Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3991–3998

TETRAHEDRON: *ASYMMETRY*

# Composition of the activated complex in the stereoselective deprotonation of cyclohexene oxide by a chiral lithium amide

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Received 21 August 1999; accepted 9 September 1999

**Abstract**

Chiral lithium amides are being developed for stereoselective synthesis of chiral allylic alcohols in high yields and with high enantiomeric excess. However, rational design of the amides for improved stereoselectivity by computational methods, for example, has not been possible due to lack of knowledge of the activated complexes involved in the reactions. Kinetic results are presented for the stereoselective deprotonation by lithium (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidide (**1**-Li) of cyclohexene oxide **2**, in diethyl ether (DEE), to form (*S*)-2-cyclohexen-1-ol (*S*)-**3** in high enantiomeric excess. The results show that the rate limiting activated complex is composed of one lithium amide monomer and one molecule of **2** and presumably a solvent molecule. The diamine **1** is found to catalyze the deprotonation. 

## 1. Introduction

Chiral lithium amides are being developed for the stereoselective synthesis of chiral allylic alcohols in high yields and with high enantiomeric excess (ee) by deprotonation of *meso*-epoxides.[1–3] Such alcohols are useful as building blocks in the total synthesis of, for example, biologically active compounds.[4–6] Several research groups have been working with improving the stereoselectivity of chiral lithium amides in the deprotonation of *meso*-epoxides.[7–17] However, rational design of the amides has not been possible due to lack of knowledge of the activated complexes involved in the reactions. The amides are aggregated in solution and more detailed mechanistic studies aimed at determining the transition state composition have been hampered by lack of knowledge of the composition of the aggregates present in the initial states of the reactions. Interpretation of kinetic reaction orders for the reactions in terms of compositions of activated complexes demands knowledge of the composition of reactant complexes. Based on the determined composition of the activated complexes rational design of new chiral lithium amides with improved stereoselectivity by computational methods should be possible.

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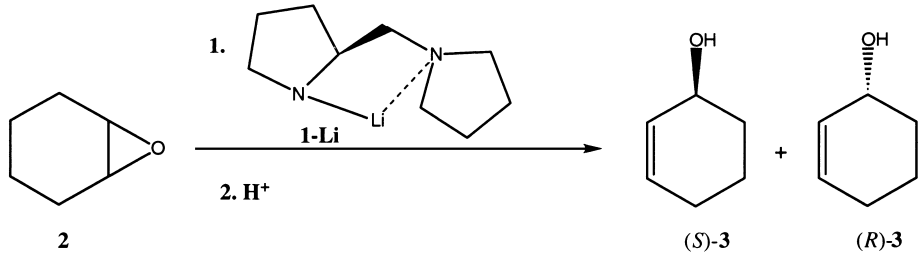
0957-4166/99/$ - see front matter 
*PII:* S0957-4166(99)00405-X

Asami et al. have reported that lithium (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidide **1**-Li stereoselectively deprotonates cyclohexene oxide **2**, in tetrahydrofuran (THF), to form (*S*)-2-cyclohexen-1-ol (*S*)-**3** in 80% ee (Scheme 1).[7,9,10]




Scheme 1.

In diethyl ether (DEE) the stereoselectivity is lower (55% ee of (*S*)-**3**)[9] and the solvent also induces isomerization of **3** to form 3-cyclohexen-1-ol via a 1,3-proton transfer reaction.[18–20]

Studies by NMR recently performed in our laboratories have shown that **1**-Li in THF does not exhibit well resolved signals needed for a structure determination. **1**-Li is insoluble in DEE but solubilizes upon addition of the diamine **1**, forming a dynamic diamine solvated chiral lithium amide dimer (Fig. 1) as determined by NMR spectroscopy.[21] This finding opens up the possibility of using the kinetics of the epoxide deprotonation to determine the composition of the rate limiting transition state for the stereoselective deprotonation.

