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Mechanism of the Reaction of Lithium Reagents with Esters

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The kinetics and mechanism of the reactions of esters with alkyllithium reagents in cyclohexane and benzene have been investigated by infrared stopped-flow spectroscopy. Esters have been found to form complexes with *sec*-butyllithium, *n*-butyllithium, and cyclopentyllithium aggregates and the equilibrium constants for complexation were evaluated for several compounds. The rates of disappearance of esters are inversely dependent on the concentration of the lithium reagent. Complexation equilibrium constant data and rate data for the reactions of a series of substituted ethyl benzoates with *sec*-BuLi exhibit a substituent effect. A mechanism in which complexed ester can yield ketone and free ester can react with monomeric alkyllithium to give free ketone followed by a similar scheme for free and complexed ketone to give final products is proposed.

The preparation of tertiary alcohols by the addition of organolithium reagents to esters is a common synthesis. Although a ketone intermediate is generally presumed to be involved, the mechanism of this reaction has received little attention. Holm[1] has reported a kinetic study of the reaction of *n*-BuLi with methyl trifluoroacetate in ether at −28 °C. He found the reaction was first order in *n*-BuLi and zero order in ester and concluded that the dissociation of *n*-BuLi tetramer to reactive monomer is the rate limiting step. The reactions of methyllithium-lithium bromide with ethyl 4-methylthiobenzoate and phenyl 4-methylthiobenzoate in ether have been reported[2] to be one-fourth order in lithium reagent. Scheme I was proposed to accommodate the rate data.

Scheme I

$$\mathrm{Me_4Li_4 \rightleftharpoons 4MeLi}$$

$$\mathrm{MeLi + ester \rightarrow product}$$

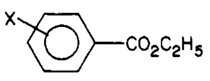
Recently, we reported[3] the observation of a ketone–lithium reagent complex in the reactions of ketones with alkyllithium reagents in cyclohexane. The formation of the complex plays a crucial role in the proposed kinetic course of the reaction (Scheme II). We now report the observation of an ester–lithium reagent complex in the reactions of esters with several alkyllithium reagents. This paper describes an investigation of the reactions of substituted ethylbenzoates **1a–i** with *sec*-BuLi, *n*-BuLi, and cyclopentyllithium in cyclohexane and benzene which is directed toward the elucidation of the kinetic and mechanistic role of the ester–lithium reagent complex in these reactions.

Scheme II

$$\mathrm{R}_n\mathrm{Li}_n \rightleftharpoons n\mathrm{RLi}$$

$$\mathrm{ketone} + \mathrm{R}_n\mathrm{Li}_n \rightleftharpoons \mathrm{complex} \rightarrow \mathrm{product}$$

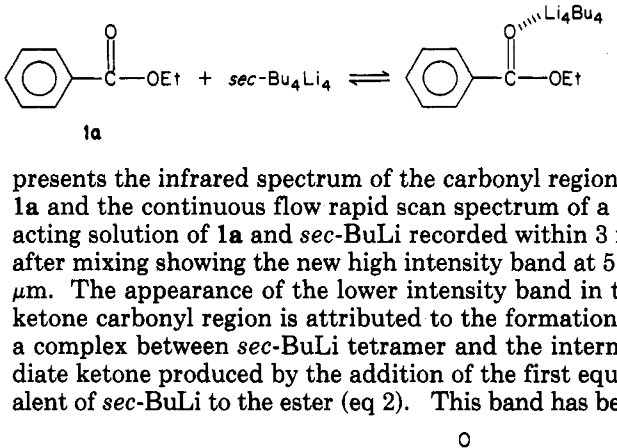
$$\mathrm{ketone + RLi \rightarrow product}$$



1a, X = H
b, X = 4-C_6H_5O
c, X = 4-CH_3O
d, X = 4-*t*-Bu
e, X = 4-Cl
f, X = 3-F
g, X = 3-CH_3
h, X = 3,5-Cl_2
i, X = 3,5-$(CF_3)_2$

