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How Does Methyllithium Invert? A Density Functional Study

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Quantum chemical studies (B3LYP) of the inversion of methyllithium in both tetrameric and dimeric aggregates have been carried out. Results show that inversion occurs either via dissociation of the tetramer into the dimers, passage of a four-membered-ring transition state, and association of the dimers to form the inverted tetramer, or via a nonconcerted route involving an eight-membered-ring transition state. The activation energies of these two mechanisms are similar. However, the dissociative mechanism is ruled out by NMR experiments.

Introduction

Chiral organolithium reagents have gained large importance in synthetic organic chemistry.[1−3] These compounds have low inversion barriers (∼15 kcal/mol), and much effort has therefore been done to increase the stability of these toward racemization.[4] Heteroatom-stabilization and additives such as TMEDA and MTBE in hydrocarbon solvents have been shown to slow the racemization process.[5−7] It is known that organolithiums aggregate in solution. In hydrocarbon solvents alkyllithiums form hexamers, and in etheral solvents such as THF and dimethyl ether they exist as a dimer−tetramer equilibrium.[8] One important issue is in what aggregation state the organolithium inverts. A dimer is the minimal aggregate for inversion, and it has been suggested to facilitate the inversion.[9] This raises an interesting question: is inversion of organolithiums only possible when the organolithium is in the form of a dimer, or can it occur when the organolithium is in the form of a tetramer or even in hexameric forms? Recently, a NMR study was reported where mixing of 3 equiv of butyllithium with 1 equiv of a chiral lithiumamide in dimethyl ether lead to the observation of four nonidentical lithium atoms. Measurement of the intra-aggregate two-site lithium exchange rates using 2D NMR exchange spectroscopy (EXSY) revealed six different rate constant values. The authors of this study suggest a tetrameric ladderlike intermediate pathway to inversion.[10]

We have undertaken a density functional theory (DFT) study to investigate these mechanisms for inversion of MeLi in THF, summarized in Figure 1. Both dimeric and tetrameric aggregates of methyllithium (MeLi) were studied. The influence from THF solvation was studied using the polarizable continuum model (PCM).

Methods and Procedure

Ground state and transition state geometries were optimized using density functional theory with the B3LYP exchange−correlation functional and the split-valence 6-31+G* basis set. Single-point calculations were done using the 6-311+G* basis set on all structures. All stationary points were characterized by means of frequency calculations using B3LYP/6-31+G*. The thermal free energy contributions to the total energies were computed at 253 K and the normal-mode frequencies were not scaled.

Solvation energies were calculated at the B3LYP/6-31+G* level using the recent implementation of the polarizable continuum model (PCM)[11] in Gaussian 98.[12] The solute cavities in these calculations were made up of overlapping spheres centered at the atomic nuclei. The radii of these spheres were taken as the van der Waals radii of Pauling, as implemented in Gaussian 98, and scaled by a constant of 1.2.[11] The solvent parameters, including the dielectric constant, were the same as those implemented for THF in the program. The final free energies in solution were calculated by adding the solvation energies to the computed gas phase free energies. Thus, using

