Effects of Ion Pair Separation on Inversion and Rotation of Sulfur-, Selenium-, and Silicon-Stabilized Organolithium Reagents

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Most vinyl,[11] cyclopropyl,[12] and 2-alkoxy[13] lithium reagents are configurationally stable. Other types racemize too rapidly for trapping experiments[4a, 9] or require very low temperatures to avoid rapid equilibration[4b, 61]. Advances in the utility of chiral organolithium reagents depend on detailed structural information[3] and mechanistic understanding of their racemization. One limiting mechanism for organolithium reagent epimerization is a bimolecular associative process through intermediate 1.[4b1] An alternative ion pair dissociation process via 2 has been frequently proposed since polar solvents usually accelerate racemization,"", but this has not been directly testable since the ion pair status of most organolithium reagents is not known. Our hexamethylphosphoric triamide (HMPA) titration technique[2, 3] addresses this problem by allowing the unequivocal identification of contact and separated ion pairs. The correlation between ion pair structure and inversion barriers for several organolithium reagents can now be established.

We selected compounds 3[9] and 4 for detailed study. These and related compounds are valuable reagents[10] that are easily prepared and stable in polar solvents. The presence of several NMR-active nuclei (1H, 13C, 7Li, 29Si, and 77Se) facilitates careful NMR investigations. Figure 1 shows the results of an HMPA titration of 3. The 7Li, 31P, and 13C data, as well as other spectra not shown, indicate that in THF 3 is a contact ion pair (\(J_{\text{Li-C}} = 18.5 \text{ Hz}\)) with a pyramidal carbanion center (\(J_{\text{C-H}} = 132 \text{ Hz}, J_{\text{C-Si}} = 75 \text{ Hz}\)).[9] The dimethyl(phenyl)silyl group served as a probe and indicated the configurational equilibration of 3; below -100 °C 3 is chiral on the NMR timescale. The adduct 3 · 1 HMPA is also a pyramidal (\(J_{\text{C-H}} = 136 \text{ Hz}, J_{\text{C-Si}} = 85 \text{ Hz}\)), chiral contact ion pair (\(J_{\text{C-Li}} = 14.4 \text{ Hz}\)). After the addition of three equivalents of HMPA, 3 is a fully solvent-separated ion pair, as shown by the characteristic \(R^-/\text{Li}^+\) quartet and \(R^-/\text{Li}^+\) quintet in the 7Li NMR spectra and absence of coupling between lithium and carbon. Formation of separated ion pairs did not result in the loss of diastereotopicity of the SiMe3 group even though increases in \(J_{\text{C-H}}\) from 136 to 148 Hz and \(J_{\text{C-Si}}\) from 85 to 106 Hz[44] indicate significant planarization at the carbanion center.

Variable-temperature 13C NMR spectra of 3 in THF, THF/HMPA, and THF/3HMPA are shown in Figure 2. In THF, coalescence is observed at -100 °C and in THF/HMPA at -112 °C. The slight lowering of the barrier on coordination to HMPA (AG* = 8.0 to 7.8 kcal mol\(^{-1}\)) for 3, 8.2 to 7.8 kcal mol\(^{-1}\) for 4) would seem to indicate that inversion of the pyramidal structure is accelerated by the strong donor ligand HMPA which loosens C–Li coordination. One might, therefore, expect an even lower barrier for the separated ion pair. The separated ion pair, however, racemizes more slowly (approximately 1/20 as fast at -101 °C)
with a coalescence temperature above $-80\,^\circ\text{C}$ ($\Delta G^\ast = 9.1\, \text{kcal mol}^{-1}$ for 3, $9.5\, \text{kcal mol}^{-1}$ for 4). The separation of the ion pair (formation of 2) cannot be the rate-determining step for the racemization of 3 and 4. These data cannot easily be explained by an inversion process but fit well for rotation.