Results

Reaction of *sec*-BuLi with 1a–i in Cyclohexane. The kinetics of the reactions of (2–30) × 10^{-2} M *sec*-BuLi with (7–9) × 10^{-3} M substituted ethyl benzoates in cyclohexane at 25.0 °C were investigated by infrared, stopped flow spectroscopy. Mixing of an ester with lithium reagent produced two new bands in the infrared spectrum: a strong band that is immediately present at a longer wavelength relative to the ester carbonyl stretch and a second lower intensity band that grows in and disappears in the ketone carbonyl region. The appearance of the high intensity band is attributed to the reversible formation[4] of an ester–*sec*-BuLi tetramer complex (eq 1). Figure 1 presents the infrared spectrum of the carbonyl region of **1a** and the continuous flow rapid scan spectrum of a reacting solution of **1a** and *sec*-BuLi recorded within 3 ms after mixing showing the new high intensity band at 5.88 μm. The appearance of the lower intensity band in the ketone carbonyl region is attributed to the formation of a complex between *sec*-BuLi tetramer and the intermediate ketone produced by the addition of the first equivalent of *sec*-BuLi to the ester (eq 2). This band has been observed previously in the reaction of phenyl *sec*-butyl ketone with *sec*-BuLi.[3] An infrared scan of a reacting solution of **1a** that was aged slightly revealed the presence of the intermediate ketone–*sec*-BuLi complex at 5.91 μM as a shoulder on the ester **1a** complex band (Figure 2a). This was confirmed by an increase in the intensity of this



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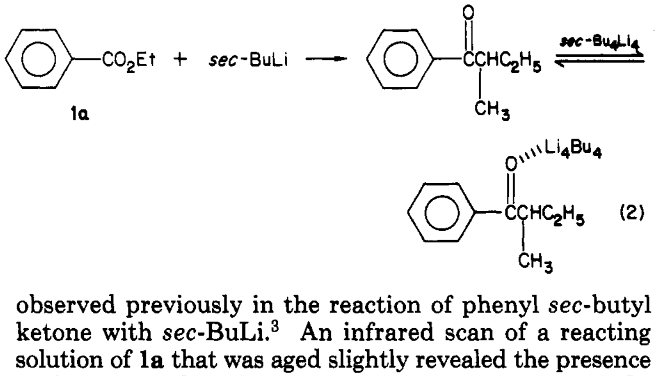

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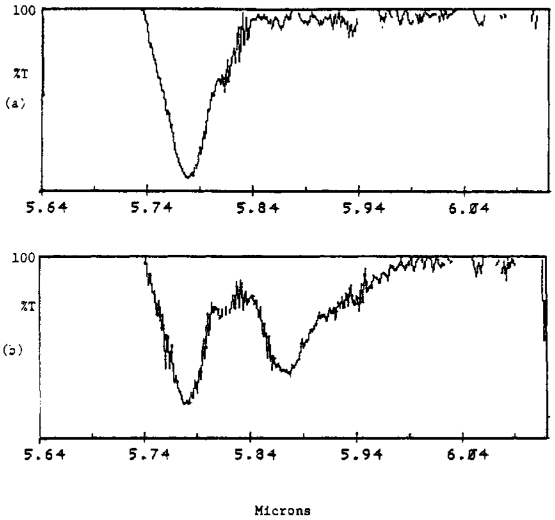


Figure 1. Plot of percent transmission vs. wavelength: (a) 7.2 × 10^{-1} M ethyl benzoate; (b) reacting mixture of 7.2 × 10^{-3} M ethyl benzoate and 1.5 × 10^{-2} M *sec*-butyllithium 25 °C. The spectra were digitized by using 384 data points and generated by subtracting the absorbance spectrum of the solvent, cyclohexane, from the absorbance spectrum of interest.

