

The Effect of HMPA on the Reactivity of Epoxides, Aziridines, and Alkyl Halides with Organolithium Reagents

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The reaction of epoxides with nucleophiles is a widely used and effective method for the synthesis of alcohols.¹ Related reactions with N-activated aziridines provide access to amines. Simple alkyl,² vinyl-, or alkynyllithium³ reagents and ketone^{4,5a} or ester enolates⁶ work poorly, but more nucleophilic carboxylate dianions, metalloenamines,⁴ and stabilized organolithium reagents such as metalated dithianes give generally clean reactions and high yields.⁷ Because of their relatively low reactivity, it is frequently advantageous to either activate epoxides by addition of a Lewis acid like boron trifluoride etherate^{3,8} or activate the nucleophile by addition of lithium-complexing reagents such as HMPA or DMPU.^{7b,9} We report here some observations on the latter reaction of interest to synthetic chemists.

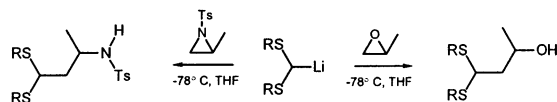
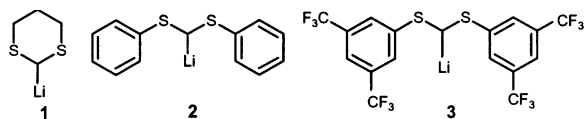


Figure 1 shows the results of a kinetic study of the effect of HMPA on the rate of reaction of three bis-thio substituted organolithium reagents, **1**, **2**, and **3**, with methyloxirane, *N*-tosyl-2-methylaziridine, and primary alkyl halides.¹⁰

The reactivity order of **1**:**2**:**3** in THF was 1:29:5 for the epoxide and 1:16:3 for the aziridine. On addition of HMPA, the three lithium reagents showed wildly different rate effects, as did the electrophiles. With **1** as the nucleophile, the rate increase on addition of >10 equiv of HMPA was 8000 for the epoxide, 800 000 for the aziridine, and ca. 140 000 000 for BuCl. For **2**, the rate decreased by a factor of 350 for the epoxide (after an initial small increase), but increased by 40× for the aziridine and 380× for BuCl. For **3**, the rate decreased by >2500 for the epoxide and 15× for the aziridine, but stayed constant for the reaction with allyl chloride, BuBr, and BuI. Thus, the indiscriminate use of cosolvents for organolithium reactions without mechanistic understanding can be counterproductive — HMPA can act as a potent catalyst or inhibitor depending both on the structure of RLi and on the nature of the electrophile.

How can we rationalize these behaviors? S_N2 reactions involving strongly contact ion-paired organolithium reagents exhibit the “product-separated ion pair” problem — the cation is unable to intimately follow the charge.^{11a} When the monomeric contact ion pair (CIP) of RLi is the nucleophile in a backside S_N2 attack (such

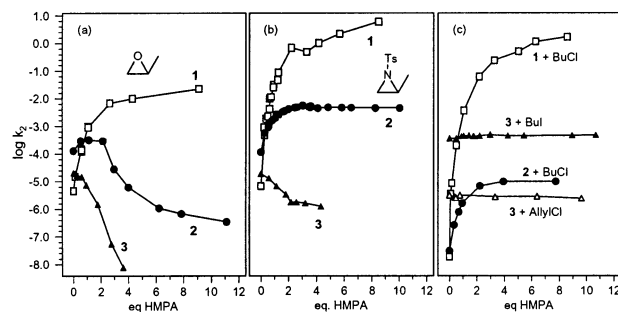
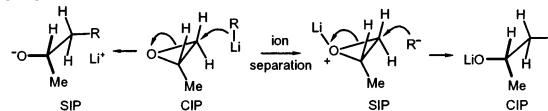


Figure 1. Effect of HMPA on rates of reaction of (a) methyloxirane, (b) *N*-tosyl-2-methylaziridine, and (c) BuCl, BuI, and/or allyl chloride with **1**, **2**, and **3** in THF at -78°C (k_2 is the second-order rate constant in $\text{M}^{-1}\text{s}^{-1}$).¹⁰

Scheme 1



as an epoxide in Scheme 1), the developing negative charge on oxygen cannot be stabilized by the lithium counterion because a least-motion pathway results in the Li⁺ separated from the oxyanion. Extensive ab initio calculations on the reaction of LiH, MeLi,^{11a,b} and cuprate species^{11c} with oxirane and alkyl halides have defined the strong requirement for catalysis by lithium and the ion separation problems of backside S_N2 displacements by a CIP. Separated ion pairs (SIPs) should be inherently favored as reactants in such reactions.¹²

The key to understanding our data is the dual role played by HMPA. Strong complexation to lithium weakens the C—Li interaction and increases the fraction of SIP present, with a great enhancement of nucleophilic reactivity.¹³ However, the Li⁺—HMPA complexes are much weaker Lewis acids than THF solvates, so any lithium assistance to departure of the leaving group is reduced or eliminated.¹⁴

We have developed NMR techniques that allow reliable assessment of RLi ion pair status in the presence of HMPA.^{15a} Application to the lithium reagents **1**, **2**, and **3** led to the data in Figure 2.^{15b,c} Qualitatively, **1** is a strong CIP, with little ion pair separation until 2 equiv of HMPA have been added, and incomplete separation even at 10 equiv of HMPA. Reagent **2** is a weak CIP in THF, with substantial formation of SIP even before 1 equiv of HMPA was added. In contrast, **3** is ca. 80% SIP in THF at -78°C .

