Chiral Organometallic Reagents, XIV[1]

Theoretical Investigations into the Mechanism of Inversion of Configuration at the Carbon Center of α-Sulfur-Substituted Carbanions

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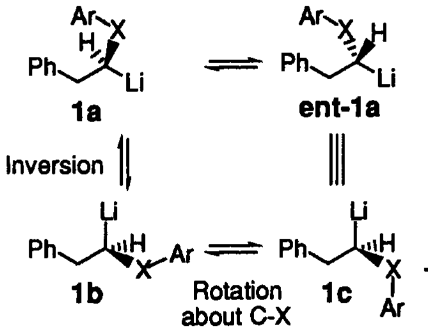
Ab initio calculations showed that the two elementary steps in the racemization of the α-methylthioethyl anion (**7**), inversion of the pyramidal anionic center, and rotation around the C^--S bond, occur in sequence and are not concerted. The former process passes over a barrier of 1.1 kcal/mol, the latter over one of 10.9 kcal/mol. MNDO calculations on the α-phenylthioethyl anion (**8**) revealed a preferred conformation of the S–aryl bond, allowing maximum delocalization of the sulfur lone pairs into the π* orbital of the aryl group. This orientation is maintained during rotation around the C^--S bond and is the origin of steric hindrance in the racemization of certain α-arylthio-, α-arylseleno-, and α-aryltelluroalkyllithium compounds **1** to **6**.

Introduction

Chiral α-hetero-substituted alkyl-metal compounds are valuable reagents in stereoselective synthesis[2]. Their utility depends on their configurational stability, i.e. our ability to control their ease of racemization. α-Thio- and α-selenoalkyllithium compounds have been noted for their low barrier to racemization[3]. Recently, activation parameters for the racemization of representative lithium compounds, such as **1** to **6**, have been determined by dynamic NMR spectroscopy[4]. In this context the compounds **4** to **6** were conspicuous, because their racemization was slow to the point that racemization could not be observed by NMR-spectroscopic techniques[4c].



X	X-Ph	XDur
S	1	4
Se	2	5
Te	3	6

Dur = 2,3,5,6-Tetramethylphenyl

In this paper we report on calculations carried out to identify the nature of the barrier in the racemization process and the possible reasons for the steric effects reported above.

It has been suggested that α-arylseleno- and α-sulfur-substituted organolithium compounds adopt an antiperiplanar arrangement of the C–Li and X–Ar bonds in the ground state in order to allow maximum delocalization of the carbanion lone pair into the X–Ar-σ* orbital[5]. Stabilization of such carbanions by negative hyperconjugation has also been revealed by several calculations on H_2C^--SH and related systems[5,6].

One consequence of this preferred ground-state geometry of such a carbanion is that configurational inversion (racemization) has to include at least two elementary steps, inversion of the carbanion center and rotation about the C–X bond in order to restore the conformation favorable for negative hyperconjugation[4b]. We carried out ab initio calculations on H_3C-HC^--SMe (**7**) to find out whether inversion and rotation occur in concert, or whether these are unrelated elementary steps. Moreover, we investigated by MNDO calculations the influence of the sulfur substituent on the rotation step. With respect to the experiments described before, calculations were carried out for **8** having a phenyl substituent on the sulfur atom.

$H_3C\text{-}CH^-\text{-}SMe$ **7**

$H_3C\text{-}CH^-\text{-}SPh$ **8**

Methods

Structures and energies of stationary points on the energy surface of **7** were obtained at the MP2(full)/6-31+G* level with Gaussian 92[7] and confirmed by frequency calculations. Zero point energies were scaled by 0.89[8]. The energies and selected bond lengths of **7** are compiled in Table 1. The structures and energies of **8** were calculated with VAMP 4.40[9] by using the MNDO approximation[10] (Table 2).