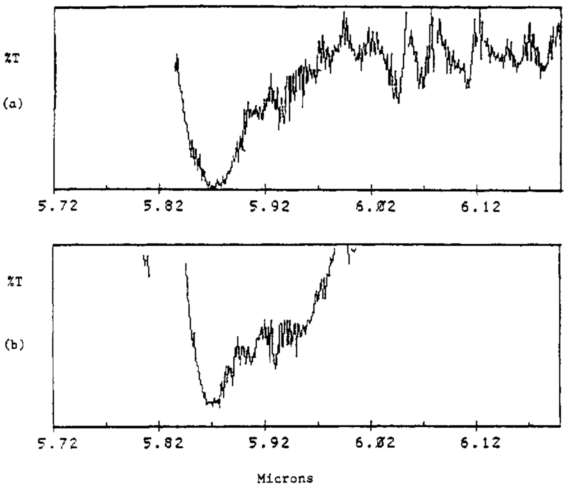


Figure 2. Plot of percent transmission vs. wavelength: (a) reacting mixture of 7.6 × 10^{-3} M ethyl benzoate and 0.12 M *sec*-butyllithium in cyclohexane at 25.0 °C; (b) reacting mixture of 7.6 × 10^{-3} M ethyl benzoate, 7.5 × 10^{-3} M phenyl *sec*-butyl ketone, and 0.12 M *sec*-butyllithium in cyclohexane at 25.0 °C. The spectra are digitized by using 384 data points and generated by subtracting the absorbance of the solvent, cyclohexane, from the absorbance spectrum of interest.

band when a scan for the reaction of *sec*-BuLi with a mixture of ethyl benzoate and phenyl *sec*-butyl ketone was recorded under similar conditions (Figure 2b).

The equilibrium constant for complexation, K_c, for an ester was determined from initial absorbance measurements of the ester as it was mixed with reagent solutions of various concentrations (eq 3–5), where b and ϵ are the

$$K_c = [\text{ester}{\cdot}sec\text{-Bu}_4\text{Li}_4]/[\text{ester}][sec\text{-Bu}_4\text{Li}_4] \quad (3)$$

$$K_c = ([\text{ester}]_0 - [\text{ester}])/[\text{ester}]([sec\text{-Bu}_4\text{Li}_4]_0 - [\text{ester}]_0 + [\text{ester}]) \quad (4)$$

$$[\text{ester}] = A_{\text{ester}}/b\epsilon_{\text{ester}} \quad (5)$$

infrared cell path-length and extinction coefficient of the ester, respectively. A_{ester} is the absorbance of the ester solution immediately after mixing with *sec*-BuLi but before any reaction has occurred. Values of K_c and the carbonyl wavenumber shift (i.e., difference in frequency of the ester and ester–reagent complex carbonyl stretches) for selected compounds are listed in Table I. Correlation of K_c values with Hammett σ constants gives ρ = −1.33 ± 0.07.

Table I. Infrared Carbonyl Wavenumber Shifts and Equilibrium Constants of Complexation for the Reaction of *sec*-Butyllithium with Substituted Ethyl Benzoates in Cyclohexane at 25.0 °C

substituted ethyl benzoate	$\Delta\nu_{CO}$, cm^{-1}	K_c, M^{-1}
4-C_6H_5O	−31	138 ± 17
H	−26	87 ± 7
3-CF_3	−22	46 ± 4
3,5-Cl_2	−22	35 ± 2
3,5-$(CF_3)_3$	−18	27 ± 2

The disappearance of esters **1a–h** upon reaction with excess *sec*-BuLi could be followed at either the free ester carbonyl band or the ester–reagent complex band, though the latter is preferred as most of the ester exists in the complexed form at higher reagent concentrations. Both carbonyl bands exhibit pseudo-first-order kinetics for the rate of disappearance and yield the same rate constants within experimental error. The intermediate ketone–reagent complex gives a band which grows in rapidly and disappears. The dependence of the pseudo-first-order rate constant, k_{obsd}, on *sec*-BuLi concentration is complex. In nearly every case, k_{obsd} reached a maximum and then decreased with increasing alkyllithium concentration. Figure 3 contains k_{obsd} vs. *sec*-BuLi concentration plots for esters **1a–i**.

The observed pseudo-first-order rate constant has been found to be directly dependent on initial ester concentration in these reactions. Figure 4 illustrates this relationship for esters **1a**, **1b**, and **1g**.

The rate of the reaction of **1a** with *sec*-BuLi was greatly accelerated by the addition of a small amount of tetramethylethylenediamine (TMEDA). A 9.6 × 10^{-3} M ester **1a** solution containing ca. 9.6 × 10^{-4} M TMEDA was allowed to react with 0.116 M *sec*-BuLi in cyclohexane. The reaction was too rapid to allow for accurate measurement of the rate constant (i.e., $k_{\text{obsd}} \geq 600$ s^{-1}). The addition of TMEDA to the alkyllithium solution effects a similar rate enhancement. The presence of 2% TMEDA (by concentration) in *sec*-BuLi solution was sufficient to increase k_{obsd} by a factor of 50. Addition of a small amount of diethyl ether to the solvent also accelerates the reaction rate. The reaction of 0.01 M ethyl benzoate with 0.082 M *sec*-BuLi in a 2.5:97.5 ether–cyclohexane solvent system had a rate constant of 500–600 s^{-1}.

