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The Two Alternative Rate-Determining Steps in Benzylic Lithiation Reactions of Esters and Carbamates

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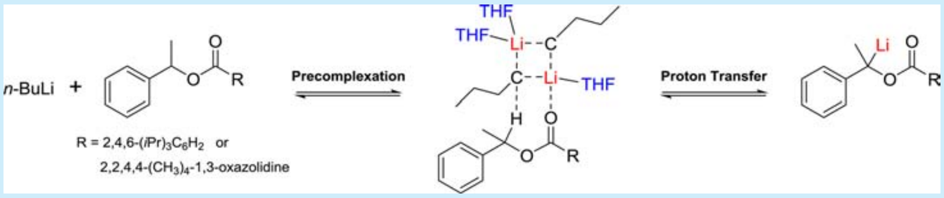
Supporting Information



ABSTRACT: Lithiation reactions of tertiary benzylic esters and carbamates have been studied. Kinetic methodology revealed that a two-step reaction pathway should be considered for these reactions, where either the lithium precomplexation and/or the proton transfer steps can be rate determining. Kinetic isotopic effects were evaluated by comparison of the lithiations of the corresponding protio/deutero substrates, and the results obtained support the notion that lithium precomplexation is taking place on the reaction pathway and that it is the rate-determining step in this transformation.

The mechanisms of heteroatom-directed lithiations continue to be the focus of theoretical and experimental investigations due to the key role that deprotonative lithiations play in many carbon−carbon and carbon−heteroatom bond-forming synthetic reactions.[1] These processes are commonly hypothesized to occur via coordination of the lithium atom of the base with a lone pair of a donor heteroatom of the directing group of the acid, to form a prelithiation complex where the basic center and the acidic hydrogen are located close to each other. A large number of studies support the existence of this type of lithium coordination to heteroatoms in ground states,[2] their involvement in determining the degree of aggregation of organolithium reagents in donor solvents being, perhaps, the more paradigmatic example.[3−5] Nevertheless, only a few studies confirm that the prelithiation complex is on the reaction pathway.[6]

Trapping experiments have been reported to not distinguish between one- (direct deprotonation without prior RLi coordination) and two-step (formation of a prelithiation complex followed by deprotonation) processes.[7] This limitation makes advisible the use of kinetic studies to gain accurate information about deprotonation pathways, especially when two-step processes are suspected to be taking place.[8]

Our studies on the lithiation of benzyl methyl ether (**1**)[9] (Figure 1) with *n*-BuLi in THF/hexane at −80 °C showed that a precoordination step between base and acid occurs prior to the rate-determining proton transfer reaction. We now describe the results of a study on the lithiation of benzyl ester **2** and carbamate **3**, substrates analogous to ether **1** in which the *O*-substituents show enhanced donor ability. The main goal of the present study was to establish which is the rate-determining step for the deprotonation of benzyloxy systems substituted with strong donor groups, the lithium precomplexation or the proton transfer reaction, since neither reactivity scales based on product yield after quenching nor competitive experiments provide accurate information concerning the nature of the intermediates and/or the detailed reaction mechanism.

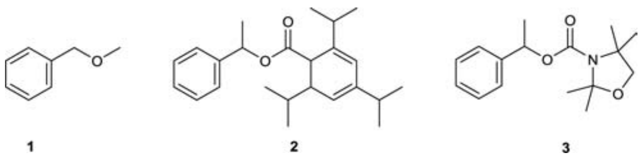


Figure 1. Compounds used in the kinetic study.

Evolution of absorbance vs time for the reaction of ester **2** (5×10^{-5} M) with a large excess of *n*-BuLi (0.114 M) in THF/hexane (3:1) at −80 °C gives an excellent fit to a monoexponential increase (see Figure S1 in Supporting Information). Figure 2 shows the dependence of the pseudo-first-order rate constant, k_{obs}, on [*n*-BuLi] in three different solvent mixtures. Two main observations are derived from these plots: (*i*) there is a nonlinear influence of [*n*-BuLi] on k_{obs}, and (*ii*) k_{obs} decreases when the amount of THF in the reaction mixture increases.