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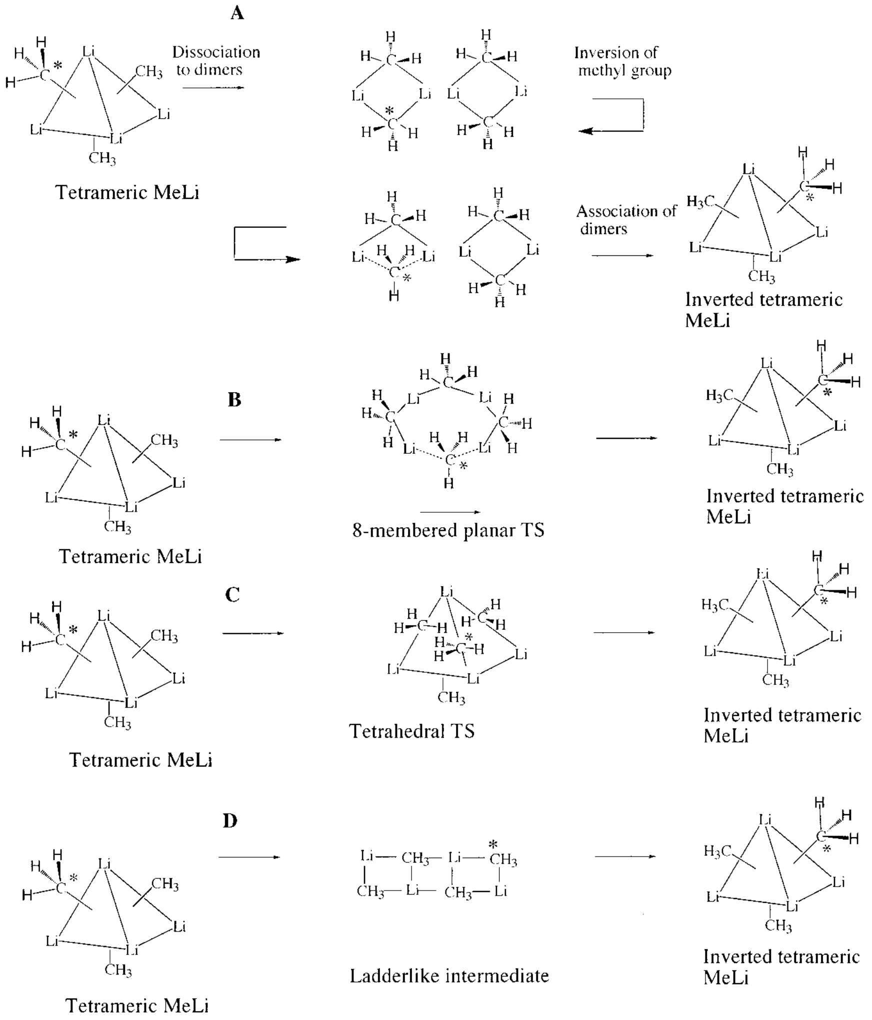

Figure 1. Mechanisms of inversion of methyllithium proposed in the literature. (A) The tetrameric ground state dissociates into two dimers with subsequent inversion of one of the methyl groups. The dimers then associate back to the tetrahedron. (B) eight-membered planar ring transition state in which one of the methyl groups inverts. (C) Three of the four methyl anions rotate in a synchronous manner around the tetrahedron at the transition state, center-to-edge to center-to-edge, passing the Li−C edges as planar sp^2-hybrized anions. (D) A ladderlike intermediate is involved in the MeLi inversion mechanism. The asterisk denotes the inversion center.

this approach, the loss in translational and rotational entropy upon forming a molecular complex will be the same in the gas phase and in solution. This is in agrement with the findings of Jencks.[13] He has argued that the loss in translational and rotational entropy upon forming molecular complexes in solution is not that different from the gas phase. Others have calculated the entropy losses in aqueous solution upon forming molecular complexes and covalent bonds to be around 50−70% of those in the gas phase.[14−16] Since we are studying reactions between neutral molecules in an organic solvent, it should be a relatively good approximation to estimate the entropy changes from their gas phase counterparts. However, the calculated rotational and translational entropy effects should be considered as upper bounds to their true values.

The Gaussian 98 suite of programs were used for all calculations reported in this article.[12]

Results and Discussion

The most stable MeLi aggregate in etheral solvents is a tetramer in which the four lithium ions form a tetrahedral core with the methyl anions positioned over each of the four planes; see Figure 1. From this ground state structure four routes (A−D) to inversion of one of the MeLi monomers were considered; see Figure 1. Following route A, the tetramer first dissociates into two dimers. The geometries of the tetramer and the dimer are depicted in Figure 3 and Figure 2, respectively. Our B3LYP/6-31+G* computed bond lengths and bond angles are in good agreement with those obtained in earlier ab initio studies.[17,18] However, the computed gas phase dissociation energy at the B3LYP/6-311+G*//B3LYP/6-31+G* level is around 8 kcal/mol lower than the MP4SDQ/6-31+G*//MP2/6-31+G* value.[18] The latter calculation is expected to exhibit a larger basis set superposition error than the former, and in addition post-Hartree−Fock methods generally require much larger basis sets than 6-31+G* to produce reliable binding energies. Consequently, we believe our B3LYP

