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# A Theoretical Investigation into the Inversion Barrier of Dipole-Stabilized α-Aminoorganolithiums

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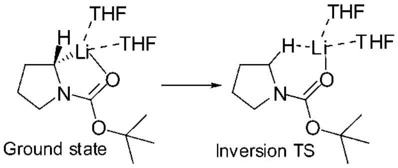
## ABSTRACT

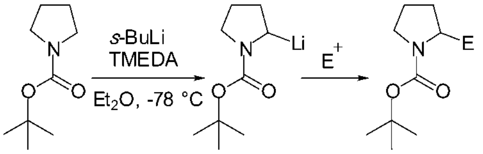


**Results from density functional theory calculations (B3LYP/6-31+G*) suggest that inversion of the monomer of 2-lithio-*N*-formylpyrrolidine (2) in coordinating ethereal solvent occurs with an activation barrier of 15.7 kcal/mol, while the inversion of the monomer in a noncoordinating hydrocarbon solvent is considerably slower. However, aggregation into a trimer in hydrocarbon solvent restores the low inversion barrier. This study suggests that solvation and aggregation may influence the mechanism and rate of racemization of dipole-stabilized α-aminoorganolithiums.**

Organolithium chemistry plays an important role in synthetic organic chemistry.[1] It is therefore important to understand in detail the mechanisms that control the reactivity and selectivity of these reactions. Enantioselective deprotonation of *N*-Boc-pyrrolidines with alkyllithiums (i.e., BuLi) in the presence of (−)-sparteine produces chiral dipole-stabilized carbanions.[2,3] These can be reacted further with electrophiles ($E^+$) to give a variety of useful compounds; see Scheme 1. The deprotonation reaction is believed to start when the organolithium coordinates to a functional group close to the proton, which is removed in the reaction to form the carbanion. This hypothesis, known as the CIPE (complex induced proximity effect) was suggested by Beak and Meyers and has been verified by kinetic data.[4,5] A mechanism of how the asymmetric deprotonation occurs has recently been suggested from theoretical studies by Wiberg et al.[6,7] However, the mechanism of how the lithiated chiral compound racemizes is not understood in detail.

Much effort has been directed toward finding compounds that upon deprotonation are stable long enough to give enantiomerically enriched products after electrophilic quench. In parallel, the stabilizing effect from the solvent has been investigated, and several studies have been published where the solvent (and cosolvents such as TMEDA) have been demonstrated to significantly influence the configurational

**Scheme 1**



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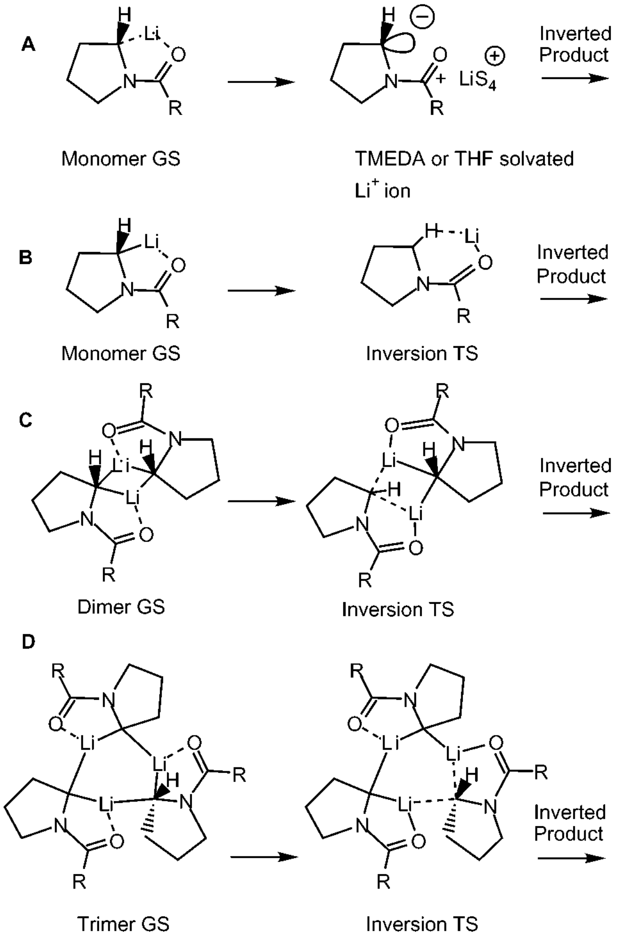
stability of the organolithium.[8−10]The solvents most commonly used are coordinating ethereal solvents such as THF and noncoordinating hydrocarbon solvents such as hexane.[11]

