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Complex-Induced Proximity Effects: Evidence for a Prelithiation Complex and a Rate-Determining Deprotonation in the Asymmetric Lithiation of Boc-Pyrrolidine by an *i*-PrLi/(−)-Sparteine Complex

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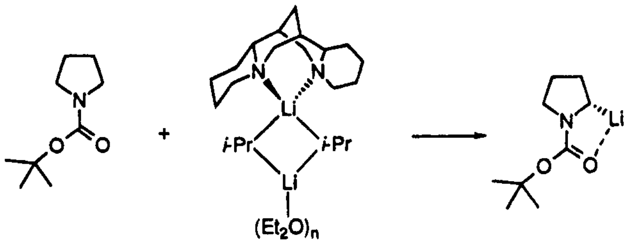
The use of organolithium/chiral diamine complexes for synthetically useful asymmetric deprotonation reactions has been of interest since Hoppe reported the use of *s*-BuLi/(−)-sparteine to lithiate α- to the oxygen of carbamates.[1] We have reported that *i*-PrLi/(−)-sparteine and *s*-BuLi/(−)-sparteine complexes carry out the asymmetric deprotonation of Boc-pyrrolidine (**1**) and that the resulting configurationally stable lithiated species **3** can be trapped with electrophiles to give 2-substituted Boc-pyrrolidines with high enantiomeric excesses.[2] The structure of *i*-PrLi/(−)-sparteine was established by NMR spectroscopy to be an unsymmetrical dimer (**2**) in which one of the lithium atoms is complexed by sparteine and the other lithium atom is complexed by Et_2O.[3] We now report an investigation of the kinetics of the asymmetric deprotonation of Boc-pyrrolidine by the *i*-PrLi/(−)-sparteine reagent. The results are consistent with formation of a complex of *i*-PrLi/(−)-sparteine/Boc-pyrrolidine with a large equilibrium constant prior to a rate-determining deprotonation to give **3**.



1 **2** **3**

The most straightforward mechanism for the formation of **3** is a one-step reaction between **1** and **2** to give the lithiated product. Alternatively, breakdown of dimer **2** to form small amounts of RLi/(−)-sparteine monomer which reacts with **1** is also a plausible reaction pathway. These two possibilities can be distinguished by determination of the kinetic reaction order in organolithium dimer.[4,5] If reaction occurs via breakdown into monomeric subunits, the observed order in RLi should be 0.5, while reaction through dimer would provide an order of 1. Another possibility, recently illustrated by the work of Klumpp and co-workers, is a fractional order which is the result of the formation of a complex along the reaction pathway.[5]

Table 1. Initial Rate of Appearance of 2-Deuterio-Boc-pyrrolidine (1-*d*)

[**1**][a] (M)	[dimer][b] (M)	Δ[**1**-*d*]/Δ*t* (M min^{-1})[c]	ln[dimer]	ln(Δ[**1**-*d*]/Δ*t*/[**1**]
3.22×10^{-3}	0.0264	6.65×10^{-5}	−3.63	−3.88
1.90×10^{-3}	0.0299	4.86×10^{-5}	−3.51	−3.67
1.06×10^{-3}	0.0160	2.11×10^{-5}	−4.14	−3.91
6.57×10^{-4}	0.00970	1.37×10^{-5}	−4.63	−3.88
3.45×10^{-4}	0.00525	7.63×10^{-6}	−5.24	−3.81

[a] Initial concentration of **1**. [b] Initial concentration of dimer **2**, calculated as 1/2 *i*-PrLi concentration. [c] Estimated initial rates (see supporting information).

Kinetic studies of the initial rates of lithiation of **1** by *i*-PrLi/(−)-sparteine (1:1) were carried out under pseudo-first-order conditions using excess **2**. The formation of **3** was followed by addition of AcOD/MeOD to aliquots of the reaction solution and analysis for 2-deuterio-Boc-pyrrolidine (**1**-*d*) by mass spectrometry. Initial rates of lithiation were estimated from plots of [**1**-*d*] versus time.[6] The concentration and initial rate data are tabulated in Table 1.