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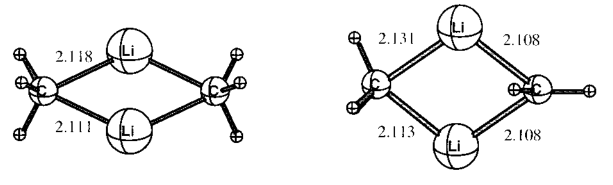
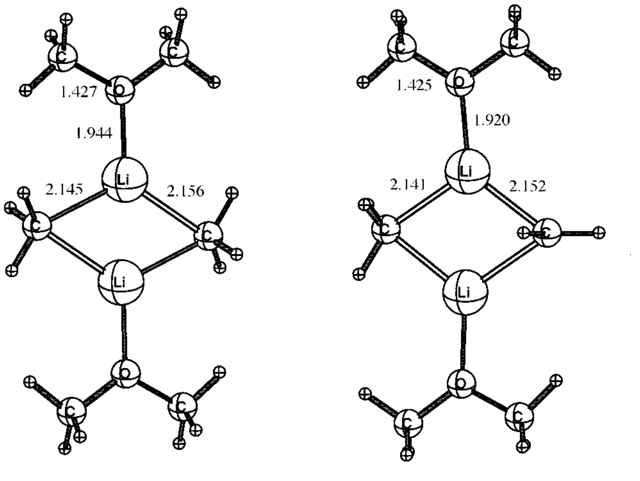


Dimeric ground state

Dimeric transition state



Solvated dimeric ground state

Solvated dimeric transition state

Figure 2. Dimeric ground state and transition state in the gas phase and solvated with two dimethyl ether molecules. The structures were geometry optimized using B3LYP/6-31+G*. Bond lengths are given in ångströms.

results to be more reliable than the previously reported MP4SDQ values.[18] We computed the free energy of dissociation in the gas phase to be 22.1 kcal/mol. Thus, in the gas phase methyllithium exists exclusively as a tetramer. With the PCM energies added, the dissociation free energy in THF solution was computed to be 8.0 kcal/mol. This is in agreement with experiments which show that the tetramer is the major aggregate in THF solution.[19,20] However, the computed free energy of dissociation of $(MeLi)_4$ might be a bit high. It should be noted, however, that the experiments have been performed using butyllithium, and the tetramer $(BuLi)_4$ might be less stable than $(MeLi)_4$ relative to the dimer. This can explain the somewhat high computed value. From the dissociated dimers, a transition state was located for one of the dimers, where one of the methyl anions inverts between the two lithium ions; see Figure 2. The free energy of activation in solution from the dissociated dimer to the dimer transition state was computed to be 16.0 kcal/mol. The overall activation barrier for route A in THF solution would then be about 24.0 kcal/mol when the dissociation energy is taken into account. This value agrees reasonably well with the experimental value of 15 ± 2 kcal/mol,[4] considering that the computed free energy of dissociation is an upper limit. Thus, the computations show that inversion of MeLi via a dimer is a possible route, as suggested by earlier theoretical studies.[9]

To validate the solvation model used in this study, we solvated the dimer ground state and the dimer transition state with two dimethyl ether molecules. Dimethyl ether is expected to be a good model of THF. These structures were then reoptimized to the corresponding solvated ground state and transition state; see Figure 2. Frequency calculations (B3LYP/6-31+G*) and single-point calculations (B3LYP/6-311+G*) were performed. Together with computed PCM energies on these structures, the resulting free energy of activation was calculated to be 15.9 kcal/mol. This is almost identical with the free energy of activation (16.0 kcal/mol) computed for the gas phase structures without explicit solvent molecules. Consequently, our calculations indicate that the polarizable continuum model (PCM) supplies a good representation of the THF solvent for the system studied herein. This may seem surprising since one would expect to have specific first solvation layer effects, due to interactions between the oxygens of the solvent and the positive lithium atoms of the solute. However, previous studies have shown that the PCM model surprisingly well can account for the effects of specific interactions in the first solvent layer.[21-23] For example, it has been shown in a study of the hydrolysis of methyl phosphate anion in aqueous solution that the PCM method gives a good representation of the solvent effects on the potential energy surface.[21]

By forcing the four lithium ions toward a plane, a first transition state (TS1) was located and geometry optimized in route B. This transition state then collapsed into an eight-membered ring intermediate (inter-1). This structure has been suggested to be of importance for the inversion.[24,25] From this intermediate one of the methyl groups rotated around an axis perpendicular to the ring plane, passing a second transition state (TS2), and proceeded into a second intermediate (inter-2). From this intermediate the methyl group inverted via a third transition state (TS3). Geometries of this mechanism are presented in Figure 3, and free energies in solution relative to the ground state are shown in Figure 4. The TS2 and TS3 transition states were found to be the highest in energy of the stationary points and correspond to the energy of activation of the MeLi inversion process. The free energy was computed to be 18.8 kcal/mol higher in energy than that of the tetrameric ground state; see Table 1. This is in excellent agreement with experimental data (15 ± 2 kcal/mol).[4] The energy of inter-2 was computed to be only 2.5 kcal/mol (B3LYP/6-311+G*) lower than that of the transition state TS3. This shows that the actual inversion of the methyl center is very low, which has been demonstrated by earlier theoretical calculations.[26]

