established, we can calculate that the dimer/tetramer  $K_{\text{eq}} = [\text{T}]/[\text{D}]^2 = k_{\text{DT}}/k_{\text{TD}} \geq 2.1 \times 10^6 \text{ M}^{-1}$  at  $-84^\circ\text{C}$ .



**Figure 4.**  $^{19}\text{F}$  RI-NMR spectra of the aldol reaction of  $(1\text{-Li})_4$  with **4** in 3:2 THF/Et<sub>2</sub>O at  $-120\text{ }^\circ\text{C}$ . The starred peaks identify the 3:1 enolate–aldolate mixed tetramer (the third  $^{19}\text{F}$  NMR signal would be in the broad peak at  $\delta = -106.5$  for  $\text{F}^c$ ). Lines correspond to simulation of the kinetic path involving successive reaction of  $(1\text{-Li})_4$  ( $k_{\text{T}} = 0.29\text{ M}^{-1}\text{ s}^{-1}$ ) and the 3:1 mixed aggregate ( $k_{3:1} = 0.66\text{ M}^{-1}\text{ s}^{-1}$ ).<sup>7</sup>

Ever since the supramolecular structure of enolates was established, it was postulated that tetrameric structures may directly participate in the aldol reaction.<sup>1b,c</sup> Lower aggregates of several types of organolithium species have been shown to be much more reactive than higher ones,<sup>3c,5f,i,j</sup> and their involvement has been often detected by fractional order kinetics. The participation of more reactive but less stable lower aggregates depends, among other things, on the relative rate of reaction with electrophile versus the rate of deaggregation. With clean solutions of the dimer and tetramer of **1-Li** available in the same solvent, and the barrier to interconversion established, we were in a unique position to directly address this issue. We chose the aldol reaction with 4-fluorobenzaldehyde (**4**). Almost nothing is known about the mechanism of lithium enolate aldol reactions because the high rates limit techniques for kinetic investigations.<sup>2b-e,5g,18</sup>

The reaction of  $(1\text{-Li})_4$  with **4** was monitored by  $^{19}\text{F}$  RI-NMR at  $-120\text{ }^\circ\text{C}$  (Figure 4).<sup>2e</sup> The  $^{19}\text{F}$  NMR signals for the enolate and aldehyde are well resolved from the signals of the resulting aldolate, allowing the concentrations of all reactants and products to be monitored. In the first few seconds a 3:1 ratio of product signals at  $\delta_{\text{F}} = -118.2$  and  $-119.1$  appeared, which we have assigned to the enolate and aldolate signals of a 3:1 enolate/aldolate mixed tetramer.<sup>19</sup> The smaller upfield signal was absent when benzaldehyde instead of **4** was used. The 3:1 mixed aggregate could be detected as a minor component throughout the reaction time of about 5 min, but by 30 s two broad peaks ( $\delta = -106.7$  and  $-119.6$ ), corresponding to the keto and alcoholate  $^{19}\text{F}$  signals of the aldolates, were the major product signals.

The reactions of  $(1\text{-Li})_4$  with **4** ( $t_{1/2} = 45\text{ s}$ ) and benzaldehyde ( $t_{1/2} = 62\text{ s}$ ) at  $-120\text{ }^\circ\text{C}$  are much faster than its dissociation rate, estimated from the data in Figure 1 to have a  $t_{1/2} \geq 4.2 \times 10^{10}\text{ s}$ , so a mechanism involving predissociation to the dimer can be ruled out. The aldol reaction was first order in both  $(1\text{-Li})_4$  and **4**. The rate-limiting transition state thus consists of 1 equiv of the tetramer and aldehyde, as suggested by Seebach and et al.<sup>1b,c</sup> The

observation of an intermediate 3:1 enolate/aldolate mixed adduct supports this mechanism. Since this mixed tetramer never accumulates to  $>15\%$  of total solution concentrations it reacts with **4** significantly faster than the homogeneous tetramer (we estimate by a factor of 2.3 from kinetic simulations such as those shown in Figure 4). A scheme where the 3:1 adduct dissociates unimolecularly to lower aggregates before reacting with aldehyde does not fit the kinetic traces. No other intermediates were detected, so the 2:2 adduct formed next, and all subsequent intermediates, must be even more reactive toward **4** than the 3:1 adduct, or they rapidly dissociate to yield more reactive dimeric enolate complexes.

