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

Xiufeng Sun, Sarita L. Kenkre, Julius F. Remenar, James H. Gilchrist, and David B. Collum* 

Department of Chemistry, Baker Laboratory Cornell University, Ithaca, New York 14853-1301

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Lithium diisopropylamide (LDA) is one of the most important Bronsted bases in organic synthesis.1 While LDA structure determinations2-4 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 determinations of LDA structure and pseudo-first-order reaction order in THF. IR spectra were recorded with a ReactIR press.

Figure 1. Plot of kobsd versus [THF] in toluene cosolvent for the disappearance of ester 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 $k = ax^n$ ($b = 1.15 ± 0.06$).

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.7 However, upon completion of each kinetic run, the spectral baseline was reestablished, a


(7) ASI Applied Systems, Millersville, MD 21108.

(8) Addition of ester 2 to solutions of LDA (0.1 M) and EtOH (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. Rec. 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.

(9) For an extensive bibliography and leading references to mixed aggregation of lithium amides, see: Romesberg, F. E.; Collum, D. B. J. Am. Chem. Soc. 1994, 116, 9198.
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 $2\text{-}d_1$ in neat THF reveals an isotope effect ($k_H/k_D = 22 \pm 1$) 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 $-53 \pm 0.5 \, ^\circ\text{C}$. 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).

$$\begin{align*}
1/2(i\text{-Pr}_2\text{NLi} \cdot \text{THF})_2 + 2 & \overset{k_{\text{eq}[\text{THF}]}}{\rightleftharpoons} i\text{-Pr}_2\text{NLi}(\text{THF})_2 \cdot 2 \quad (1) \\
i\text{-Pr}_2\text{NLi}(\text{THF})_2 \cdot 2 & \overset{k_3}{\longrightarrow} \text{enolate} \quad (2) \\
-d[2]/dt &= k_3 K_{\text{eq}[\text{THF}]}[i\text{-Pr}_2\text{NLi} \cdot \text{THF}]^{1/2} \quad (3)
\end{align*}$$

In 1976, Ireland and co-workers suggested that LDA-mediated enolizations may proceed via cyclic transition structures based upon dissolved 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 dissolved 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 dissolved monomer-based transition structures. Nevertheless, we can now begin to focus upon complementary techniques including computational methods\(^{(13)}\) 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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