The aggregation of simple alkyllithiums have been studied for several decades using X-ray crystallography and NMR spectroscopy.[12−14] On the basis of ab initio and density functional theory calculations, various mechanisms relating to how inversion of the carbanion center of these alkyllithiums occurs have been suggested. Schleyer et al. proposed that inversion of methyllithium proceeds via a dimeric aggregate in which the anionic carbon center inverts along its planar sp$_2$-hybridized geometry between the two lithium ions,[15] which is simply an S$_E$2inv reaction.[16] Haeffner et al. proposed that inversion of methyllithium can occur via a tetrameric aggregate where the inversion takes place via an eight-membered planar ring transition state.[17]

To our knowledge no theoretical studies describing a detailed mechanism of how α-heteroatom-stabilized organolithiums racemize have been published. However, a few mechanisms, summarized in Scheme 2, have been proposed in the literature.

**Scheme 2.** Suggested Reaction Mechanisms



Beak et al. suggested that dissociation of the lithium ion and the carbanion first occurs. This is followed by inversion of the carbanion center, followed by association of the inverted carbanion and the lithium ion (mechanism A in Scheme 2).[18]

In the present study, we have investigated the chelate-assisted *conducted tour* mechanism[19] of inversion of the monomer (mechanism B) and the mechanisms C and D involving the dimer and the trimer of **1** and **2** (Figure 1) using density functional theory. Ground states and transition states of the monomer of **1** and **2** and the dimeric and trimeric aggregates of **1** were geometry-optimized. Thereafter, the lithium atoms in the geometry-optimized structures of the monomer of **1** and **2** were solvated with two dimethyl ether molecules, and the ground-state structures and the transition-state structures were reoptimized. Attempts to find a dimethyl ether solvated dimer ground state or transition state of **1** failed.

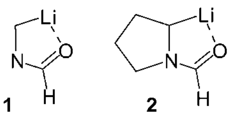


**Figure 1.** Model systems.

The gradient corrected B3LYP functional was used together with the split-valence 6-31+G* basis set. The optimized geometries were investigated with frequency calculations at the B3LYP/6-31+G* level of theory. All structures were found to have only real frequencies, with the exception of transition-state structures that display one imaginary frequency each. The surrounding solvent was modeled by the polarizing continuum model (PCM) by Tomasi and co-workers.[20] Single point PCM calculations were conducted using the Hartree−Fock method and the basis set 6-31+G*. The PCM parameters of THF and heptane were used to compute the ethereal solvation and the

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hydrocarbon solvation. All calculations were performed with the Gaussian 98 program.[21]

The computed activation energy to inversion of the monomers of **1** and **2** in the gas phase are high (26.6 and 25.7 kcal/mol, respectively). Single-point PCM calculations using parameters for heptane indicates insignificant solvation effects. Thus, in noncoordinating solvents, the monomers of **1** and **2** should be configurationally stable at room temperature, which is not the case.

When the monomers of **1** and **2** were solvated with two dimethyl ether molecules, the energies decreased to 17.7 and 17.0 kcal/mol, respectively. PCM solvation of these two systems lowered the barriers even further to 13.9 and 15.7 kcal/mol, respectively. Not surprisingly, solvation of the monomer by a coordinating ethereal solvent has a pronounced effect on the activation barrier to inversion.

The optimized ground-state geometries and transition-state geometries of the monomer of **2** in the gas phase and solvated with two dimethyl ether molecules are presented in Figures 2 and 3 (mechanism B, Scheme 2).

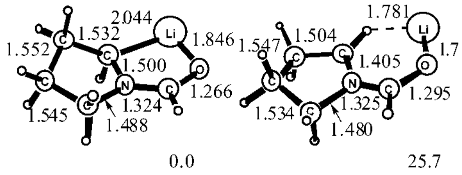

**Figure 2.** Ground-state and transition-state structures and energies (kcal/mol) of monomeric **2**.

Beak et al. have reported that the configurational lability of 2-lithio-*N*-Boc-pyrrolidines is much higher in the presence of TMEDA.[18] We therefore computed the ground state and the transition state of the monomer of **2** chelated to one TMEDA molecule. The computed activation barrier is only 15.0 kcal/mol, and the suggested mechanism above (mechanism B, Scheme 2) seems attractive.

The transition state for inversion of the dimer of **1** lies 22.6 kcal/mol above the ground state in the gas phase, suggesting it will invert only slowly in a hydrocarbon solvent. The dimer of **1** was solvated with four dimethyl ether molecules, and a ground state was sought. During the geometry optimization the dimeric structure fell apart to the monomers. Thus, the calculations above suggest that these compounds may exist as monomers in ethereal solvents.