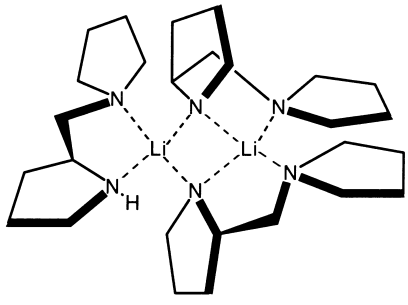


Figure 1. The solution state structure of **1**-Li in the presence of **1** in DEE as determined by [$^{13}$C]- and [$^{6}$Li]-NMR spectroscopy[21]

Using a calibrated quench–extraction–gas chromatography procedure initial rates and reaction orders for the reactions have been determined. The results show that the activated complex of the asymmetric deprotonation of **2** in DEE by the chiral lithium amide **1**-Li is built from one monomer of **1**-Li and one molecule of **2** and presumably one molecule of DEE (Fig. 2). The results also indicate that a fraction of the products have been formed via transition states in which the solvating molecule of DEE has been replaced by a molecule of diamine **1**, e.g. the diamine catalyzes the deprotonation.

## 2. Results and discussion

Amide **1**-Li was prepared in DEE from **1** by addition of equivalent amounts of *n*-butyllithium. The asymmetric deprotonation was started by addition of **2** to the solution of **1**-Li and was carried out at 20.0±0.1°C. The reactions were performed using excess of diamine **1** assuring that **1**-Li is present as the diamine solvated amide dimer (**1**-Li)$_2$·**1**.

It has previously been shown that in DEE the allylic alkoxides **3**-Li undergo further reversible rearrangement to homoallylic alkoxides resulting in racemization of both allylic and homoallylic alkoxides.

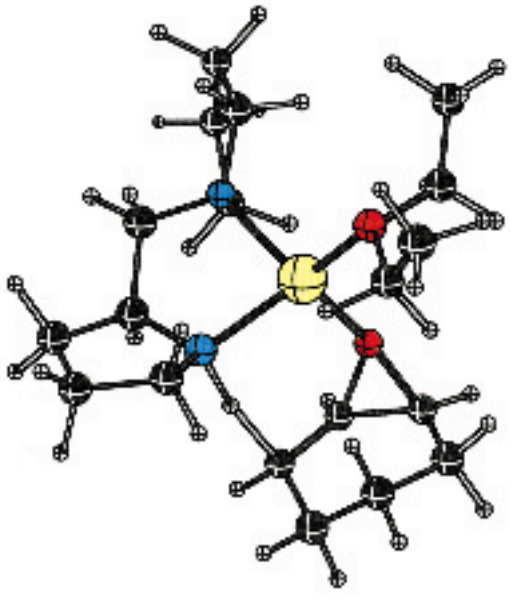


Figure 2. Activated complex of the asymmetric deprotonation of **2** by **1**-Li, solvated by one molecule of DEE, giving (*S*)-**3**-Li. Geometry was optimized at the PM3 level of theory

Therefore, only the initial part of the epoxide opening has been used for the kinetic investigations. In the experiments described below no racemization has been observed. The stereoselectivity is found to be higher than reported previously during at least the first 10% reaction constant (73% ee of (*S*)-**3**). Previously reported ees are lower due to the above mentioned racemization reaction.

The progress of the reaction was monitored by gas chromatographic analysis of quenched samples on an achiral column (Fig. 3). The formation of the allylic alcohol **3** was measured using 1-hexanol as a standard at different reagent concentrations for the initial few percent of the reaction.

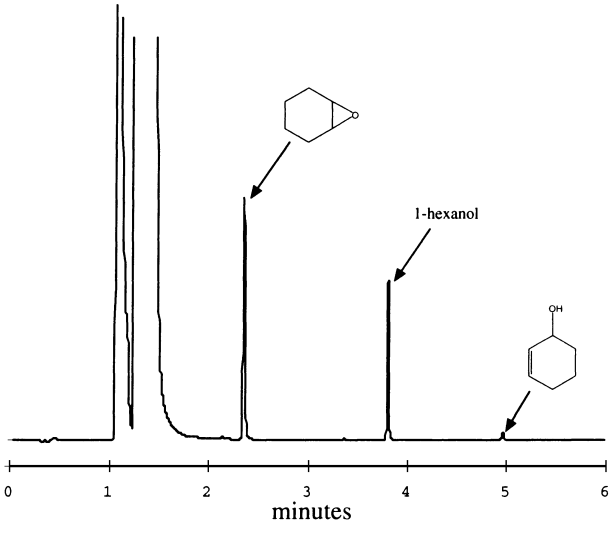



Figure 3. Typical chromatogram used for the kinetics

Initial rates were obtained as slopes of linear curves like those shown in Fig. 4. The results are shown in Table 1.