Reactions of *n*-BuLi with 1a and 1h in Cyclohexane. The addition of (2–25) × 10^{-2} M *n*-BuLi to 8.6 × 10^{-3} M **1a** and 8.3 × 10^{-3} M **1b** in cyclohexane gives rise to a new absorptions (ca. 5.86 μ for **1a**, 5.83 μm for **1h**) in the infrared spectra of the esters. The new bands in the carbonyl region signify the presence of ester-*n*-butyllithium complexes. The infrared carbonyl wavenumber shifts of the ester **1a** and ester **1h**–*n*-BuLi complex are 20 cm^{-1} and 18 cm^{-1}, respectively. The rates of disappearance of the esters were measured by following the disappearance of the carbonyl bands of the complexes. The k_{obsd} for both reactions was again inversely related to the *n*-BuLi concentration.

Reactions of Cyclopentyllithium with 1a in Cyclohexane. Ethyl benzoate, upon mixing with cyclopentyllithium, produced a strong new band in the infrared spectrum at 5.85 μM. The new band is attributed to the formation of a complex between **1a** and cyclopentyllithium hexamer. A value of 80 ± 20 M^{-1} was determined for the equilibrium constant of complexation. Three bands are observable in the infrared spectrum of the reacting solu-

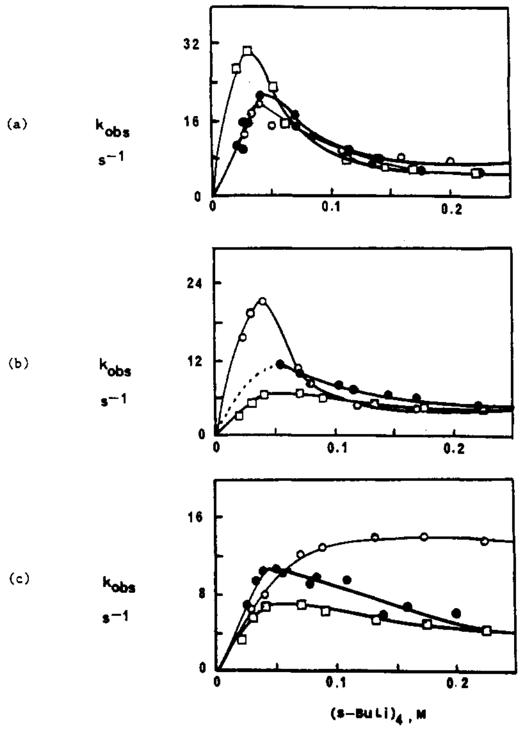


Figure 3. Plots of k_{obsd} vs. *sec*-BuLi concentration: (a) reaction with 8.25 × 10^{-3} M **1b** (□), 8.10–8.35 × 10^{-3} M **1a** (●), 9.5 × 10^{-3} M **1c** (○); (b) 8.2 × 10^{-3} M **1d** (○), 8.05 × 10^{-3} M **1e** (□), 9.05 × 10^{-3} M **1f** (●); (c) 7.5–11.7 × 10^{-3} M **1g** (●), 8.35 × 10^{-3} M **1h** (□), 8.0 × 10^{-3} M **1i** (○). Rate constants were measured in cyclohexane at 25.0 °C.

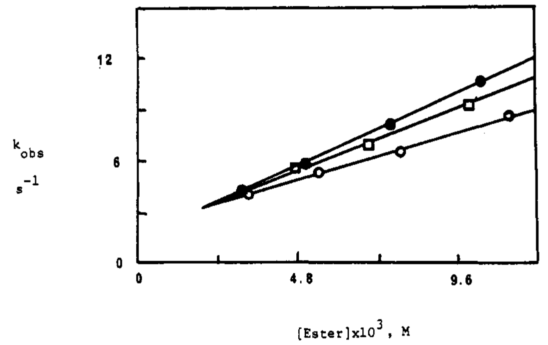


Figure 4. Plot of k_{obsd} vs. initial ester concentration for the reactions of **1b** (□), **1a** (●), and **1f** (○) with 0.091 M *sec*-BuLi in cyclohexane at 25.0 °C.

tion: the free ester band, the band due to the ester–reagent complex, and the band due to the intermediate ketone–reagent complex at 5.92 μm. The observed first-order rate constant for the disappearance of the ester and ester complex is dependent on initial ester concentration and inversely dependent on cyclopentyllithium concentration. The band due to intermediate ketone complex at 5.92 μm grows in at a rate comparable to the rate of disappearance of ester **1a** or the ester **1a** complex.