Route C was then investigated. It was speculated that three of the four methyl anions rotate in a synchronous manner around the tetrahedron at the transition state, center-to-edge to center-to-edge, passing the Li−Li edges as planar sp^2-hybridized anions.[9] We searched for such a transition state, but could not find any. Instead

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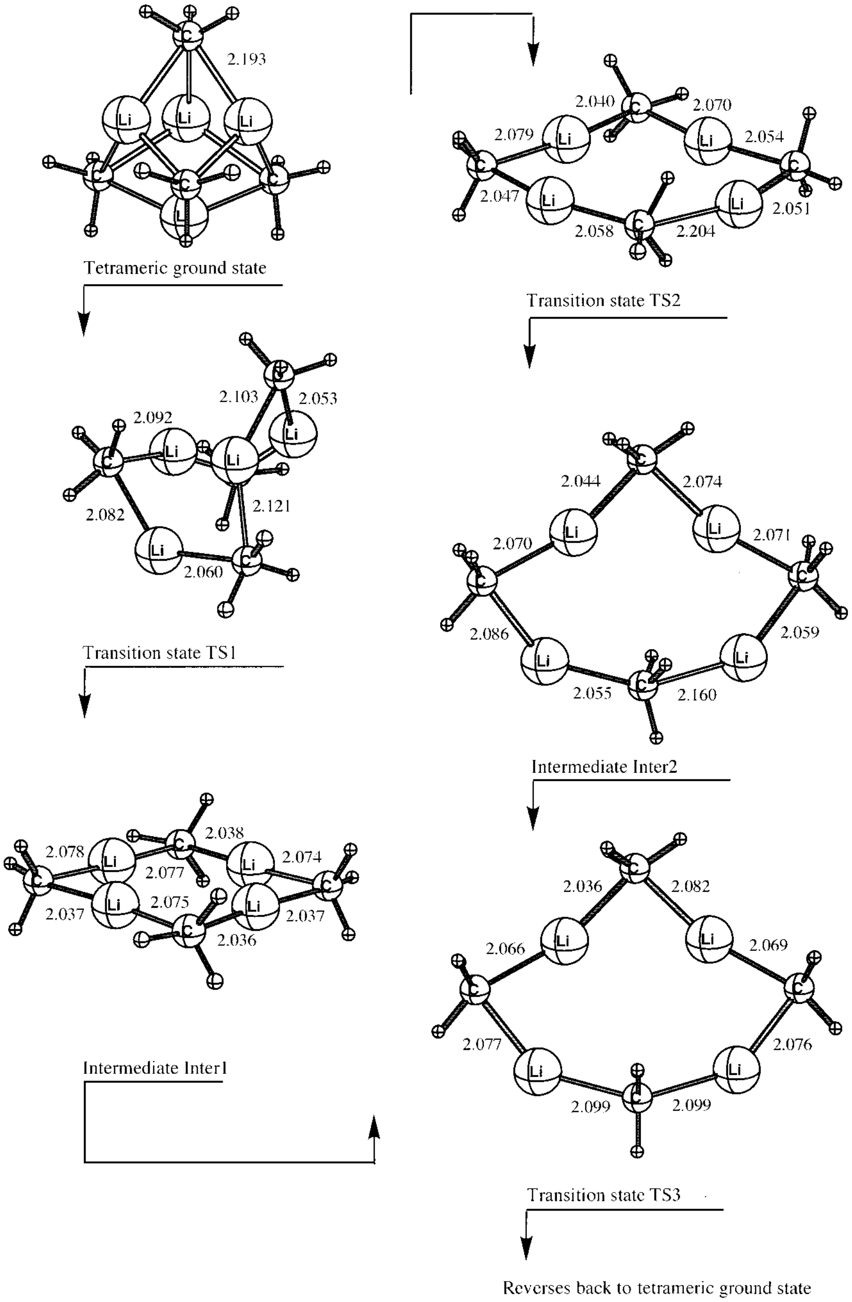

Figure 3. Tetrameric ground state, intermediates inter-1 and inter-2, and the transition states TS1, TS2, and TS3. The structures were geometry optimized using B3LYP/6-31+G*. Bond lengths are given in ångströms.