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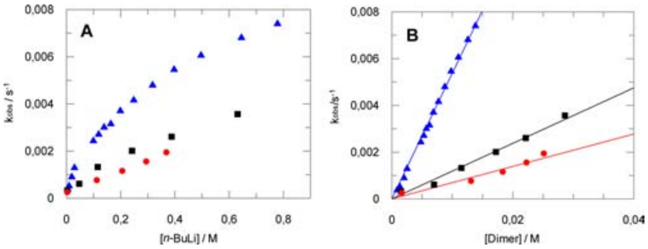


Figure 2. (A) Dependence of the pseudo-first-order rate constant, k_{obs}, on [*n*-BuLi] for lithiation of **2** at −80 °C in different THF/hexane mixtures: (▲) 15:85; (■) 50:50; (●) 75:25. (B) Pseudo-first-order rate constants vs $[n\text{-BuLi}]_{dimer}$.

Because reactivity is strongly dependent on *n*-BuLi aggregation,[10] the lithiation of benzyl ether **1** follows a pathway in which *n*-BuLi tetramer−dimer deaggregation occurs in a fast equilibrium step, followed by dimer complexation to the oxygen atom of the ether, and a subsequent proton transfer as the rate-determining step.[9] When the same mechanistic scheme is applied to the lithiation of ester **2**, a rate equation is obtained, $k_{obs} = K_1k_2$ [dimer] (K_1 and k_2 being the precomplexation equilibrium and proton transfer rate constants respectively), which predicts a linear dependence between the observed rate constant and [dimer] (see Figure 2, right).

Slopes in the Figure 2 right-side plot, i.e. $(5.37 \pm 0.1) \times 10^{-1}$ M^{-1} s^{-1}, $(1.19 \pm 0.1) \times 10^{-1}$ M^{-1} s^{-1}, and $(6.94 \pm 0.2) \times 10^{-2}$ M^{-1} s^{-1} for solutions with 15%, 50%, and 75% THF in hexane, respectively, indicate that the lithiation rate increases on decreasing solvent polarity. A tentative explanation considering proton transfer being the rate-determining step, $k_{obs} = K_1k_2$[dimer], implies that the slope of k_{obs} vs [dimer] does not correspond to a single bimolecular rate constant, but instead to the product of the proton transfer rate constant multiplied by the equilibrium constant for *n*-BuLi dimer precomplexation with ester **2**. Because *n*-BuLi self-aggregation increases on decreasing THF percentage,[11] we expect a similar effect on the equilibrium constant for *n*-BuLi precomplexation with compound **2**.

The observed difference, about 30 times, for lithiation of ester **2** and ether **1** (see Figure S2 in SI) in THF/hexane (50:50) cannot account for the larger ability of **2** to coordinate *n*-BuLi and its higher acidity (at least 3 pK_a units[12]) with respect to ether **1**.[13] These results suggest a different rate-determining step operating in both deprotonation processes.

Deuterated ester **2-D** was synthesized and reacted with *n*-BuLi in a mixture of THF/hexane (75:25). Unexpectedly, we did not observe single exponential behavior, as shown in Figure S1 for the lithiation of **2-H** (see Supporting Information), but double exponential behavior was observed instead (Figure 3). This double exponential behavior cannot be attributed to instability of the α-lithiated ester, as only starting material **2-D** was observed after quenching the reaction mixture with deuterated methanol and checking the crude product by ^{1}H NMR spectroscopy (see Supporting Information).

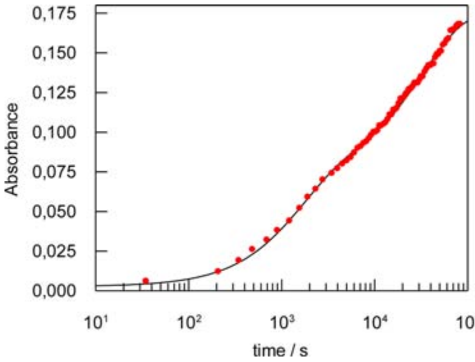


Figure 3. Time evolution of the absorbance (λ = 330 nm) for reaction of **2-D** (5.0×10^{-5} M) with *n*-BuLi (0.114 M), in THF/hexane (75:25) at −80 °C. Curve shows the fitting of experimental data to a double exponential rate equation. Note that experimental conditions are the same as those shown in Figure S1.