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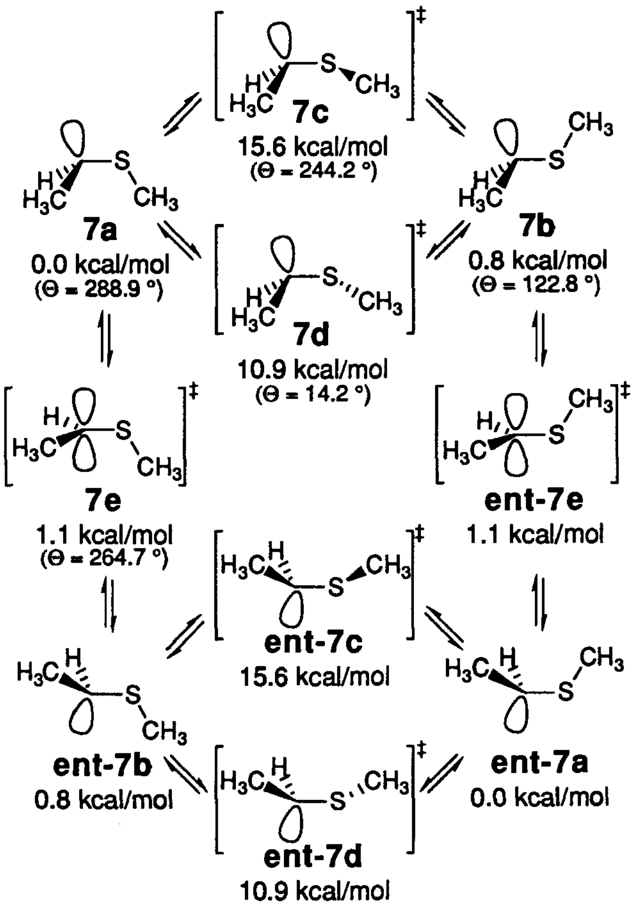
Results and Discussion

Using the model compound **7**, we attempted to establish by calculations whether or not the rotation and inversion processes are concerted or independent of another. Geometry optimization of **7** led to the energy minima structures **7a** (E_{rel} = 0.0 kcal/mol) and **7b** (E_{rel} = 0.8 kcal/mol), in which the lone pair orbital on the carbanion and the S–Me bond are antiperiplanar [torsion angle Θ_{7a} (H–C$^-$–S–Me) = 288.9°] and synperiplanar [Θ_{7b}(H–C$^-$–S–Me) = 122.8°], respectively. Both conformers have a pyramidal carbanion and are stabilized by negative hyperconjugation, which is stronger in **7a** than in **7b** as a result of the better overlap of the n_C and the σ^*_{S-Me} orbitals. The relative strength of negative hyperconjugation goes along with an increased bond length of the S–Me bond in **7a**, i.e. R(S–Me) in **7a** = 1.884 Å vs. R(S–Me) = 1.830 Å in **7b**.

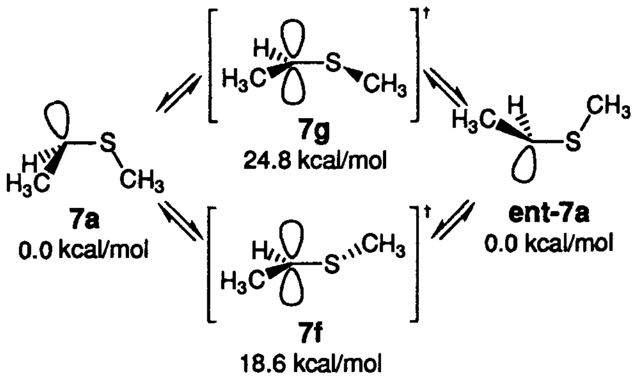


Θ: = torsion angle (H-C$^-$-S-CH$_3$)

Conversion of **7a** into **7b** by rotation around the α-C$^-$–S bond passes through two transition states, **7c** and **7d**. In both transition states pyramidal configuration at the anionic carbon is retained. The transition states are located at the torsion angles at Θ_{7c} = 244.2° (E_{rel} = 15.6 kcal/mol, SMe being synperiplanar relative to C$^-$–Me) and at Θ_{7d} = 14.2° (E_{rel} = 10.9 kcal/mol, SMe being almost synperiplanar relative to C$^-$–H). The energies of the transition states largely reflect the loss of hyperconjugative stabilization. In addition, transition state **7c** is destabilized by the energy required to overcome the steric repulsion resulting from the proximity of the two methyl groups[11].