The rate of disappearance of the band due to the ester **1a** complex is strongly increased by lithium alkoxide present in the reacting mixture. Table II summarizes the effect of added lithium ethoxide (generated by the addition of ethyl alcohol to cyclopentyllithium solutions before mixing with ethyl benzoate) on k_{obsd} and K_{eq}.

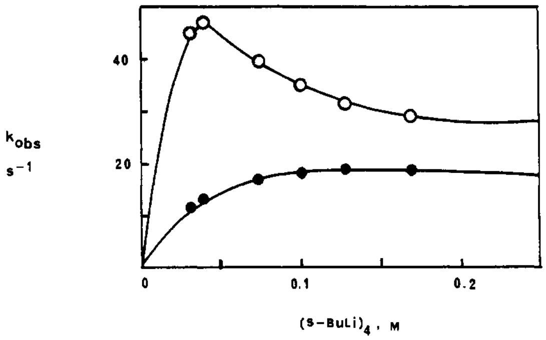


Figure 5. Plot of k_{obsd} vs. *sec*-BuLi concentration for the reactions of 8.6 × 10^{-3} M **1a** (○) and 7.4 × 10^{-3} M **1h** (●) in benzene at 25.0 °C.

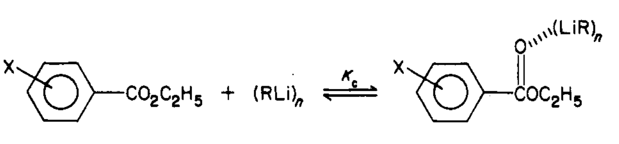
Table II. Effect of Lithium Ethoxide on the Observed Pseudo-First-Order Rate Constant and Equilibrium Constant of Complexation for the Reaction of Cyclopentyllithium with 1.33 × 10^{-2} M Ethyl Benzoate (1a) in Cyclohexane at 25.0 °C

[cyclopentyllithium], M	[LiOEt]/[cyclopentyllithium]	k_{obsd}, s^{-1}	K_c, M^{-1}
0.0730	0	2.60	122
0.0650	0.06830	4.70	98.1
0.0550	0.161	7.69	91.1
0.0364	0.365	12.2	55.4

Reaction of *sec*-BuLi with 1a and 1h in Benzene. The addition of *sec*-BuLi to ester **1a** or **1h** in benzene gives a new carbonyl band, which is attributed to an ester–*sec*-butyllithium complex in benzene. The free ester **1a** carbonyl stretch and the ester **1a** complex carbonyl stretch are observed in the infrared scan at 5.82 μm and 5.89 μm, respectively. Compared to the analogous complexes in cyclohexane, the carbonyl wavenumber shift of the ester **1a** complex in benzene (ca. 20 cm^{-1}) is smaller. The equilibrium constant of complexation for ethyl benzoate is qualitatively smaller in benzene than in cyclohexane. The rate of disappearance of esters **1a** and **1h** upon reaction with excess *sec*-BuLi was measured at the ester complex bands. The k_{obsd} for the reaction of ester **1a** exhibits inverse dependence on *sec*-BuLi concentration while k_{obsd} for ester **1h** reaction rises rapidly and levels off with increasing reagent concentration (Figure 5).