Experimental behavior shown in Figure 3 cannot be explained also as a consequence of **2-D** being contaminated with a small fraction of nondeuterated compound **2**, because the variation in absorbance detected for the first exponential is almost half of the overall variation, which would mean that **2-D** would have to be contaminated with approximately 50% of the protio-ester **2**. This level of contamination is not supported by the NMR spectrum of **2-D**. The observed double exponential behavior can, instead, be justified by the accumulation of an intermediate along the reaction pathway. We propose that this intermediate is a complex of *n*-BuLi and **2-D**, where **2-D** has replaced one of the THF molecules in the coordination sphere of the *n*-BuLi dimer.[14]

Figure 4 shows the [*n*-BuLi] dependence of the observed rate constants of the fast, k_{obs}^{fast} (intermediate formation), and slow, k_{obs}^{slow} (intermediate decomposition), processes calculated by fitting the experimental absorbance vs time data with a double exponential equation (e.g., Figure 3) for the lithiation of **2-D**. The observed rate constants for the lithiation of compound **2** are plotted for comparison purposes. The results shown in Figure 4 agree with the reaction mechanism proposed in Scheme 1. From Figure 4 it can be seen that the ratio between both processes, k_{obs}^{fast} and k_{obs}^{slow}, is larger than 10, so they can be treated independently.[15] Considering that the tetramer−dimer disaggregation is much faster than the lithiation step,[16] we can define the following rate equations for the intermediate formation and its decomposition.

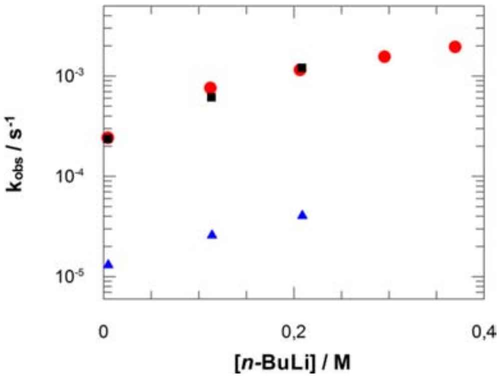
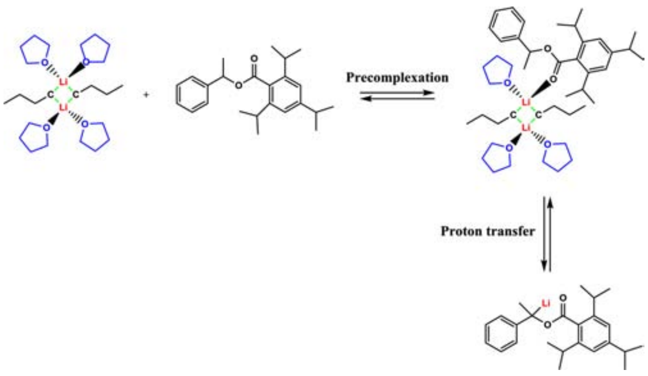


Figure 4. Influence of [*n*-BuLi] for lithiation of **2** and **2-D** in THF/hexane (75:25) at −80 °C. (●) Lithiation of **2** where a single exponential kinetics has been observed. For **2-D**, a double exponential behavior has been observed with experimental values corresponding to (■) fast exponential behavior, k_{obs}^{fast}, and (▲) slow exponential behavior, k_{obs}^{slow}.

$$k_{obs}^{fast} = k_1[\text{dimer}] + k_{-1} \quad (1)$$

Scheme 1. Proposed Reaction Pathway



$$k_{\mathrm{obs}}^{\mathrm{slow}} = \frac{K_1k_2[\mathrm{dimer}]}{1 + K_1[\mathrm{dimer}]} \qquad (2)$$

In proposing eq 2 we have assumed that the second step is irreversible, because of the large pK_a difference between butane and lithiated **2**. Analysis of the fast process yields k_1 = (5.8 ± 0.7) × 10^{-2} M^{-1} s^{-1} for the lithiation of **2-D** (under the experimental conditions it is not possible to gain an accurate determination of the intercept, k_{-1}). This value agrees well with the slope previously obtained for lithiation of **2** (see Figure 2), Slope = (6.94 ± 0.2) × 10^{-2} M^{-1} s^{-1}. As the precomplexation of ester **2** with *n*-BuLi will be mainly unaffected by isotope substitution, we propose that the rate-determining step in this reaction is the formation of the precomplexed species rather than the proton transfer process. Consequently slopes in Figure 2 can be assigned to the rate constant for the precomplexation step, k_1.