A plot of ln(initial rate)/[**1**] versus ln[dimer] provides a line whose slope is equal to the empirical order in organolithium dimer **2**.[5] A plot of the data in Table 1 shows the reaction to be zero order in the organolithium reagent. This result is not consistent with the first two kinetic schemes discussed above.[7]

A mechanistic scheme and kinetic equations which are consistent with the observed nondependance on organolithium concentration under these conditions are shown in Scheme 1. This scheme includes the formation of a Boc-pyrrolidine/*i*-PrLi/sparteine prelithiation complex **C**. The formation of the lithiated product **3** is proportional to the concentration of complex **C** (eq 1). An expression for [**C**] under these conditions can be derived from the equilibrium equations (eqs 2 and 3). The rate expression for formation of **3** is then given by eq 4. Such an expression would be expected to give fractional orders in organolithium if K_c were significant ($K_c[\mathbf{2}_i] \approx 1$), as noted previously.[4,5] If K_c is large (>300), eq 4 simplifies to eq 5, which is independent of organolithium concentration. Thus, under pseudo-first-order conditions in **1** and with a large complexation constant K_c, the reaction pathway of Scheme 1 would provide little dependence on the organolithium concentration.[8]

The kinetic analysis of Scheme 1 assumes that deprotonation is the rate-determining step in the reaction. Experimental support for this condition is provided by the observation of a large intermolecular isotope effect.

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[1] Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394.

[2] Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

[3] Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872.

[4] Brown, T. L. *J. Organomet. Chem.* **1966**, *5*, 191. Brown, T. L. *Adv. Organomet. Chem.* **1965**, 365.

[5] Luitjes, H.; de Kanter, F. J. J.; Schakel, M.; Schmitz, R. F.; Klumpp, G. W. *J. Am. Chem. Soc.* **1995**, *117*, 4179.

[6] A solution of **1** was added to an Et_2O solution of RLi/(−)-sparteine at −78 °C, mixed, and separated into aliquots at −78 °C, and the aliquots were quenched at appropriate times with excess CH_3OD/AcOD (10:1). After workup, the deuterium content of the product from each aliquot was determined by GC−MS. A more detailed description and the plots used to estimate initial rates are available as supporting information.

[7] We have made a conservative estimate of the errors in these experiments of ~10−20% and believe that we could have detected a slope of 0.20 or greater.

[8] According to the reaction pathway shown in Scheme 1, the use of pseudo-first-order conditions in organolithium and determination of the empirical reaction order in **1** should also provide small fractional orders in **1**. In order to do these experiments, the change in organolithium concentration would have to be followed by NMR after addition of excess **1**. Specialized NMR techniques such as rapid injection NMR spectroscopy may allow this approach. See: McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810.

0022-3263/95/1960-7092$09.00/0

Scheme 1

$$\mathbf{1} \quad + \quad \mathbf{2} \quad \underset{}{\overset{K_c}{\rightleftharpoons}} \quad \mathbf{C} \quad \xrightarrow{k_2} \quad \mathbf{3}$$

$$\frac{dP}{dt} = k_2[C] \qquad \text{eqn 1}$$

$$K_c = \frac{[C]}{[2_i - C][1_i - C]} \qquad \text{eqn 2}$$

$$\text{Since } [\text{Dimer}]_i >> [\text{Boc}] \text{ or } [C]: \quad K_c = \frac{[C]}{[2_i][1_i - C]} \qquad \text{eqn 3}$$

Solving for [C] and substitution into eqn 1:

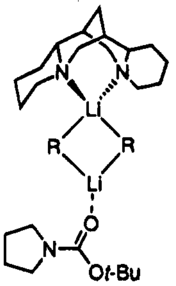
$$\frac{dP}{dt} = \frac{k_2K_c[2_i][1_i]}{1 + K_c[2_i]} \qquad \text{eqn 4}$$

$$\text{If } K_c \text{ large:} \quad \frac{dP}{dt} = k_2[1_i] \qquad \text{eqn 5}$$

