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Rate of Deprotonation of a Simple Ketone by Lithium Diisopropylamide

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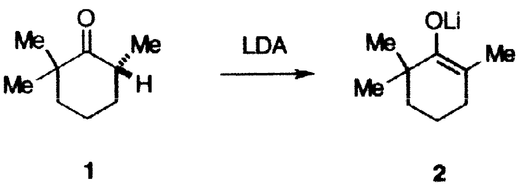
Abstract: Rate studies on deprotonation of a simple ketone (R-2,2,6-trimethylcyclohexanone) with lithium diisopropylamide are described. The data are consistent with the reaction being first order in ketone and half order in the base, corresponding to the rate equation: v = k[ketone][LDA]$^{1/2}$.

Deprotonation of C-H acids with strong bases yields reactive intermediates (carbanions, enolate anions) which can undergo a variety of reactions with diverse species, making the overall deprotonation - electrophilic attack sequence one of the most useful methods in organic synthesis.[1] Amongst the processes which employ this sequence, deprotonation of ketones with lithium dialkylamides occupies a central place. Lithium dialkylamides, and most notably lithium diisopropylamide (LDA), were studied in detail during the last decade by experimental and theoretical methods and a lot of progress has been made in unraveling their structure and properties.[2] However, little is known about the kinetics of deprotonation of ketones with lithium amides.[3] On the practical level, the conditions for deprotonation of ketones (amide, solvent, temperature and time) are usually chosen arbitrarily, and the length of time necessary for deprotonation seems to depend greatly on the structure of both the ketone and the lithium amide.[4] A decade ago, Saunders and Beutelman studied the kinetics of ketone enolization with LDA using UV spectroscopy, but, due to experimental problems, the results were inconclusive.[5] Recently, Collum and coworkers have described the first rate studies of ester enolization, which was monitored by IR spectroscopy.[6] This prompts us to report our preliminary results on rate studies of the reaction of a simple ketone with LDA.

Scheme 1



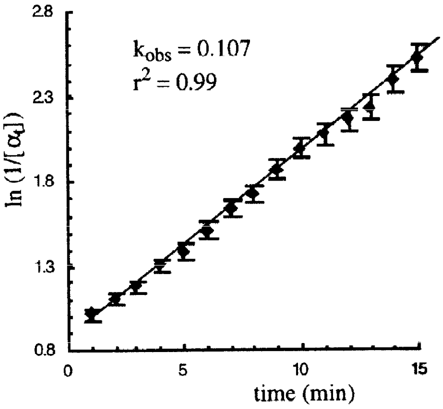


Figure 1: Plot of optical rotation data for the deprotonation of **1** (initial conc. 0.019 M) with LDA (initial conc. 0.186 M) in THF at –78 °C.

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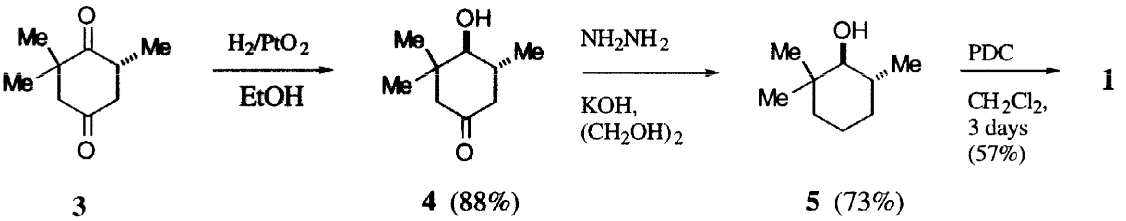
Our method involved enolization of a chiral ketone **1** with LDA in THF (Scheme 1); since the resulting enolate **2** is achiral the decrease in optical rotation provides a convenient way of monitoring the progress of the reaction. The starting material **1** was synthesized from the commercially available diketone **3** by catalytic reduction, followed by a Wolff-Kishner reduction and oxidation of the resulting alcohol **5** with PDC (Scheme 2). The pure R isomer of **1** had $[\alpha]_D^{24}$ –120.0 (c, 1.66; $CHCl_3$) and bp 175-177 °C. One remarkable feature of this otherwise well-precedented synthesis was the selective reduction of the more hindered carbonyl group of the diketone **3** on Adams' catalyst to give only **4**. This unusual selectivity, which is highly catalyst-dependent, had been observed before on the racemic compound.[7]