Similar conclusions have been reached by R. W. Hoffmann et al. in a study of arylseleneno- and aryllEtluoro-substituted alkylithium reagents. Barriers to rotation in carbamions have origins in stabilizing $\sigma^\ast$ interactions when the carbamion lone pair is aligned with the $S\cdots\text{Ph}$ or $Si\cdots\text{R}$ bonds, and destabilizing repulsions between lone pairs when the carbamion is not aligned. Such interactions should be stronger in a free carbamion than in a contact ion pair. When the carbamion $C$ atom rotates away from the favored orientation, the charge density on the $C$ atom must increase. This extra charge is more effectively stabilized by lithium in a contact rather than in a separated ion pair.

The racemization of 3 in THF is independent of concentration (0.04 to 0.64 M). In addition, the presence of 1 mol equiv of the separated ion pair lithium fluoroenide had no effect on the racemization rate, so the reaction does not involve intermediate 1. Since lithium fluoroenide did lower the coalescence temperature for loss of Li-C coupling from $-92 \to -112\,^\circ\text{C}$, Li-Li exchange may be intramolecular.

The complex behavior of 3 and 4 prompted us to examine a system in which there is no ambiguity between inversion and rotation. The organolithium reagent 5 is achiral in the absence of rotational barriers even if inversion is slow. We studied this compound, as well as the related PhS(Ph-Se)ClLiSiMe$_2$Ph (6). Both are largely separated ion pairs in THF as well as in THF/HMPA, and both show diastereotropic SiMe$_2$ groups up to at least $-20\,^\circ\text{C}$. For 5 in a 1:3 mixture of THF/ether the SiMe$_2$ signals coalesce at $-12\,^\circ\text{C}$ ($\Delta G^\ast = 13.3\, \text{kcal mol}^{-1}$), whereas for 6 in a 3:2 mixture of THF/ether coalescence is reached at 7 $^\circ\text{C}$ ($\Delta G^\ast = 14.3\, \text{kcal mol}^{-1}$). The measured barrier probably corresponds to rotation about the $C\cdots S$ bond, which converts the chiral conformation of 5 to the achiral.

These findings provide a basis for understanding one odd facet of the behavior of 3: the racemization barrier of the separated ion pair increased as more HMPA was added ($T_c = -98\,^\circ\text{C}$ at 2 equiv of HMPA, $-79\,^\circ\text{C}$ at 3 equiv, and $-75\,^\circ\text{C}$ at 6 equiv). This suggests that the racemization of the separated ion pair R"LiH might actually proceed via the contact ion pair. If the rotation barrier for the separated ion pair 3 is as high as those measured for 5 and 6, then a mechanism involving recoordination of lithium to carbon (accompanied by loss of one or more coordinated HMPA molecules) explains the rate-retarding effect of high HMPA concentrations.

Clearly, the racemization is mechanistically complex. A coupled inversion-rotation process fits our data: the inversion is more significant for the contact ion pair in THF, and rotation dominates for the (probably planar) solvate-separated ion pair in THF/HMPA. We envision a mechanism in which lithium coordination to $S$ or $Se$ allows the lithium to move from one face of the carbamion to the other without separation of the ion pair. Coupled rotation-inversion processes have been extensively studied for sulfonium, which are isoelectronic with phenylcarbanions.

Substantial rotation barriers have been reported for lithiated sulfides,22,24,25 in which lithium coordinates to oxygen, but not for lithiated sulfides, selenides, or silanes.22 However, the strong preference of Li for the equatorial position in dithianes23 is equivalent to high rotation barriers in acyclic systems. The observation of a diastereotopic CH$_2$ group in the tetramethylethlenediamine (TMEDA) adduct of Ph$_3$PCH$_2$Li ($\Delta G^\ast = 7\, \text{kcal mol}^{-1}$)13 interpreted as indicating a barrier to inversion, implies that there is a significant rotation barrier associated with C-P bonds as well. The relatively high epimerization barriers of $\alpha$-lithio selenides,24,26 sulfides,24,25 amines,65 and ethers13 take on a new perspective with this information.

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