Planarization of the anionic carbon of **7a** leads to the transition state for the inversion **7e** with E_{rel} = 1.1 kcal/mol. In this transition state the lone pair orbital of the carbanion and the σ* orbital of the S–Me bond are in parallel orientation maintaining the stabilizing negative hyperconjugation. The structures **7e** and **7c** or **7d** represent the transition states on the potential hypersurface, which result from the independent inversion and rotation of **7a** during conversion to its enantiomer ***ent*-7a**.

When starting from **7e**, if the planarity of the carbon is maintained during rotation, two stationary points of higher order (i = 2) on the potential surface are obtained, **7f** and **7g**, with Θ_{7f} = 0.0° (E_{rel} = 18.6 kcal/mol) and Θ_{7g} = 180.0° (E_{rel} = 24.8 kcal/mol), respectively. **7f** and **7g** represent the structures which must occur during concerted inversion and rotation of **7a**.

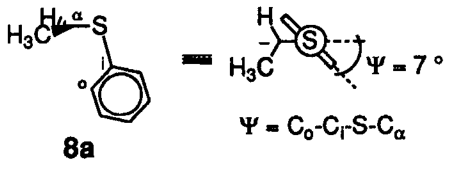


†Stationary points of higher order (i=2)

From the considerably lower energies of the transition states **7c**, **7d**, and **7e** compared with those of **7f** and **7g** it follows that the rotation and inversion processes are not coupled but successive steps, as calculated for H_2C^-SH and $H_2C^-SCH_3$[5,6]. As the energy of the transition state of inversion (**7e** with 1.1 kcal/mol) is significantly lower than the energies of the transition states of rotation (**7c** and **7d** with 15.7 and 10.9 kcal/mol, respectively) for free α-sulfur-substituted carbanions, the inversion of the carbanion is a fast and the rotation about the C–S bond a slow process.

Changing the sulfur substituent from methyl to phenyl, e.g. going from **7** to **8**, reveals interesting details of the rotation step. With respect to the larger number of atoms in **8**, we used the MNDO method for these calculations. The calculated minimum-energy structure **8a** exhibits a planar geometry at the anionic carbon atom[12], as well as a parallel orientation of the charge-carrying orbital on the carbon atom and the S–Ph bond, thus allowing a maximal negative hyperconjugation. As a result of the repulsion between the electrons in the charge-carrying orbital on the carbon atom and the lone pairs on the sulfur atom, there is a tendency for the latter to delocalize into the π* orbital of the phenyl substituent on the sulfur atom.

In order to obtain optimal overlap of the n_S orbitals and the π^*_{Ph} orbital, the S–Ph bond of **8** adopts a conformation in which the phenyl substituent is coplanar to the carbanion-sulfur bond, i.e. C_{ortho}–C_{ipso}–S–C_{alpha} lie in one plane (deviation from coplanarity defined as torsion angle ψ: in **8a** $\psi = 7°$).

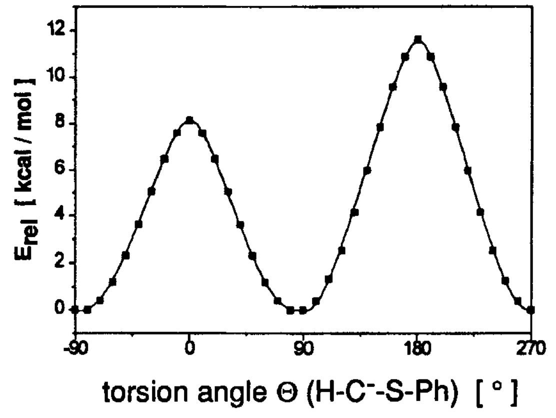


8a

Although this places the phenyl ring in a sterically disfavored position, such a coplanar preference is also observed in the solid-state structures of phenylthio methyllithium (deviation 4°) and diphenylphosphino methyllithium[13].