Scheme 2

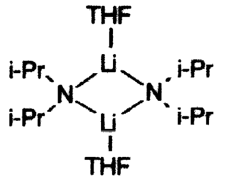


During the kinetic study, all deprotonation reactions were done at –78 ± 1 °C, with an excess of LDA which was generated *in situ* from n-BuLi and diisopropylamine in THF. The reaction rate was defined as the rate of the ketone disappearance (v = –d[ketone]/dt). A typical experiment was done in a quartz cell (4.8 ± 0.1 cm width and a volume of 18 mL) in a cooling bath. Optical rotation measurements were taken at λ = 436 nm. Temperature was monitored with an immersed thermocouple, and the deviations were not greater than ±1 °C. The optical rotation was directly proportional to concentration in the range of concentrations used. One set of data is shown in Figure 1 in all cases we observed a very good straight line fit corresponding to a pseudo first order in ketone up to at least 75 % conversion. The rate constant k_{obs} was calculated as a weighted average of three runs for each experiment. The order in LDA was determined by the isolation method,[8] (Table 1, Figure 2) and was 0.58±0.06 for the reaction in THF. Changing the solvent to diethyl ether resulted in an approximately five-fold decrease of the rate constant (Table 1, entries 2 and 5), addition of one molar equivalent of LiCl, which is known to affect the aggregation and reactivity of lithium amides,[2,9] had only slight effect on the rate constant (entries 3 and 6), and running the reaction in the presence of an excess of diisopropylamine (1.25 equivalent of the amine per 1 equivalent of BuLi) caused a very small increase in the rate constant (entries 2 and 7).

Table 1: Observed rate constants for enolization of ketone **1** with LDA.

Entry	[Ketone] (M)	[LDA] (M)	$k_{obs} \times 10^3$ (s^{-1})	Solvent (additive)
1	0.0186±0.0006	0.557±0.011	3.42±0.30	THF
2	0.0186±0.0006	0.372±0.010	2.72±0.24	THF
3	0.0186±0.0006	0.186±0.010	1.78±0.09	THF
4	0.0186±0.0006	0.093±0.009	1.23±0.06	THF
5	0.0190±0.0006	0.381±0.011	0.44±0.02	Et_2O
6	0.0093±0.0006	0.186±0.010	1.15±0.09	THF (LiCl)[a]
7	0.0376±0.0007	0.372±0.010	3.77±0.33	THF ($^iPr_2NH$)[b]

a. Concentration of LiCl 0.186 M. b. Concentration of added diisopropylamine 0.093 M.



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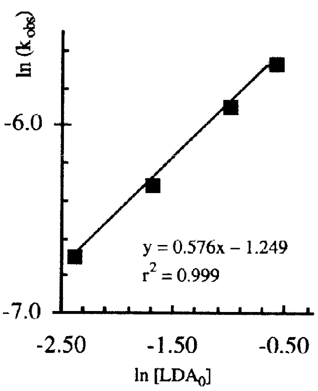

Figure 2: Plot of ln(k_{obs}) vs. initial conc. of LDA for enolization of ketone **1** (Table 1, entries 1-4).

$$1/2(\mathrm{LDA})_2 + \text{ketone} \longrightarrow \text{LDA-ketone} \qquad \text{eq. 1}$$

$$\text{LDA-ketone} \longrightarrow \text{enolate} \qquad \text{eq. 2}$$

Lithiation of ketone **1** with LDA is thus first order in ketone and 0.5 order in the base. We did not attempt to determine the order of the reaction in THF. The reacting system can be approximated as shown in equations 1 and 2 (well known processes like aggregation of lithium enolates[10] and diisopropylamine complexation to the enolate[11] are ignored). Lithium diisopropylamide exists in THF as the dimer **6** which can equilibrate with the monomer.[2] Either species could, in principle, form a complex with the ketone and then undergo a proton transfer to form the enolate. Fractional order in LDA suggests a pathway involving the monomer of the amide and the rate-determining proton transfer, analogous to the mechanism proposed by Collum for ester deprotonation.[6] The following rate equation applies:

$$\text{rate} = -d[\mathbf{1}]/dt = k[\mathbf{1}][\mathrm{LDA}]^{1/2}$$

where the rate constant k contains the [THF] term.[6]

It should be pointed out that the results should be treated with caution, a combination of both the monomer and the dimer pathways is possible, especially for substrates less hindered sterically.

Our system involves the sterically hindered ketone **1** and, despite that, enolization proved fairly fast at the standard low temperature conditions (–78 °C). In synthetic experiments a typical concentration range of the ketone might be ca 0.1 - 0.2 M and the half life of ketone **1**, deprotonated with the equimolar amount of LDA under such conditions would be ca 5 minutes. How much time should one allow for enolization of a typical simple ketone? In order to address this question we tried a competitive deprotonation experiment: a mixture of cyclohexanone (1 mmol) and ketone **1** (1 mmol) was enolized by LDA (1 mmol) and the decrease of optical rotation of the mixture was monitored. Since cyclohexanone is achiral, comparing the optical rotation data with an analogous run involving pure **1** allows to monitor consumption of both **1** and cyclohexanone, assuming that there are no side reactions. Calculations following a similar model of Beak[3d] indicated that cyclohexanone was deprotonated approximately 80 times faster than ketone **1**. Thus the deprotonation of cyclohexanone and, presumably, other simple ketones by LDA in THF at –78 °C is rapid.

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