A small Hammett plot was constructed using the initial rates of aldol reaction of  $(1\text{-Li})_4$  with 3-F-, 4-F-, 4-H-, and 4-OMe-benzaldehydes, which gave a  $k_{\text{rel}}$  of 7.7, 1.7, 1.0, and 0.02, respectively ( $-120\text{ }^\circ\text{C}$ ), and a Hammett  $\rho$  value of  $4.0 \pm 0.8$ . This follows the electrophilicity of the aldehyde rather than its basicity and rules out mechanisms in which the aldehyde as base catalyzes opening or deaggregation of the tetramer in the rate-determining step, as was found for an aldehyde-RLi reaction.<sup>5i</sup>

Our success in making metastable solutions of the enolate dimer of **1-Li** allowed us to directly compare its reactivity with that of the tetramer. The reaction of  $(1\text{-Li})_2$  with benzaldehyde (reaction with **4** produces overlapping signals in the  $^{19}\text{F}$  NMR spectra) is 17 times faster ( $t_{1/2} = 2\text{ s}$ ,  $-120\text{ }^\circ\text{C}$ ) than that of  $(1\text{-Li})_4$  and at the limits of measurability with our RI apparatus.<sup>7</sup> A single intermediate species with two  $^{19}\text{F}$  NMR signals is seen ( $\delta = -106.61$  and  $-118.93$ ) and is presumed to be a mixed dimer. Although a detailed kinetic study could not be done, the reaction appeared to be first order in aldehyde. The dimer, like the tetramer, thus reacts directly with the aldehyde to produce a mixed enolate-aldolate species. This intermediate is more reactive than the homogeneous aggregate since it builds up to a maximum of 30% of species present. The surprisingly small difference in reactivity of the tetramer and dimer may in part have its origin in structural effects. Enolates differ fundamentally from alkyl- and aryllithium reagents (where  $k_{\text{D}}/k_{\text{T}}$  or  $k_{\text{M}}/k_{\text{D}}$  ratios of  $>10^3$  are known<sup>3c,5f,i</sup>) in that the nucleophilic carbon center is not directly encumbered by the metal upon aggregation. A similarly low monomer/dimer reactivity ratio has been observed for lithium enolate Claisen acylations.<sup>3d</sup>

The aggregation state of the lithium aldolates (**5-Li**) was not characterized, but the spectra typically indicated several distinct species, which were slightly different for the tetramer and dimer reactions, and also different from the equilibrated products and aldolate formed by deprotonation of the aldol adduct.<sup>13d</sup>

In summary, the deprotonation of **1-H** with LDA at low temperatures occurs through a dimer process to yield a mixed dimer **3**, then an enolate homodimer  $(1\text{-Li})_2$ , which then dimerizes to an enolate tetramer  $(1\text{-Li})_4$ . Both the metastable dimer and the stable tetramer reacted directly with aldehyde in an aldol reaction under non-Curtin–Hammett conditions to give mixed enolate-aldolate aggregates (3:1 species for the tetramer, 1:1 species for the dimer), which were more reactive than the homoaggregate. The modestly higher basic or nucleophilic reactivity of several mixed aggregates over the homoaggregates reported here contrasts with a number of previous studies which found opposite trends.<sup>4i,5f</sup> Clearly there is much we do not understand about lithium reagent aggregate reactivities.

## ■ ASSOCIATED CONTENT

Supporting Information. Experimental details, NMR spectra and kinetic traces of all reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

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- (10) These chemical shifts were nearly identical to the shifts of a TMEDA-complexed dimer of **1**-Li prepared as reported by Collum and co-workers.<sup>4a,b</sup>
- (11) Experiments in which a 4-fold excess of LDA was used gave a ca. 1:1 ratio of (**1**-Li)<sub>2</sub> and **3**, allowing spectroscopic characterization of **3**. Carbon NMR data:  $\alpha$ -carbon  $\delta$  166.0,  $\beta$ -carbon  $\delta$  74.6. Mixed aggregates of lithium amides and ketone or ester enolates have been frequently detected<sup>14c,d,12,13a,b,c</sup> and have been invoked to explain selectivity effects.<sup>1d,14</sup>
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- (15) The rate of LDA dimer dissociation has been reported as  $k_{DM} = 7 \times 10^{-7}$  s $^{-1}$  at  $-78$  °C in THF.<sup>4k</sup> This is slower by a factor of 100 than the deprotonation rate of **1**-H by LDA at 47° lower temperature.
- (16) COMplex PATHway SIMulator. Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. *Bioinformatics* **2006**, *22*, 3067–3074.
- (17) An alternative mechanism where **3** disproportionates to (**1**-Li)<sub>2</sub> and (LDA)<sub>2</sub> rather than reacting directly with **1**-H did not fit the experimental concentration–time plots and could be ruled out by an RINMR experiment where additional LDA was injected at  $-120$  °C into a solution of the enolate dimer. No change in concentration of **3** was detected over a time period during which most of the enolate dimer was converted to tetramer.<sup>7</sup>
- (18) Even with ketones as substrates, the lithium aldol reaction is fast at  $-78$  °C, and aldehydes are at least  $10^4$  faster: Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302–1312.
- (19) An alternative assignment of the 3:1 intermediate as an enol ether aldehyde adduct (ArC(O-CHR-OLi)=CH<sub>2</sub>) could be ruled out on the basis of the <sup>19</sup>F chemical shifts: the trimethylsilyl enol ether (ArC(O-SiMe<sub>3</sub>)=CH<sub>2</sub>,  $\delta$  -114.9) and MOM enol ether (ArC(O-CH<sub>2</sub>-OMe)=CH<sub>2</sub>,  $\delta$  -114.4) of 4-fluoroacetophenone had chemical shifts over 4 ppm downfield from the observed adduct at  $\delta$  -119.1.