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A DFT-Derived Model Predicts Solvation-Dependent Configurational Stability of Organolithium Compounds: A Case Study of a Chiral α-Thioallyllithium Compound

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Effort is being made to enhance the configurational stability of functionalized chiral organolithium compounds. These compounds are useful in asymmetric synthesis, and finding ways to enhance their resistance toward racemization is consequently of large importance.[1] Several types of organolithium compounds, such as dipole-stabilized α-amino-organolithiums, *N*-methylpyrrolidines, *N*-methylpiperidines, 1-oxyalkyllithiums, and α-thioallylorganolithiums have been demonstrated to resist inversion at temperatures up to −40 C° or higher.[2,3] In parallel with the search for configurationally stable organolithiums it was found that the solvent and cosolvents could have a pronounced effect on the racemization rate of organolithiums.[4] Much effort has therefore been made to find mixtures of solvents and cosolvents that slow the racemization process. However, the results of several of these studies have been puzzling. For example, the cosolvent TMEDA can for some compounds in one solvent slow the racemization, while in other solvents it instead accelerates this process.[5] Thus, despite all research devoted to this field, no clear and general picture has emerged of how the solvent and cosolvent affect the configurational stability.

In addition, a detailed understanding of the origin of configurational stability and the mechanisms of how the organolithiums invert are still unclear. A few mechanisms have been suggested for the inversion of functionalized organolithiums. In the so-called conducted-tour mechanism the lithium ion travels (guided by the adjacent heteroatom) from one side of the enantiotopic carbanion to the other during the inversion in a concerted manner.[6] The dissociative mechanism assumes that the lithium ion is pulled off from the carbanion by the solvent and the now naked carbanion can easily invert.[2i,7] Note that these mechanisms assume that the organolithium inverts as a monomer.

It is known that organolithiums form aggregates. From Raman spectroscopy it was suggested that ethyllithium and *tert*-butylithium form tetrameric aggregates in hexane,[8] and since then many organolithium aggregates have been characterized by X-ray crystallography and NMR spectroscopy.[9] Variations in reactivity of organolithiums due to aggregation have been investigated.[10] However, possible relationships between configurational stability and aggregation have received little attention. A few theoretical papers have appeared which propose mechanisms for inversion of simple organolithiums, facilitated by aggregation.[11]

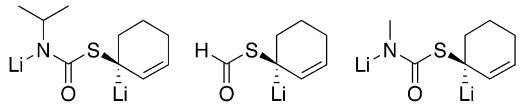
Recently we presented a model of how dipole-stabilized α-aminoorganolithiums may racemize in ethereal and hydrocarbon solvents.[12] The model nicely explains why different solvents affect the organolithium's ability to withstand racemization only to a minor extent.

The idea is simple: In coordinating solvents such as THF the organolithium exists in its monomeric form, and the efficient solvation prohibits aggregation. The racemization can therefore only occur along one of two possible ways: the conducted-tour mechanism or the a dissociative route mechanism.

Fast racemization can be caused by solvent stabilization of the more charge-separated transition state of the conducted-tour mechanism. With a very efficient solvation of the lithium ion, the carbanion can be separated from it with the formation of an ion pair. The naked carbanion then easily inverts.

In noncoordinating solvents such as hexane or toluene, the organolithium will aggregate. The inversion of an organolithium in its aggregated form can easily occur where both the lithium ion and the forming sp_2-planar carbanion transition state are efficiently stabilized by the neighboring carbanions and lithium ions.

Hoppe and co-workers discovered that the chiral α-thioallyllithium compound **1** is remarkably configurationally stable in diethyl ether and THF.[3] However, it racemizes quickly in the hydrocarbon solvent toluene. How can this be possible?



1 **2** **3**

We decided to test our model, which suggests that the solvent and aggregation should play an important role on the configurational stability of chiral organolithiums. We performed density functional theory (DFT) calculations on the model compounds **2** and **3**. Ground-state, transition-state, and inverted-product structures of the monomer and the dimer were geometry-optimized in the gas phase and solvated with up to four dimethyl ether molecules at the B3LYP/6-31+G* level of theory. Frequency calculations were computed on some selected transition states at the same level of theory, as indicated in Table 1. Solvent effects were additionally estimated using the polarized continuum model (PCM/HF/6-31+G*) on the microsolvated structures. The calculations were performed with the Gaussian 98 program package.[13] See Supporting Information for more details of the inversion mechanism.