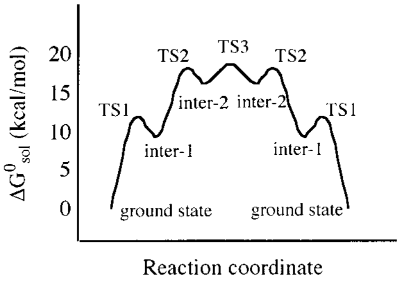

Figure 4. Free energies of the stationary point structures in solution. Energies are in kcal/mol and are relative to the tetrahedral ground state.

the eight-membered-ring transition state (TS3) was located in every attempt.

A ladderlike intermediate has been suggested to be crucial for the inversion process (route D).[10] However, no such structure could be found. Instead, the eight-membered-ring intermediate (inter-1) was located when searching for such a geometry. The mechanism for MeLi inversion can be rationalized as follows. From the tetrahedral ground state, stretching/rotation of two lithium ions, while the methyl anions simultaneously slide along the tetrahedral planes, brings these into the same plane as the other two lithium ions, via TS1 toward the planar eight-membered-ring intermediate (inter-1); see Figure 3. The B3LYP/6-31+G* computed normal frequency of the tetrahedral ground state with wavenumber 376.6 cm^{-1} corresponds to the vibration in which the four lithium ions and the four methyl carbanions move toward a plane. One of the Li−C−Li sides breaks in transition state TS2. Inter-2 is then passed, the methyl center inverts via TS3, and the tetramer folds back into its tetrahedral ground state

Table 1. Computed Energies[a] (kcal/mol) Relative the Tetrameric Ground State

structure	ΔE	$\Delta\Delta G_g$	$\Delta\Delta G_{PCM}$	$\Delta G°_{sol}$	exptl
TS1	18.0	−5.1	−0.9	11.9	
inter-1	13.0	−5.3	2.0	9.7	
TS2	21.3	−4.5	1.3	18.0	
inter-2	20.6	−5.3	1.0	16.3	
TS3	22.9	−6.1	2.0	18.8	15 ± 2

[a] The definitions for the energetics (with respect to the reactant tetrameric MeLi) are as follows: ΔE, classical energy computed at the B3LYP/6-311+G* level; $\Delta\Delta G_g$, thermal free energy correction, $\Delta\Delta G_{PCM}$, PCM solvation free energy correction; $\Delta G°_{sol} = \Delta E + \Delta\Delta G_g + \Delta\Delta G_{PCM}$. $\Delta\Delta G_{PCM}$ energies were computed with B3LYP/6-31+G*. $\Delta\Delta G_g$ was calculated at 253 K and 1 atm, with the vibrational frequencies obtained at the B3LYP/6-31+G* level. The $\Delta G°_{sol}$ values correspond to a standard state of 1 M solution in THF at 253 K.

mirror image. There are three two-site Li−Li pairs which can rotate clockwise and counterclockwise; see Figure 5. This results in six diastereomeric transition states with six different rate constant values, as has been observed.[10]

It is known that the solvent has a small effect on the MeLi inversion energy barrier,[9] which is in agreement with our calculated PCM solvation energies; see Table 1. The computed activation entropy is large and positive. This can be explained by the tight tetrahedral ground state which breaks up into the more flexible transition state. This has also been observed in experimental studies.[19]

In summary, the computed activation energies of both the dimeric and tetrameric methyllithium aggregates agree well with the experimentally determined activation barrier. However, the tetrameric aggregate mechanism explains why the observed Li−Li two-site exchange rate constant values are different for chiral organometallic tetramers as has been measured with EXSY NMR.[10] The dissociation of the tetramer into dimers and with subsequent inversion followed by recombination back to the inverted tetramer is ruled out by EXSY NMR experiments due to the lack of cross-peaks between the α-carbon atoms in inter-aggregate positions.

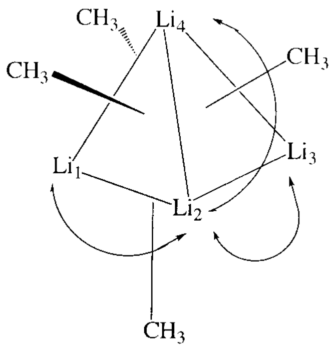

Figure 5. Rotation of three pairs of two lithium ions clockwise or counterclockwise relative to the other two lithium ions in a chiral tetrahedron, giving rise to six different diastereomeric transition states.

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