During rotation about the C^-–S bond, the system passes from the ground state **8a** through the transition states **8b** [Θ_{8b} (H–C^-–S–Ph) = 0.0°, E_{rel} = 8.2 kcal/mol, the phenyl group moves past the hydrogen substituent of the carbanion] and **8c** [Θ_{8c} = 180.0°, E_{rel} = 11.6 kcal/mol, the phenyl group moves past the methyl substituent of the carbanion]. The heat of formation (MNDO) of **8** as function of the torsion angle Θ is shown in Figure 1.

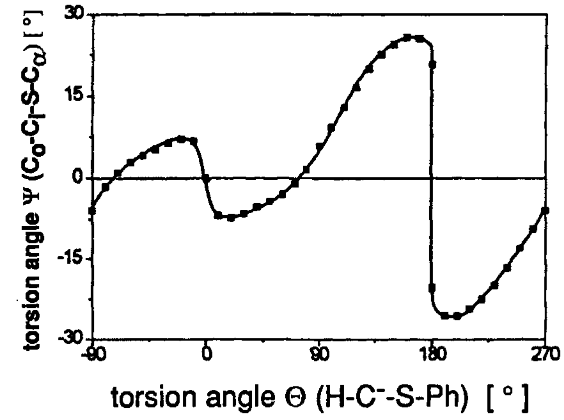
Figure 1. E_{rel} [kcal/mol] of H_3C–HC^-–SPh (**8**) as function of the torsion angle Θ (H–C^-–S–Ph)

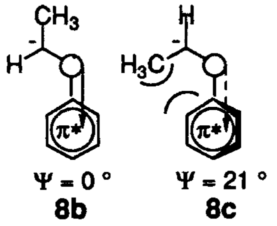


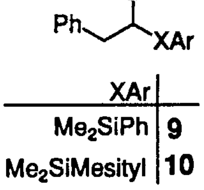
For both transition states it is noteworthy that, as a consequence of the then orthogonal relationship between the n_C and the $\sigma^*_{S\text{-}Ph}$ orbitals, no stabilization of the carbanion lone pair by negative hyperconjugation is possible. The "coplanar" orientation of the phenyl group ($\Psi \approx 0°$) is maintained in the transition state **8b**. In the transition state **8c**, however, this is not possible due to the *syn*-pentane interaction between the phenyl group and the methyl substituent. In **8c** the phenyl ring is forced to twist by $\psi = 21°$ out of the electronically preferred coplanar arrangement, as depicted in Figure 2.

The attendant decrease in n-π^* delocalization and the steric hindrance cause the transition state **8c** to be 3.4 kcal/mol higher in energy than transition state **8b**. Thus, the increase in the racemization barrier of the duryl-substituted compound can be traced to a steric hindrance, which originates from the need to delocalize the lone pairs on the heteroatom into the π^* orbital of the aryl group. Hence, no such effect should be seen in the aryl(duryl)-silicon analogs of e.g. **4**, having no lone pairs on the heteroatom. This has in fact been observed, as **9** (X–Ar = Me_2Si–Ph) with $\Delta G^‡_{269}$ = 11.3 kcal/mol and **10** (X–Ar = Me_2Si–Mesityl) with $\Delta G^‡_{269}$ = 11.9 kcal/mol have essentially the same racemization barrier[4c].