On the assumption 1 ≫ K_1[dimer], a linear dependence between the rate constant and [dimer] is expected. From Figure 4 a value of K_1k_2 = (2.2 ± 0.3) × 10^{-3} M^{-1} s^{-1} can be obtained. Comparison of the rate constants for the lithiation of **2** and **2-D** suggests an isotope effect of $k_H/k_D \geq 31$. This estimation is based on the fact that rate constants for the proton transfer step with compound **2** should be faster than *n*-BuLi precomplexation in such a way that only single exponential behavior has been observed. This observed isotope effect is close to those previously determined for other lithiation reactions.[17]

Further evidence of *n*-BuLi complexation as part of the reaction pathway was obtained from the study of the lithiation of carbamate **3**, a substrate of higher donating ability than ester **2**. Double exponential behavior was observed in the lithiation reaction of carbamate **3** in THF/hexane (3:1) mixtures at −80 °C (see Figure S31 in SI). As in the previous case, decomposition of the carbanion can be ruled out by NMR analysis of the products after quenching (see SI). Comparison of lithiation reactions of ester **2** and carbamate **3** shows that, on increasing the electron donating ability of the substrate, a change from monoexponential to double exponential behavior is observed. The higher electron-donating ability of the carbamate group strengthens the lithium complexation and, therefore, increases the overall rate of the process. This is consistent with an increase in reactivity over 500 times going from **2** to **3**, regardless of the pK_a values being very close.[12] Using a double exponential equation we were able to obtain the rate constants corresponding to the fast (precomplexation, k_1 = (4.7 ± 0.1) M^{-1} s^{-1}) and slow (proton transfer reaction, K_1k_2 = (0.67 ± 0.09) M^{-1} s^{-1}) processes for carbamate **3** at different [*n*-BuLi] (Figure S36 in SI). It should be noted that both k_1 and the product K_1k_2 are 10^2 times larger for **3** than **2-D**, due to its higher donor ability and the isotope effect.

Lithiation of deuterated-carbamate **3-D** has also been kinetically studied with double exponential behavior being observed. Due to the isotopic substitution, the lithiation reaction of **3-D** proceeded slower than in the case of carbamate **3** and longer time scales were required. Under the experimental conditions the existence of two exponential processes was confirmed, but we have been unable to obtain accurate data for the first one corresponding to *n*-BuLi precomplexation. Figure S4 also shows the rate constants observed for the slow process in the lithiation of deuterated carbamate **3-D**, allowing us to obtain the product K_1k_2 = (1.9 ± 0.1) × 10^{-2} M^{-1} s^{-1}. Assuming that precomplexation binding constants are mainly unaffected by isotopic substitution, we derived a kinetic isotope effect of k_H/k_D = 35, similar to that previously estimated for the **2**/**2-D** lithiation.

In summary, our results show clear evidence that lithium precomplexation is taking place along the reaction pathway, discarding the occurrence of one-step mechanisms with a single transition state where complexation and proton transfer occur simultaneously. We have also uncovered evidence that the rate-determining step may be either the formation of the intermediate complex or the proton transfer reaction. Most importantly, it has been shown that kinetic methodology is more informative than competitive or quenching experiments to provide a reactivity scale because the existence of different rate-determining steps along the reaction pathway are invisible to traditional methodologies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02753.

Full experimental details, kinetic experiments, characterization data, and NMR (PDF)

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Notes

The authors declare no competing financial interest.

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(11) *n*-BuLi aggregation constants increase from 44 M^{-1} in THF (100%) to 849 M^{-1} in THF/hexane (25:75) at −80 °C on decreasing the solvent polarity. See ref 9.

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(13) Based on a difference of 3 pK_a units, we expect **2** to be at least 30 times more reactive than **1** just by considering a slope equal to 0.5 in a typical Brønsted plot between acids and bases with a very large pK_a difference. Moreover, the difference in reactivity must be increased by a factor accounting for the different donor ability of **1** and **2**. Therefore, a difference in reactivity not smaller than 10^2 times should be expected.

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