Our working hypothesis is that these reactions involve nucleophilic attack of the organolithium SIP on the electrophile. The differences in behavior can be rationalized by competition between the ease of formation of the SIP (**3** > **2** > **1**, see Figure 2), the inherent nucleophilicity of the separated anions (**1** > **2** > **3**, as indicated by the relative reactivities at high HMPA equivalents,

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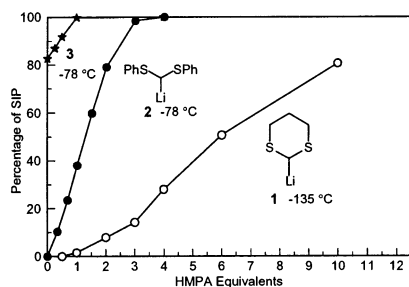


Figure 2. Effect of HMPA on the fraction of SIP for **1**, **2**, and **3**. The fraction of SIP for **1** was determined in 3:2 THF/Me₂O by line shape simulation of the ⁷Li NMR spectra during an HMPA titration at -135 °C.^{15a-c} The fraction of SIP for **2** and **3** was determined from the ¹³C chemical shift at -78 °C of the phenyl C-S carbon, which moves from δ 150.3 for the CIP in THF to δ 158.3 for the SIP in THF-HMPA for **2**, and from δ 151.9 for the CIP in ether to δ 162.3 for the SIP in THF-HMPA for **3**.

Figure 1), and the extent to which Li⁺ coordination assists the departure of the leaving group (large for the epoxide, minor for the aziridine, none for the halides).¹⁶

One indication that SIPs are involved is the inversion of reactivity between **1** and **2** in THF with all three electrophiles when HMPA was added. The unexpectedly high relative reactivity of **2** and **3** in THF results from a more favorable preequilibrium between CIP and SIP that more than compensates for the much lower inherent nucleophilicity of the carbanion formed from **2** (ca. 10⁻⁴) or **3** (ca. 10⁻⁸) as compared to **1**. Some other observations support the notion that only SIPs are involved: (1) The rate increase on addition of HMPA was identical within experimental error for the reaction of several halides with **2**. (2) The relative rate of 2-methyloxirane and 2,2-dimethyloxirane opening with **1** (1.64) was identical in THF and THF-HMPA. (3) The addition of up to 10 equiv of LiClO₄ had no detectable effect on the reaction of 2-methyloxirane with **1** or **2** in THF.¹⁷ It is the lithium counterion of the SIP which complexes the epoxide at the transition state; external lithium salts are not involved. Rate-enhancing effects of LiClO₄ and other salts on epoxide opening have been reported for lithium reagents where ion separation is much more difficult than for **1**–**3**, such as lithium acetylides^{5b} and enolates.^{5a}

The situation is simplest for **3**. The reagent is essentially fully separated in THF and thus already has maximal nucleophilic reactivity. Addition of HMPA reduces the Lewis acidity of Li⁺, with a concomitant decrease in the rate of epoxide opening (Figure 1a). The rate drops much less for the aziridine opening (Figure 1b), so lithium assistance is less important and is essentially absent for the alkyl halides, which show no change in rate on addition of HMPA.

For **1**, the opposite effect dominates. The C–Li bond is strong, and the equilibrium concentration of SIP in THF is exceedingly small. The addition of HMPA enhances the reaction rate with all electrophiles, in our hypothesis by increasing the fraction of SIP present. However, as compared to epoxide opening, the rate increase is greater by a factor of 100 for the aziridine and 18 000 for the 1-chlorobutane alkylation, a reflection of the decreasing importance of Li catalysis in this series.

Intermediate behavior is shown by **2**. At low equivalents of HMPA, the increased fraction of SIP leads to a small increase in the rate of epoxide opening. At this stage, the principal form of the counterion is Li(HMPA)₂⁺,¹⁸ which presumably still provides some electrophilic assistance. Past 2 equiv, conversion to SIP is complete, and additional HMPA inhibits the reaction as the less electrophilic higher HMPA solvates of Li⁺ predominate. In contrast to the reaction with epoxide, the rate of reaction of **2** with the

aziridine and alkyl halides increases until ion separation is complete at ca. 3 equiv of HMPA, consistent with minimal or no Li⁺ assistance.

In summary, the cosolvent HMPA can have either rate-accelerating or rate-retarding effects on the S_N2 reactivity of sulfur-substituted organolithium reagents, depending on the balance between three factors: the ease of ion pair separation, the inherent nucleophilicity of the carbanion, and the extent to which lithium assists the departure of the leaving group (HMPA reduces the Lewis acidity of Li⁺).¹⁶ In THF with 0–2 equiv of HMPA, there is a complex interplay between all three effects. In THF with excess HMPA, the relative reactivity is largely determined by the nucleophilicity of the bare carbanions.

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Supporting Information Available: Procedures for the kinetic experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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