

Communications to the Editor

Mechanism of Lithium Diisopropylamide-Mediated Ester Deprotonation: The Role of Disolvated Monomers

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Lithium diisopropylamide (LDA) is one of the most important Brønsted bases in organic synthesis.¹ While LDA structure determinations^{2–4} have progressed quickly, rate studies have also established rate laws for several LDA-mediated reactions.^{5,6} However, the most important reaction of LDA—enolization—has remained mechanistically opaque to date. We now report rate studies of an LDA-mediated ester enolization that constitutes the first detailed view of the key solvation and deaggregation events.

LDA was generated from diisopropylamine using *n*-BuLi and was multiply recrystallized from hexane.^{3b} Previous structural investigations have shown LDA to be a disolvated dimer (**1**) over a range of THF and LDA concentrations.^{3f,5}

Pseudo-first-order conditions were established with LDA at normal concentrations (typically 0.10 M) by restricting the ester concentration to 0.004 M. The THF was maintained at high, yet adjustable, concentrations in toluene to determine the reaction order in THF. IR spectra were recorded with a ReactIR

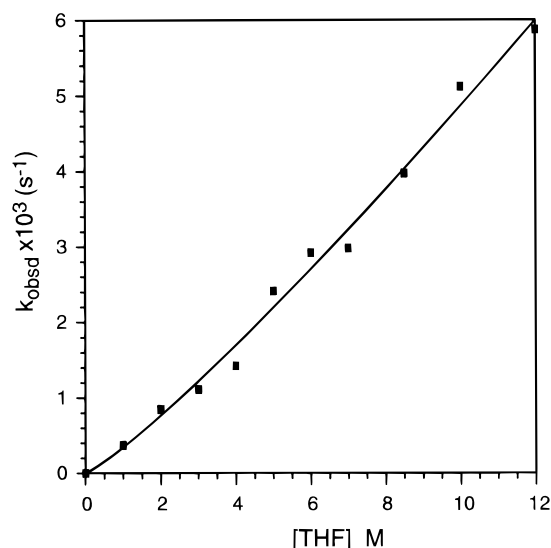
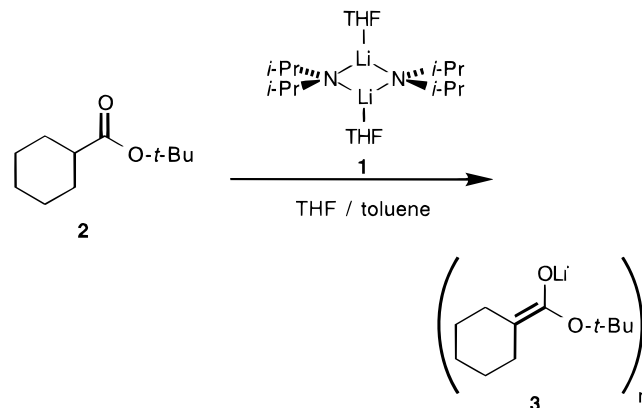


Figure 1. Plot of k_{obsd} versus [THF] in toluene cosolvent for the disappearance of **2** (0.004 M) by LDA (0.10 M) at -53 ± 0.5 °C. The curve depicts the result of an unweighted least-squares fit to $f(x) = ax^b$ ($b = 1.15 \pm 0.06$).

1000 fitted with an immersible SiComp ATR probe.⁷ The disappearance of ester **2** (1727 cm^{-1}) and the appearance of enolate **3** ($1646\text{--}1664 \text{ cm}^{-1}$) was readily monitored. An ester–LDA complex is not observable under these conditions.⁸



The metalation of **2** in THF/toluene is first order in **2** to greater than five half-lives. The rate constants are comparable over a 10-fold range of initial ester concentrations (0.004–0.04 M). In principle, low concentrations of LDA–lithium enolate mixed aggregates or any undetected byproduct of the reaction (such as diisopropylamine or metalated THF) could measurably influence the enolization rate.⁹ However, upon completion of each kinetic run, the spectral baseline was reestablished, a

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(8) Addition of ester **2** to solutions of LDA (0.1 M) and Et₂O (0.2 M) in toluene at -78 °C affords appreciable concentrations of a precomplex as evidenced by a new absorbance at 1703 cm^{-1} . Further addition of 2.0 equiv of THF affords uncomplexed **2** quantitatively. For leading references to detectable organolithium–substrate pre-complexation, see: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. For theoretical studies of substrate precomplexation, see: Bachrach, S. M.; Ritchie, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 3134 and references cited therein.