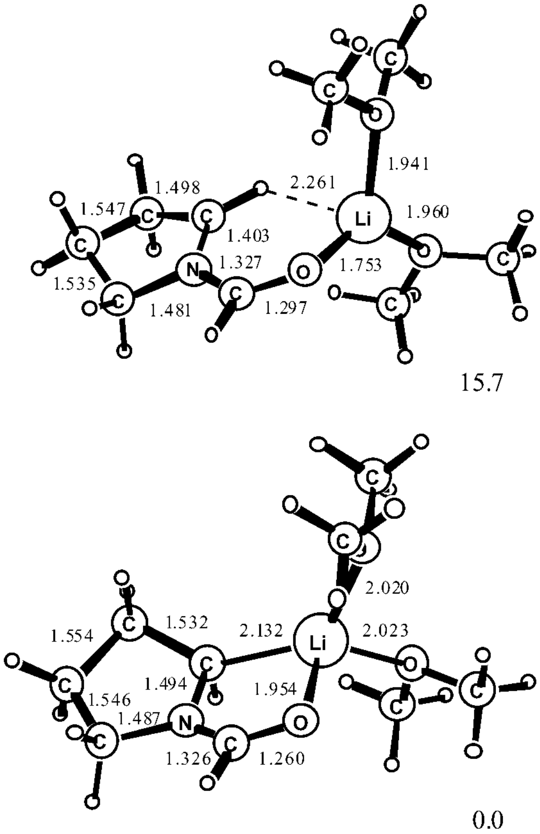

**Figure 3.** Ground-state and transition-state structures and energies (kcal/mol) of solvated monomeric **2**.

The transition state of the corresponding trimeric aggregate is much lower in energy relative to the homochiral ground state; see Figure 4 (mechanism D, Scheme 2). It racemizes with a computed activation barrier of only 12.6 kcal/mol. An explanation of this can be seen in Figure 4. The angle 1−2−3 increases for increasing aggregate size, and this indicates that the aggregate experiences decreasing strain.[22]

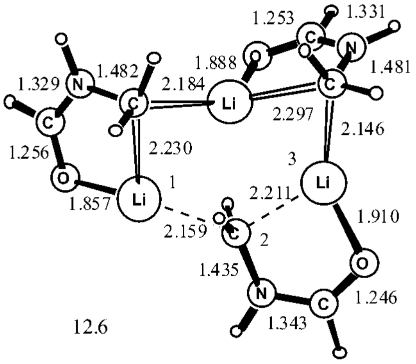

**Figure 4.** Transition-state structure and activation energy (kcal/mol) of trimeric **1**.

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**Table 1.** Activation Energies (kcal/mol)

| complex | gas phase | PCM (heptane) | DME[a] solv | DME + PCM (THF) |
|---|---|---|---|---|
| monomer TS of **1** | 26.6 | 25.0 | 17.7 | 13.9 |
| monomer TS of **2** | 25.7 | 27.1 | 17.0 | 15.7 |
| monomer TS of **2** | | | 18.2[b] | 15.0[b] |
| dimer TS of **1** | 22.6 | 22.8 | | |
| trimer TS of **1** | 12.6 | 12.6 | | |

[a] DME = dimethyl ether. [b] TMEDA solvated TS.

Unfunctionalized alkyllithiums often form higher aggregates in noncoordinating solvents.[23] The calculations show that the formation of the trimeric $C_3$-symmetrical ground state from the monomers is an exothermic process with an enthalpy of −37.8 kcal/mol. The nonfavorable entropic contribution to the free energy upon complexation is not likely to impede this process.

This study has demonstrated the importance of organolithium aggregation and solvent assistance on the reaction mechanisms and rates and may have relevance to the understanding of the pyramidal inversion of dipole-stabilized α-aminoorganolithiums in noncoordinating hydrocarbon solvents vs coordinating ethereal solvents.

In summary, we suggest that inversion of **1** and **2** can take place in ethereal solvents, with computed barriers of 13.9 and 15.7 kcal/mol, respectively. However, a mechanism in which the lithium ion and the carbanion dissociate with subsequent inversion and recombination is not ruled out.[24] The results suggest that inversion of the monomer in a noncoordinating solvent such as a hydrocarbon would occur slowly. However, upon aggregation to a trimer, inversion occurs again with a low activation barrier. This could explain the difficulty of finding solvents in which racemization occurs only slowly.

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[22] A second TS was identified on the reaction path, connecting the heterochiral trimer with the intermediate formed by the TS shown in Figure 3. The barrier for this TS was found to be 3 kcal/mol lower in energy. However, this activation energy is expected to increase considerably for tertiary carbanions.

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[24] In fact, we have found a transition state for the inversion of **2** where the lithium is solvated by an additional dimethyl ether solvent molecule. This results in an increased stabilization of the TS and a conducted tour mechanism (mechanism B) approaching the solvent separated ion-pair mechanism (mechanism A).