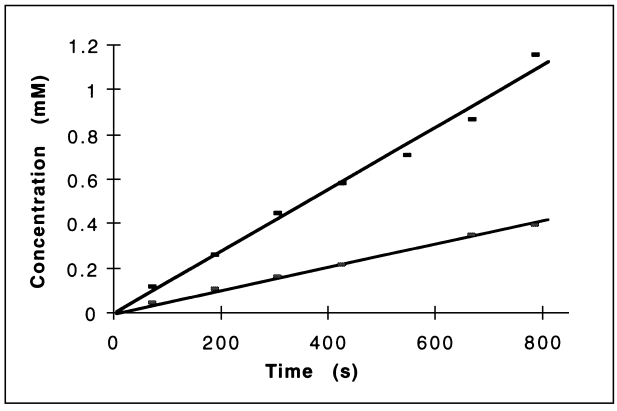



Figure 4. Initial rate plot at 20.0±0.1°C for the formation of allylic alcohol **3**. Initial concentrations of **2**: 60 mM (upper curve) and 20 mM (lower curve). For other conditions cf. runs 6 and 7 in Table 1

Table 1
Initial rates at different concentrations of components **2**, (**1**-Li)$_2$·**1** and **1**

| Run | [**2**]/mM | [(**1**-Li)$_2$•**1**]/mM | [**1**]/mM | (d[**3**]/dt)$_i$/10$^6$ M/s |
|---|---|---|---|---|
| 1 | 60 | 10 | 90 | 0.77 |
| 2 | 60 | 10 | 90 | 0.84 |
| 3 | 60 | 30 | 90 | 1.44 |
| 4 | 60 | 30 | 90 | 1.56 |
| 5 | 60 | 50 | 90 | 2.07 |
| 6 | 20 | 30 | 70 | 0.52 |
| 7 | 60 | 30 | 70 | 1.39 |
| 1 | 60 | 10 | 90 | 0.77 |
| 2 | 60 | 10 | 90 | 0.84 |
| 8 | 60 | 10 | 30 | 0.98 |
| 9 | 60 | 10 | 290 | 0.50 |

By individual and discrete variation of the reagent concentration over 10–50 mM for (**1**-Li)$_2$·**1**, 20–60 mM for **2** and 30–290 mM for uncomplexed **1**, the reaction order with respect to each reagent was measured as the slope of plots of log(initial rate) versus log[reagent] (Figs. 5–7).

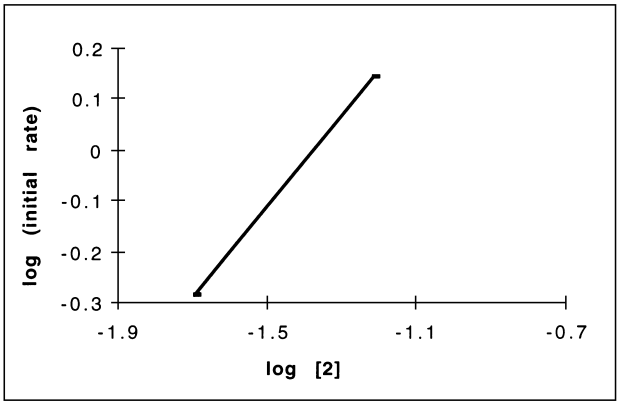



Figure 5. Plot of log(initial rate) versus log[**2**] for runs 6 and 7 in Table 1

This procedure using initial rates was chosen to avoid possible kinetic complications of product alkoxides. Since it has not been possible to vary the solvent concentration, the reaction order with respect