Discussion

Evidence has been presented for the formation of an ester–alkyllithium complex intermediate in the reactions of esters with lithium reagents in cyclohexane and benzene (eq 6). Association between the carbonyl group of the ester and the lithium of the alkyllithium aggregate in this complex is indicated by the shift to lower frequency of the carbonyl stretching band of the ester. The equilibrium constants of complexation for the substituted ethyl benzoates in cyclohexane display a trend: the greater the electron-withdrawing capacity of the substituent on the phenyl ring the smaller the complexation constant of the compound. The substituent effect on complexation is also reflected in the variation of the carbonyl wavenumber shifts of the complexed esters. A plot of log (K_c^x/K_c^H) vs. the substituent constant σ for several compounds gives a straight line with ρ = −1.3. This value of ρ is larger than the analogue value (ρ = −0.8) for the complexation of *sec*-BuLi with substituted phenyl *sec*-butyl ketones in cyclohexane reported in our previous paper.[3] This is consistent with the fact that esters as a class exhibit larger equilibrium constants of complexation than ketones in



(6)

Scheme III

$$R_nLi_n \overset{fast}{\rightleftharpoons} nRLi$$

$$\text{ester} + R_nLi_n \overset{K_{c1}}{\rightleftharpoons} \text{ester}\cdot R_nLi_n$$

$$\text{ester} + RLi \xrightarrow{k_1} \text{ketone} + LiOR$$

$$\text{ester}\cdot R_nLi_n + RLi \xrightarrow{k_2} \text{ketone}\cdot R_nLi_n + LiOR$$

$$\text{ketone} + R_nLi_n \overset{K_{c2}}{\rightleftharpoons} \text{ketone}\cdot R_nLi_n$$

$$\text{ketone}\cdot R_nLi_n \xrightarrow{k_3} \text{products}$$

$$\text{ketone} + RLi \xrightarrow{k_4} \text{products}$$

these reactions. Spectroscopic scans of reacting solutions of ester **1a** and *sec*-BuLi reveal the presence of a ketone–lithium reagent complex intermediate. In rate studies, the ketone–*sec*-BuLi complex was detected as a band which grows in and disappears in the ketone carbonyl stretching region.

The dependence of k_{obsd} on *sec*-BuLi concentration for the reactions of the substituted ethyl benzoates has been shown to vary with the substituent on the phenyl ring of the compound. In nearly all the cases examined, the pseudo-first-order rate constant reached a maximum value and then decreased with increasing reagent concentrations. Only in the reaction of ester **1i**, the compound containing the most electron-withdrawing substituent of the series, did k_{obsd} not exhibit inverse dependence on *sec*-BuLi concentration. The more electron donating the substituent on the ester the greater the rate of decrease of k_{obsd} with increasing *sec*-BuLi concentration. The substituent effect on rate data noted for the reactions of **1a–i** with *sec*-BuLi may be correlated with substituent effect on equilibrium constants of complexation with *sec*-BuLi discussed earlier. The smaller the K_c for a particular ester, the less pronounced the inverse dependence of k_{obsd} on reagent concentration. Hence, the complexation equilibrium constant of an ester determines the nature of the dependence of k_{obsd} on reagent concentration in its reaction with an alkyllithium.

The kinetics of these reactions are complicated by catalysis by lithium ethoxide product. The observed pseudo-first-order rate constants in all cases exhibit dependence on the initial ester concentration. It has been demonstrated (Table II) that the presence of lithium ethoxide in reacting solutions of ethyl benzoate and cyclopentyllithium causes a substantial rate enhancement and diminishes the complexation equilibrium constant.

A mechanism consisting of two alternate routes to product via an intermediate ketone may be envisioned for the reactions of alkyllithium reagents with esters in cyclohexane. Scheme III is an extension of the mechanism we recently proposed for the reactions of alkyllithiums with ketones in cyclohexane (Scheme II). The additional steps accommodate the formation and subsequent reaction of the intermediate ketone detected in these reactions. In Scheme III ester goes to product by means of two competing pathways involving aggregated and monomeric reagent. Based on kinetic studies in ether, reaction with monomeric alkyllithium is much more facile than reaction with aggregated reagent. The equilibrium constant of complexation is critical as it determines the fraction of ester than is complexed. For those compounds with a large K_c, as the reagent concentration increases a significant portion of the ester becomes complexed and has to go to product through the less facile complexation pathway (k_2) or through decomplexation (K_c^{-1}). The net effect is a decrease in the pseudo-first-order rate constant at higher alkyllithium concentration. On the other hand, esters possessing a small K_c remain relatively uncomplexed at higher reagent concentrations. Consequently, reactions with monomeric lithium alkyl remains the predominant pathway regardless of reagent concentration. The substituent effect on rate data observed for the reactions of **1a–i** with *sec*-BuLi confirms the crucial role of complex formation predicted by Scheme III.