A hydrocarbon solvent such as toluene cannot efficiently solvate the lithium cation, and experiments show that organolithiums are prone to aggregate in these solvents. Therefore, it was assumed that **1** can be modeled as a dimer when studying the reaction in toluene. According to the proposed model, aggregation will decrease the activation barrier to inversion. It is likely that the reason for this is the increased coordination of the lithium ion and thus an effect similar to the effect exerted by THF on the monomer.

As evident from Table 1, both the THF-solvated monomer and the toluene-solvated dimer of **2** are configurationally labile. The

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Table 1. Computed Energy Barriers (kcal/mol) to Inversion of the Monomer and the Dimer of **2** and **3**[a]

	gas phase	Me_2O solvated	Me_2O + PCM (THF)	PCM (toluene)
monomer of **2**[b]	29.7			
+ 1 Me_2O[b]		23.1	18.3	
+ 2 Me_2O[b]		15.2	12.6	
+ 3 Me_2O[b]		4.8	1.2	
dimer of **2**[b]	15.1[c]			15.0
monomer of **3**	27.4			
+ 2 Me_2O[b,d]		24.7	20.5	
+ 4 Me_2O[e]		21.7	[f]	
mimer of **3**	>9.1[g]			[f]

[a] The energy barrier is calculated relative to the identically solvated ground state. [b] Transition state verified by normal-mode analysis. [c] This TS leads to an intermediate with an energy of 10.9 kcal/mol, followed by a second TS with an energy of 12.9 kcal/mol. [d] Both solvent molecules are coordinated to the lithium atom of the carbanion. [e] Two solvent molecules are coordinated to each lithium atom. [f] Not converged. [g] This is the energy of the corresponding intermediate. The subsequent TS has an energy of 9.4 kcal/mol.

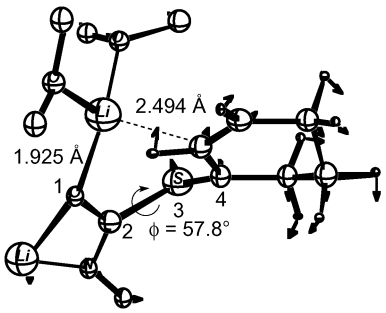

Figure 1. $[Me_2O]_2$ solvated transition state of **3**. Geometry and normal mode at B3LYP/6-31+G*. Selected bond lengths (Å). Some hydrogens have been removed for the sake of clarity.

solvent stabilization of the inverting carbanion is especially dramatic for the third Me_2O molecule, which hardly binds to the reactant but instead binds strongly to the TS.[14] Thus, the behavior of this system is not in accordance with the data for compound **3** reported by Hoppe and co-workers.[15] Therefore, we extended the model to include also the lithium amidate moiety as in model **3**. In the gas phase, the monomer of **3** inverts with a slightly lower barrier than **2** does. Although the activation energy is only about 2 kcal/mol lower than that of **2**, the structure is quite different. Thus, for **2** the dihedral angle $\phi(1-2-3-4)$ (as defined in Figure 1) is close to 0°, whereas the corresponding torsional angle is 82° in the nonsolvated TS and 67° in the tetrasolvated TS of **3**. In these latter structures, there is a close interaction between S and Li (2.31 and 2.66 Å respectively), preventing efficient solvation of the Li cation. Thus, in contrast to the racemization of **2**, solvation of **3** does not give rise to the same degree of TS stabilization.

As shown in Figure 1, the isomerization is concerted for the monomer. Thus, there is no clear distinction between carbanion inversion and torsion of the hyperconjugated S−C− bond as would be the case for a dissociative mechanism.[2i]

Locating the initial TS for the racemization of the dimer of **3** proved difficult. However, the reactant and intermediate together with the final TS were optimized, and the energies of these suggest parallel potential energy surfaces for the two systems. We therefore feel confident that the activation energy for the inversion will be low for both systems in the dimeric state.

The results can be rationalized as follows; the racemization of the monomer of **3** is only weakly accelerated by the coordinating ethereal solvent THF. This is due to a less efficient solvation of the TS, caused by the effects of the distal lithium amide moiety on the transition-state geometry (vide supra). In a noncoordinating solvent such as toluene, **3** will aggregate, and the racemization is therefore accelerated. Thus, Hoppe and co-workers have designed a chiral carbanion that is configurationally stable in coordinating ethereal solvents due to reduced solvent affinity in the transition state. This model may be used to further develop organolithium compounds which should be designed to resist aggregation and efficient transition-state solvation.

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Supporting Information Available: Geometry-optimized structures and energies of the stationary points and a reaction diagram (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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