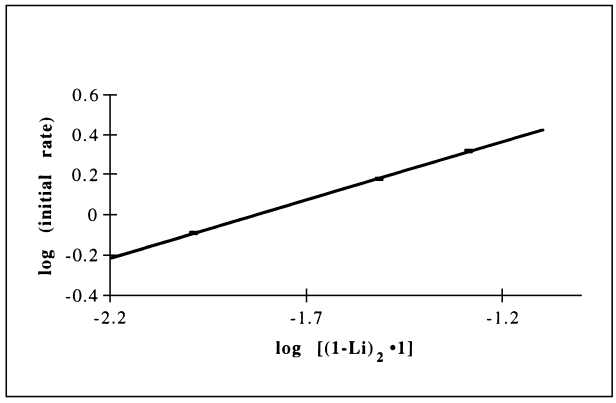



Figure 6. Plot of log(initial rate) versus log[(**1**-Li)$_2$·**1**] for run 5 and average values of runs 1 and 2 and of runs 3 and 4 in Table 1

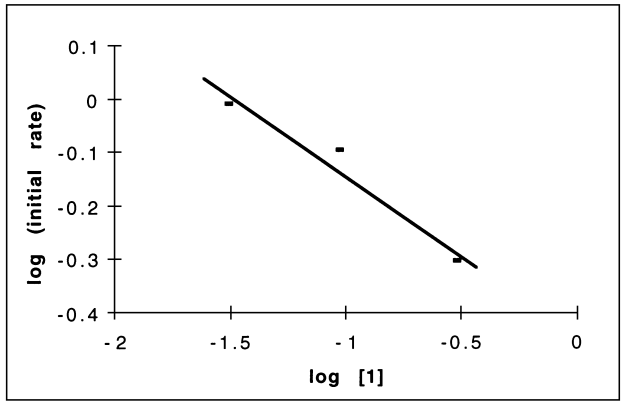



Figure 7. Plot of log(initial rate) versus log[**1**] for runs 8 and 9 and average value of runs 1 and 2 in Table 1

to the solvent has not been determined. The measured reaction orders with respect to **2**, (**1**-Li)$_2$·**1** and **1** were 1.0, 0.5 and −0.3, respectively.

Three possible rate limiting transition states all having different compositions have been considered. The activated complex (**1**-Li·**2**)$^‡$ is built from one monomer **1**-Li and one molecule of **2** and most likely one solvent molecule. The complex (**1**-Li·**2**·**1**)$^‡$ is similarly built from monomeric **1**-Li and one molecule of **2** but also contains one molecule of the diamine **1** (in replacement of the solvent molecule). The third activated complex is composed of a dimer molecule (**1**-Li)$_2$ and a molecule of **2** and is also likely to be solvated. As pointed out above, since the solvent concentration is not significantly varied in our experiments it has not been possible to determine the reaction order with respect to the solvent.

The rate limiting activated complexes are in equilibrium with the reagents in the initial states as indicated by Eqs. 1–3.

$$\tfrac{1}{2}(\mathbf{1}\text{-Li})_2\cdot\mathbf{1}+\mathbf{2} \;\rightleftharpoons\; (\mathbf{1}\text{-Li}\cdot\mathbf{2})^{‡}+\tfrac{1}{2}\mathbf{1} \;\rightarrow\; \mathbf{3}\text{-Li}+1.5\mathbf{1} \tag{1}$$

$$\tfrac{1}{2}(\mathbf{1}\text{-Li})_2\cdot\mathbf{1}+\tfrac{1}{2}\mathbf{1}+\mathbf{2} \;\rightleftharpoons\; (\mathbf{1}\text{-Li}\cdot\mathbf{2}\cdot\mathbf{1})^{‡} \;\rightarrow\; \mathbf{3}\text{-Li}+2\mathbf{1} \tag{2}$$

$$(\mathbf{1}\text{-Li})_2\cdot\mathbf{1}+\mathbf{2} \;\rightleftharpoons\; ((\mathbf{1}\text{-Li})_2\cdot\mathbf{2})^{‡}+\mathbf{1} \;\rightarrow\; \mathbf{3}\text{-Li}+1.5\mathbf{1}+\tfrac{1}{2}(\mathbf{1}\text{-Li})_2\cdot\mathbf{1} \tag{3}$$