The change in kinetics of the reactions of esters **1a** and **1h** upon changing the solvent from cyclohexane to benzene supports Scheme III. The solvent change resulted in a rate enhancement. More significantly, there was a change in the shape of the rate curves for the **1a** and **1h** ester reactions. In the former case, k_{obsd} declined less steeply with increasing *sec*-BuLi concentration after attaining a maximum. In the latter case, the maximum k_{obsd} observed for the reaction in cyclohexane is no longer present and instead k_{obsd} becomes constant at higher reagent concentrations. The decrease in the complexation equilibrium constant in benzene signifies that a great fraction of the ester is uncomplexed at higher *sec*-BuLi concentrations and thereby capable of going to product by reaction with monomeric reagent.

The reactions of ethyl benzoate with *n*-BuLi and cyclopentyllithium in cyclohexane were similar (in kinetic behavior) to the corresponding reaction with *sec*-BuLi. The rates of the former reactions, however, were substantially lower and inverse dependence of k_{obsd} on reagent concentration was more pronounced. The greater reactivity of *sec*-BulI vs. *n*-BuLi and cyclopentyllithium is apparently a consequence of its lower state of aggregation.[5]

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin-Elmer Model 237B or a Beckman IR-12 spectrophotometer in 0.1 mm NaCl cells or as films. Nuclear magnetic resonance spectra were obtained on a Varian EM-390 spectrometer. Melting points were measured on a Büchi melting point apparatus in open capillaries and are uncorrected. Gas chromatographic analysis were performed on a Hewlett Packard F&M Scientific 700 laboratory chromatograph equipped with a thermal conductivity detector. Kinetic experiments were performed with an infrared stopped flow spectrophotometer having a rapid scanning capability, which has been described previously.[6] A description of kinetic measurements and data analysis, the determination of complexation equilibrium constants and the procedure for lithium reagent preparation is found in our previous paper.[3]

Esters. Esters **1b–i** were prepared from the corresponding commercially available substituted benzoic acids by acid-catalyzed esterification with ethanol. 4-Phenoxybenzoic acid was prepared from (4-phenoxyphenyl)magnesium bromide by reaction with solid carbon dioxide.[5]

Ethyl 4-phenoxybenzoate (1b): 46% yield; bp 152–154 °C (0.4 mm); IR (neat) 1706 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ 1.5 (t, 3), 4.3 (q, 2), 7.0 (m, 4), 7.3 (m, 3), 8.0 (d, 2).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.35; H, 5.79. Found: C, 74.21; H, 5.72.

Ethyl 3-(trifluoromethyl)benzoate (1g): 67% yield; bp 28–29 °C (0.19 mm); IR (neat) 1721 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ 1.4 (t, 3), 4.4 (q, 2), 7.2–7.9 (m, 2), 8.3 (d, 2).

Anal. Calcd for $C_{10}H_9F_3O_2$: C, 55.05; H, 4.16; F, 26.12. Found: C, 55.06; H, 4.01; F, 26.18.

Ethyl 3,5-dichlorobenzoate (1h): 76% yield, mp 34–36 °C; IR (cyclohexane) 1736 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ 1.5 (t, 3), 4.4 (q, 2), 7.6 (t, 1), 7.9 (d, 2).

Anal. Calcd for $C_9H_8Cl_2O_2$: C, 49.33; H, 3.65; Cl, 32.29. Found: C, 49.23; H, 3.80; Cl, 32.50.

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Ethyl 3,5-bis(trifluoromethyl)benzoate (1i): 66% yield; IR (neat) 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.6 (t, 3), 4.5 (q, 2), 8.1 (s, 1), 8.5 (s, 2).

Anal. Calcd for $C_{11}H_8F_6O_2$: C, 46.15; H, 2.80; F, 39.38. Found: C, 46.62; H, 2.85; F, 39.64.

Products. Phenyl-*sec*-butylmethanol was prepared by the reduction of phenyl *sec*-butyl ketone with lithium aluminum hydride in ether. The ketone was added slowly to a slurry of the hydride in ether at room temperature. The mixture was stirred for 30 min and then quenced carefully with dilute sulfuric acid. Workup followed by distillation of the crude product gave the pure alcohol in high yield: bp 77–79 °C (0.82 mm); ^{1}H NMR ($CDCl_3$) δ 0.7–1.0 (m, 9), 1.8 (s, 1), 4.4 (m, 1), 7.3 (s, 5).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.49; H, 9.76. Found: C, 80.69; H, 9.59.