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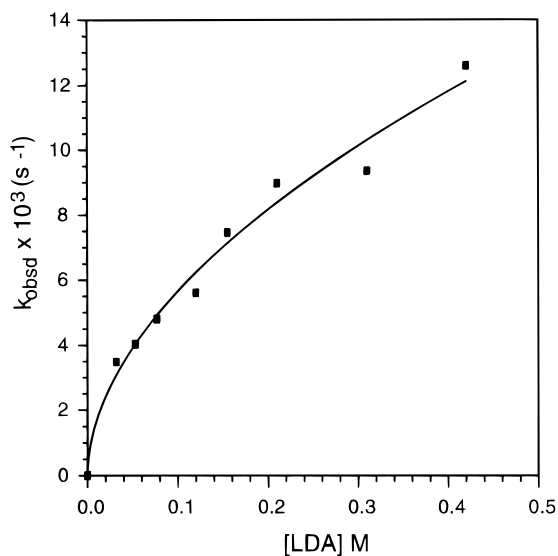
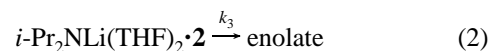
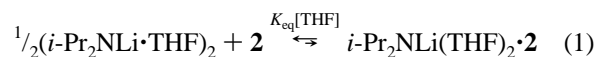


Figure 2. Plot of k_{obsd} versus [LDA] for the enolization of **2** (0.004 M) by LDA in neat THF at -53 ± 0.5 °C. The curve depicts the result of an unweighted least-squares fit to $f(x) = ax^b$ ($b = 0.53 \pm 0.03$).

second aliquot of **2** was added, and the pseudo-first-order rate constant for the disappearance of **2** was determined. The rate constants for the first and second injections were equal within experimental error ($\pm 10\%$).

Comparison of the metalation rates of **2** and **2-d₁** in neat THF reveals an isotope effect ($k_{\text{H}}/k_{\text{D}} = 22 \pm 1$) consistent with a rate-determining proton transfer. The pseudo-first-order rate constants for the metalation of **2** are proportional to the THF concentration (Figure 1; $k_{\text{obsd}} \propto [\text{THF}]^{1.15 \pm 0.06}$). While the slight upward curvature could be evidence of a competitive second-order THF dependence, secondary shell (medium) effects could accompany the changes in the THF:toluene proportions.¹⁰ Figure 2 illustrates the dependence of the pseudo-first-order rate constants on the LDA concentration (0.035–0.42 M) in neat THF at -53 ± 0.5 °C. The fractional order ($k_{\text{obsd}} \propto [\text{LDA}]^{0.53 \pm 0.03}$) is consistent with a spectroscopically invisible

dimer-monomer pre-equilibrium. We can now complete the general mechanism and the idealized rate law (eqs 1–3).



$$-\text{d}[\mathbf{2}]/\text{d}t = k_3 K_{\text{eq}}[\text{THF}][i\text{-Pr}_2\text{NLi}\cdot\text{THF}]^{1/2}[\mathbf{2}] \quad (3)$$

In 1976, Ireland and co-workers suggested that LDA-mediated enolizations may proceed via cyclic transition structures based upon disolvated LDA monomers.¹¹ While this model has received widespread attention for its predictive power, the transition structure stoichiometry remained unsubstantiated. More recent mechanistic discussions have considered the role of dimer-based transition structures.¹² The rate studies presented here implicate disolvated LDA monomers as the reactive form, providing the first direct support for Ireland's hypothesis. We hasten to add, however, that the details, including the chairlike form of the cyclic transition structure, require further evaluation.¹³ In addition, there is no evidence that other enolizations, especially those of less hindered substrates, proceed through analogous disolvated monomer-based transition structures. Nevertheless, we can now begin to focus upon complementary techniques including computational methods¹³ to probe the details of the reaction coordinate.

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Supporting Information Available: Experimental procedure for rate constant determinations, representative IR spectra, and representative first-order decay (3 pages). See any current masthead for ordering and Internet access instructions.

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