From these equilibria and transition state theory the following Eqs. 4–6 for the rate of formation of product allylic alcohol **3** by the reactions in Eqs. 1–3 have been derived, respectively.

$$\frac{d[\mathbf{3}]}{dt} = k_1 \frac{[\mathbf{2}] \times [(\mathbf{1}\text{-Li})_2 \cdot \mathbf{1}]^{\frac{1}{2}}}{[\mathbf{1}]^{\frac{1}{2}}} \quad (4)$$

$$\frac{d[\mathbf{3}]}{dt} = k_2 [\mathbf{2}] \times [(\mathbf{1}\text{-Li})_2 \cdot \mathbf{1}]^{\frac{1}{2}} \times [\mathbf{1}]^{\frac{1}{2}} \quad (5)$$

$$\frac{d[\mathbf{3}]}{dt} = k_3 \frac{[\mathbf{2}] \times [(\mathbf{1}\text{-Li})_2 \cdot \mathbf{1}]}{[\mathbf{1}]} \quad (6)$$

The rate constants in Eqs. 4–6 are the rate constants for formation of product allylic alcohol **3** via the different activated complexes from the common initial state complex. All three reactions show first order dependence on the epoxide **2** as observed. The reaction order with respect to (**1**-Li)$_2$·**1** is 0.5 for Eqs. 4 and 5 but for Eq. 6 the order is 1. The corresponding reaction orders with respect to **1** are −0.5, 0.5 and −1, respectively. The measured reaction orders were: 1 for **2**, 0.5 for (**1**-Li)$_2$·**1** and −0.3 for **1** and are close to those of Eq. 4, indicating that the major pathway for the deprotonation is via Eq. 1, e.g. the activated complex is composed of one monomer of **1**-Li and one molecule of **2** and presumably one solvent molecule.

The observed reaction order −0.3 for **1** is somewhat larger than −0.5 which is the reaction order of **1** in Eq. 4. This suggests that a fraction of the deprotonation of **2** takes place via Eq. 2, e.g. a transition state containing a molecule of **1** is also used for the deprotonation. This **1** molecule has presumably replaced a solvent molecule and may be considered as a catalyst for the reaction. Thus, our results also indicate that the diamine **1** is capable of catalyzing the lithium amide induced deprotonation.

This knowledge about the composition of the rate limiting transition state for the chiral lithium amide deprotonation of the epoxide to yield allylic alcohols has been used as a basis for rational design by computational methods of more efficient chiral amides for synthesis of allylic alcohols with high ees.[17]

## 3. Experimental

### 3.1. General

All handling of the reagents was performed with gas-tight syringes under nitrogen atmospheres. Gas-tight syringes and reaction vessels were dried overnight at 50°C in a vacuum oven and then stored inside a nitrogen atmosphere glovebox (Mecaplex GB 80), equipped with a gas purification system that removes oxygen and water. DEE was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen and then stored over 4 Å molecular sieves in septum sealed bottles inside the glovebox. Reagents were prepared in stock solutions inside the glovebox and stored in capped bottles. (*S*)-1-(2-Pyrrolidinylmethyl) pyrrolidine was prepared as described in the literature[9] and vacuum distilled from $CaH_2$. Cyclohexene oxide was purchased from Aldrich and distilled before use. Carbon tetrachloride was purchased from Riedel de Haën (>99.9% purity) and 1-hexanol was acquired from Merck (>98% purity).