Phenyl di-*sec*-butylmethanol was prepared by the addition of ethyl benzoate (1 g, 6.7 × 10^{-3} mol) to 60 mL of 0.4 M *sec*-BuLi in cyclohexane under an argon atmosphere. The mixture was stirred for 5 min and then quenched with dilute sulfuric acid. The organic layer was washed with water and aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent and fractional distillation under vacuum gave the pure alcohol in ca. 62% yield: bp 92–94 °C (0.29 mm); ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 18), 1.5 (s, 1), 7.5 (s, 5).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.82; H, 10.91. Found: C, 81.44; H, 10.62.

Product Analysis. Effluents from the stopped-flow instrument obtained from the reactions of excess *sec*-BuLi with several esters were quenched with water. Each mixture was neutralized with dilute sulfuric acid and extracted with several portions of ether. The organic layer was washed with aqueous sodium bicarbonate and water and dried over anhydrous magnesium sulfate. Removal of the solvent afforded the crude product mixture which was analyzed by NMR spectroscopy and gas chromatography. In all cases, the tertiary alcohol (addition product) was the predominant constituent (>70%) of the product mixture. The reduction and enolization side products (i.e., secondary alcohol and ketone) accounted for the remaining portion of the product mixture. For example, the stopped-flow effluent from the reaction of ethyl benzoate with *sec*-BuLi contained 80% phenyldi-*sec*-butylmethanol, 18% phenyl-*sec*-butylmethanol, and 2% phenyl *sec*-butyl ketone by GC (3 ft × 0.125-in. column of 15% Carbowax 20 M on Chromosorb P, 165 °C column temperature). Product identities were confirmed by comparison of retention times with those of authentic samples.

Registry No. 1 (X = 3-CF_3), 76783-59-0; **1a**, 93-89-0; **1b**, 31994-68-0; **1c**, 94-30-4; **1d**, 5406-57-5; **1e**, 7335-27-5; **1f**, 451-02-5; **1g**, 120-33-2; **1h**, 91085-56-2; **1i**, 96617-71-9; *sec*-BuLi, 598-30-1; BuLi, 109-72-8; *sec*-BuC(O)Ph, 938-87-4; PhCH(*sec*-Bu)OH, 3968-86-3; PhC(*sec*-Bu)$_2$OH, 92860-07-6; cyclopentyllithium, 23473-12-3.

Diels–Alder Reaction of 1-Azadienes. A Total Synthesis of Deoxynupharidine

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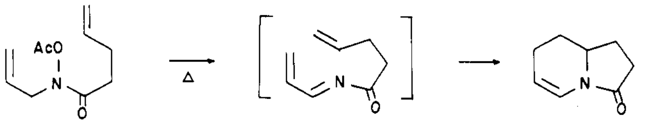
The Diels–Alder reaction of a *N*-acyl-1-azadiene was a key step in the total synthesis of the quinolizidine alkaloid (−)-deoxynupharidine.

Introduction

A six-membered ring containing a nitrogen atom is a common structural feature among the known alkaloids.[1] As a consequence, a central problem in alkaloid total synthesis has been concerned with the preparation and modification of piperidine derivatives. The Diels–Alder reaction of hetero dienes[2] and dienophiles[3] offers an important solution to this problem. The value of this reaction is that in one step two ring bonds are formed with potential control of stereochemistry at the new tetrahedral centers. Impressive demonstrations of this reaction have been provided by Weinreb and co-workers, who have applied the Diels–Alder reaction of imines to the efficient synthesis of a number of natural products.[4]

We have recently reported[5] that 1-azadienes, possessing an *N*-acyl substituent, will participate in the intramolecular version of the Diels–Alder reaction. The *N*-acylazadienes, prepared by the thermal elimination of acetic acid from hydroxamic acid derivatives 1, are not isolated but readily react under the conditions of their formation to give the Diels–Alder adduct 3.



1 2 3

An additional advantage of the Diels–Alder reaction of 1-azadienes is that the product is an endo-substituted enamine derivative.[6] Enamines are valuable intermediates in organic synthesis[7] as well as being important intermediates in alkaloid biosynthesis.[8] Thus, the Diels–Alder

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