Figure 2. Torsion angle Ψ (C_o–C_iS–C_α) in H_3C–HC^-–SPh (**8**) as a function of the torsion angle Θ (H–C^-–S–Ph)

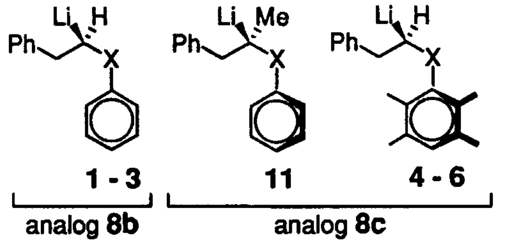






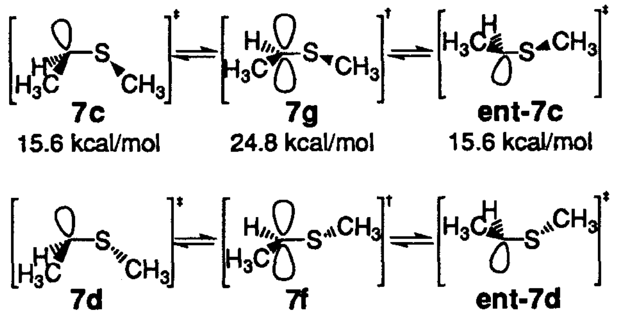
XAr	
Me2SiPh	9
Me2SiMesityl	10

On the basis of these MNDO calculations the (experimentally found) higher configurational stabilities of the α-durylthio, α-durylselenium and α-duryltellurium lithiumalkyls **4** to **6** compared to those of their phenyl analogs **1** to **3** can be understood[4b].



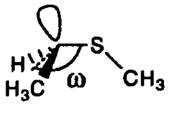
In all of these compounds there is the tendency to delocalize the lone pair electrons on sulfur, selenium or tellurium into the π^* orbital of the aryl substituent in order to minimize the destabilizing repulsion between the carbanion lone pair and the lone pairs on the heteroatom. When rotation around the carbanion-heteroatom bond (cf. Scheme 1) defines the barrier of the overall racemization process, rotation would pass through a transition state resembling **8b** in the case of the phenyl-substituted compounds **1** to **3**. Here, the phenyl substituent may move past the hydrogen at the carbanionic center. When going to the tertiary alkyllithium compound **11** the transition state for rotation (cf. Scheme 1) would correspond to **8c** in which the phenyl group has to move past either one of the two alkyl groups at the anionic carbon center. According to the MNDO calculations (cf. Figure 1), this would correspond to an increase of the racemization barrier by 3.4 kcal/mol for X = S. For this steric hindrance of rotation to occur, it does not matter whether the alkyl group is on the carbanion center or in the ortho postion of the aryl group, which have to move past one another. For this reason, the transition state of rotation for the duryl-substituted derivatives **4** to **6** would also be subject to similar steric hindrance as is present in **8c** with the concomitant increase in the energy barrier for rotation.

The results from the calculations detailed above allow a further transformation to be discussed: This is the carbanion inversion at the stage of **7c** and of **7d**:



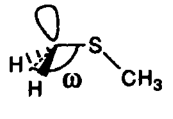
†Stationary points of higher order (i=2)

One notes that the inversion barrier for **7c** amounts to 9.2 kcal/mol and for **7d** to 7.7 kcal/mol. The former is higher, because of the coplanar arrangement of the C-methyl and the S-methyl groups in the fictive transition state **7g**[11]. The interesting phenomenon is that both inversion barriers are substantially higher than that of the ground state configuration **7a**. This difference might be associated with the different levels of negative hyperconjugation in **7a** (high) and **7c** or **7d** (zero). The hight of inversion barriers is intuitively associated with the degree of pyramidalization of the starting state. The angles of pyramidalization ω were calculated for **7a** to 145°, for **7c** to 105° (!) and for **7d** to 129°.