### 3.2. Titration of n-butyllithium

A double Gilman titration following the standard E233-90 of the American Society for Testing and Materials (ASTM) was used with some modification. *n*-Butyllithium (1.00 ml, Acros, 2.5 M in hexanes) was added to hexane (10 ml) and quenched by addition of distilled water (10 ml). Phenolphthalein (3 drops, 0.5 g/l water:ethanol (1:1)) was added and the resulting pink solution was titrated with hydrochloric acid (0.0887 M, calibrated with NaOH) to colorlessness. A second sample of *n*-butyllithium

(1.00 ml, 2.5 M in hexanes) was added to benzyl chloride (1 ml, vacuum distilled from $P_2O_5$) in dry DEE (2.5 ml) and allowed to react for a few mins. Distilled water (10 ml) and phenolphthalein (3 drops, 0.5 g/l water:ethanol (1:1)) were added and the formed pink aqueous layer was titrated with hydrochloric acid solution (0.0887 M, calibrated with NaOH) to colorlessness. The concentration of *n*-butyllithium was determined as the difference between the two titrations. Typical concentrations were around 2.4 M of *n*-butyllithium and less than 0.1 M of alkoxide material.

### 3.3. Typical kinetic experiment

Diamine **1** (160 μl, 1.00 M stock solution in DEE) was dissolved in DEE (755 μl) in the reaction vessel inside the glovebox. The vessel was transferred out of the glovebox and *n*-butyllithium (25 μl, 2.39 M in hexanes) was added under overpressure of nitrogen. The solution temperature was allowed to equilibrate at 20.0±0.1°C in a thermostat (Heto Birkeröd) for 15 mins. The reaction was started by addition of cyclohexene oxide (60 μl, 1.00 M stock solution in DEE). At intervals, samples (50 μl) were withdrawn under an atmosphere of nitrogen and quenched in hydrochloric acid solution (100 μl, 0.20 M, saturated with NaCl). Compounds **2** and **3** were extracted into carbon tetrachloride (500 μl), containing the standard 1-hexanol (1.57 μmol). The phases were separated by centrifugation and the organic phase (250 μl) was withdrawn to a vial and analyzed by capillary gas chromatography.

The quantitative transfer of **2** and **3** from the aqueous phase to the carbon tetrachloride phase during work up was determined as follows: a DEE solution (50 μl) of 70 mM **2** and 7.3 mM **3** was added to water (100 μl) saturated with NaCl and extracted with carbon tetrachloride (500 μl). The organic phase (200 μl) was withdrawn, mixed with carbon tetrachloride (100 μl) containing 1-hexanol (3.14 mM). Similarly, 50 μl of the same DEE solution was added to carbon tetrachloride (500 μl) and from the resulting solution 200 μl was withdrawn and added to carbon tetrachloride (100 μl) containing 1-hexanol (3.14 mM). Capillary gas chromatographic analysis of both samples gave the same ratio of components.

### 3.4. Gas chromatography analysis

Gas chromatography analysis was performed on a Varian 3400 chromatograph equipped with a 8200 Cx autosampler and a flame ionization detector. An achiral DBWX-30W column (0.25 μm) from J and W Scientific, using hydrogen as carrier gas at a flow rate of 2 ml/min, was used for separation. Injector temperature was kept at 225°C and detector temperature at 250°C. Reaction samples (1.0 μl) were introduced onto the column via a split injector (split flow 15 ml/min) and the components were separated by using a temperature program keeping the temperature initially at 80°C for 2 mins, then increasing it to 120°C over 2 mins and maintaining that temperature for 2 mins.

Response factors were determined using carbon tetrachloride samples of known composition and concentration similar to those in the kinetic experiments. Retention times and response factors for the different components were: cyclohexene oxide 2.3 mins and 1.01; 1-hexanol 3.8 mins and 1.00; 2-cyclohexen-1-ol 4.9 mins and 0.85.

The initial rate of reaction was determined by following the appearance of **3**, relative to the 1-hexanol standard, for the first 2–3% conversion. All samples were analyzed at least twice and the variation of the ratio of 1-hexanol and **3** peaks of different runs were usually less than ±1% from the average value. The initial rates were reproduced within ±5%.

## Acknowledgements

We thank the Swedish Natural Science Research Council for financial support, Dr. Göran Hilmersson for fruitful discussions and M.Sc. Sten O. Nilsson Lill for providing the PM3 optimized activated complex.

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