Lithiations of mixtures of **1** and 2,2,5,5-tetradeuterio-Boc-pyrrolidine (**1**-d_4) were carried out and the product **3** reacted with dimethyl sulfate to produce 2-methylpyrrolidine, which was assayed for deuterium content. The intermolecular isotope effect (k_H/k_D) was calculated to be >30.[9] This large value for k_H/k_D strongly suggests that the deprotonation step (k_2) is the rate-determining step in the asymmetric lithiation reaction and that the complexation/decomplexation equilibrium is fast relative to the deprotonation reaction.[10]

The large value for the equilibrium constant K_c indicates that the equilibrium lies heavily on the side of the complex **C**. Thus, upon addition of substrate **1** to the reaction mixture, the predominant species in solution is the prelithiation complex. Effects such as these, which have been noted before, have important implications in the design of directed lithiation reactions.[5,11]

The structure of the prelithiation complex is speculative.[12,13] Shown below are three possible structures for this complex. Complex **4** is consistent with the data, but as noted previously,[2] it is difficult to see how the chirality of (−)-sparteine induces asymmetry in the deprotonation from a distance of several angstroms. Such a prelithiation complex with coordinatively-unsaturated lithium has been proposed for the lithiation of anisole by n-BuLi/TMEDA.[14] Complex structures **5** or **6** maintain the carbamate closer to the asymmetric environment of (−)-sparteine. Complex **5** is monomeric and has lost the second RLi unit, whereas **6** remains as a linear dimer of the type proposed by Collum for lithium dialkylamide transition structures.[15] We proposed a monomeric transition state that would proceed from **5** previously,[2] but reaction through **6** cannot be ruled out. We suggest that if the reaction proceeds through **6** the reacting RLi fragment should be complexed to sparteine in order to maximize the influence of the chiral ligand.



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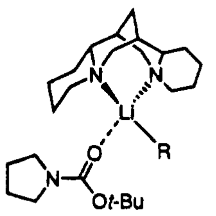

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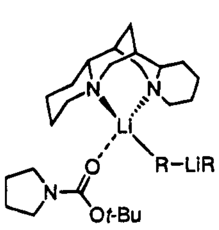

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This study has provided evidence that **1** and **2** form a complex prior to lithiation and that the equilibrium lies heavily on the side of the complex. The high value for the intermolecular isotope effect indicates that deprotonation is the rate-determining step in the asymmetric lithiation process. This asymmetric deprotonation reaction can be considered another example of a complex-induced proximity effect (CIPE).[16] Further studies of the role of prelithiation complexes in directed lithiation reaction pathways are in progress.

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Supporting Information Available: Description of the kinetic experiments, initial rate plots, plot of ln(initial rate)/[**1**] versus ln[dimer], and isotope effect calculations (5 pages).

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(9) The intermolecular competition studies involved treatment of approximately 1:1 mixtures of **1** and **1**-d_4 with s-BuLi/sparteine, followed by Me_2SO_4 trapping and analysis of the 2-methyl-Boc-pyrrolidine product for deuterium content by GCMS relative to an undeuterated standard. The extent of reaction was determined by the use of an internal standard (dodecane). The k_H/k_D values are corrected for the change in relative concentrations of **1** and **1**-d_4 during the reaction. The calculations are provided as supporting information.

(10) If complexation were rate-determining, then no intermolecular isotope effect would have been observed. For an example of such a case, see: Meyers, A. I.; Dickman, D. A.; *J. Am. Chem. Soc.* **1987**, *109*, 1263. For a case in which deprotonation is rate-determining but decomplexation is competitive, see: Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 405.

(11) Other studies have provided evidence for prelithiation complexes. See: Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145 and references cited therein.

(12) We have attempted to study a possible RLi/substrate complex by NMR spectroscopic observation of a mixture of i-PrLi/sparteine and Boc-diisopropylamine, which is not lithiated under the conditions. Changes in the ^{6}Li NMR spectrum were observed upon addition of the carbamate to the i-PrLi/sparteine solution, suggesting that complex formation is observable. However, the ^{1}H and ^{13}C NMR spectra were too complicated to deduce any structural information.

(13) Crystal structures of lithiated carbamates and amides with (−)-sparteine are known: Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321. Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887.

(14) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

(15) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166. In this case the second $LiNR_2$ unit of the complex is suggested to play an active role in the reaction.

(16) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.