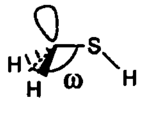
ω = 145°

7a



ω = 149°

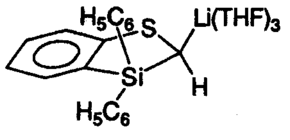
12



ω = 133°

13

Thus, in the absence of negative hyperconjugation (**7c**, **7d**) pyramidalization at the anionic center is higher than in **7a** which corresponds to a higher inversion barrier. Different degrees of pyramidalization have also been noted in the calculations by Wiberg[6d] who found a higher degree of pyramidalization in **13**[14] than in **12**[6c]. This is in line with the intuitive expectation of a higher degree of negative hyperconjugation in **12** than in **13**. This reasoning – strong negative hyperconjugation leads to low pyramidalization and a low inversion barrier; weak negative hyperconjugation leads to a higher degree of pyramidalization and a higher inversion barrier – has implications for the interpretation of experimental findings on the racemization (inversion) of **14**[15].



14

So far the inversion barrier of 10.8 kcal/mol reported by H. J. Reich for **14**[15] was considered as exceptionally high. The cyclic system present in **14** enforces a geometry about the carbanionic site that is close to **7c**, for which an inversion barrier of 9.2 kcal/mol was calculated above. This coincidence should not be overinterpreted, though: While in **14** there is a low degree of negative hyperconjugation into the S–aryl bond, there could be substantial negative hyperconjugation into the silicon–phenyl bonds, and the solvent separated ion pair corresponding to **14** has an sp^2-hybridized planar anionic structure[15]. Thus, our discussion has perhaps identified just one factor among several factors which contribute to the high activation barrier for the racemization of **14**.

Conclusion

The inversion of configuration of α-sulfur- and α-selenium-substituted carbanions consists of two steps: 1. inversion at the carbanion center and 2. rotation about the α-C^-–S bond to reestablish the favorable arrangement for negative hyperconjugation. Ab initio calculations of H_3CHC^-–SMe (**7**) show that rotation and inversion do not occur in concert but independently of one another. The inversion of the anionic carbon (energy barrier 1.1 kcal/mol) is rapid compared to the rotation about the C^-–S bond (energy barriers 10.9 kcal/mol and 15.6 kcal/mol). MNDO calculations of H_3CHC^-–SPh (**8**) demonstrate that the lone pairs of the sulfur conjugate into the π* orbital of the phenyl substituent on the sulfur atom in the ground state and probably even more so during the rotation around the α-C^-–S bond. This causes a preferred conformation of the S–Ph bond in which the phenyl substituent is coplanar to the carbanion–sulfur bond. During the rotation about the C^-–S bond the preferred conformation of the S–Ph bond is maintained, leading to a steric hindrance in the rotation step when the phenyl group moves past the methyl group at the anionic carbon. The latter effect can be used to explain the higher configurational stabilities of the α-arylchalcogeno alkyllithium compounds **4** to **6** compared to those of **1** to **3**.

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Table 1. Calculated energies[a] and selected bond lengths[b] of **7**

	E_{tot} (HF/6-31+G*)	E_{tot} (MP2/6-31+G*)	E_{rel} (MP2/6-31+G*)^c	R (C^--S)	R (S-Me)	i^d
7a	-515.107 88	-515.674 72	0.0	1.723	1.884	0
7b	-515.107 53	-515.673 50	0.8	1.755	1.830	0
7c	-515.089 17	-515.649 83	15.6	1.820	1.852	1
7d	-515.094 02	-515.657 40	10.9	1.806	1.828	1
7e	-515.102 73	-515.672 07	1.1	1.696	1.888	1
7f	-515.076 47	-515.642 53	18.6	1.768	1.794	2
7g	-515.068 20	-515.632 65	24.8	1.794	1.804	2

[a] The total energies are given in hartrees, the relative energies are given in kcal/mol. – [b] Selected bond lengths of the anion, geometry are given in Ångstrøm. – [c] Using ZPE, scaled by 0.89[8]. – [d] Number of imaginary frequencies.

Table 2. Energies of **8**

	ΔH_f (MNDO) [kcal/mol]	E_{rel} (MNDO) [kcal/mol]	State
8a	14.8	0.0	ground
8b	23.0	8.2	transition
8c	26.5	11.7	transition

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