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Regioselectivity of Addition of Organolithium Reagents to Enones: The Role of HMPA

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Hexamethylphosphoramide (HMPA) is a highly polar, aprotic solvent which coordinates well to lithium, by one measurement approximately 300 times more strongly than tetrahydrofuran (THF).[1a] HMPA is frequently used to accelerate organolithium reactions. More intriguing are the instances where it has been used to alter their course, such as the regiochemistry of additions to α,*β*-unsaturated carbonyl compounds (Figure 1).[2a] Several groups have directed extensive efforts at elucidating the effects that changes in solvent, temperature, and steric bulk have on the regioselectivity of these additions.[2,3]

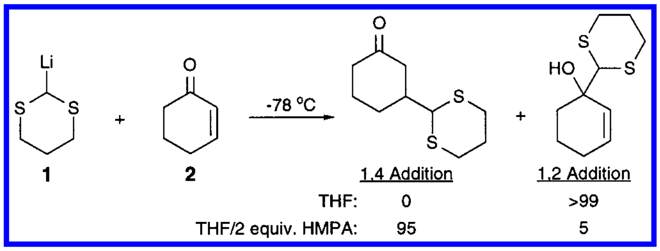

Figure 1. Demonstration of the effect of HMPA on the *kinetic* selectivity of enone addition.[2a]

Bryson[3b] and Cohen[3a] have proposed that the regioselectivity of addition is a function of the ion pair structure of the lithium reagent, where contact ion pairs (CIP) with an intact C−Li association give 1,2 addition via a four-centered transition state, whereas solvent-separated ion pairs (SIP) give predominantly 1,4 addition. This hypothesis was based on the observations that the addition of HMPA[2e,3] and colder temperatures[2b,3a] (conditions which favor SIP formation[5]) kinetically favor 1,4 addition.[4] This hypothesis could not be directly tested since no information about the solution structures of organolithium reagent − HMPA complexes was available. Here we apply our multinuclear NMR technique[1b] to quantify the amount of separated ion in solution and correlate this with changes in regioisomeric and diastereomeric product ratios to test this hypothesis.[6]

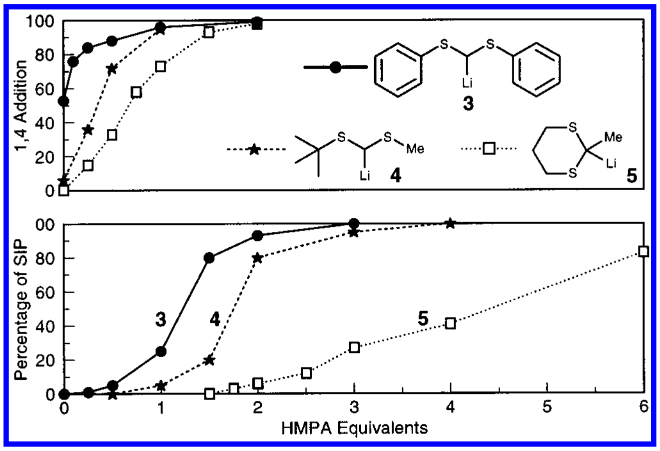

Figure 2. Comparison of the amount of SIP in solution for **3**−**5** (bottom) with the amount of 1,4 addition toward **2** (top) in 3:2 THF/Et$_2$O at −120 °C.

To simplify our analysis, we studied stabilized organolithium reagents that are known or expected to be monomeric in THF.[7] Figure 2 illustrates the effect of HMPA on the fraction of SIP and on the amount of 1,4 addition to 2-cyclohexenone (**2**)[11] for the anions bis(phenylthio)methyllithium (**3**),[1c] *tert*-butylthio(methylthio)methyllithium (**4**), and 2-methyl-1,3-dithianyllithium (**5**).[1d,8b,c] The method by which we use lithium NMR spectroscopy to determine the amount of SIP as a function of HMPA concentration has been described.[1b] The ^{7}Li NMR spectra were integrated by full line shape simulation.[12] In these SIPs the carbanion and lithium counterion are separated by at least one layer of solvent molecules, but remain intimately associated based on chemical shift[1b] and reactivity[5a] effects. The concentration of free ions for the SIPs of **3**, **4**, and **5** is not known, but in low dielectric-constant media such as THF approximately 1% of the ion pairs of 0.1 M lithium fluorenide are dissociated.[5b]

The formation of SIP and production of the 1,4 product are clearly correlated, but in each case the onset of 1,4-addition significantly precedes the appearance of the SIP. For **3**, which easily undergoes the CIP to SIP transition on addition of HMPA, over 50% 1,4 addition is observed even in the absence of HMPA. For **5**, which exhibits the tightest contact ion of the three, SIPs are not detectable until 1.5

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[4] When the addition is reversible, higher temperatures and the addition of HMPA can favor 1, 4 addition thermodynamically: see ref 2d.

[5] (a) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 307−318. Hogen-Esch, T. E. *Adv. Phys. Org. Chem.* **1977**, *15*, 153. (b) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 318−324.

[6] A second hypothesis is that the presence of HMPA may promote a single electron transfer (SET) reaction, leading to conjugate addition. However, a mechanistic study using radical probes failed to demonstrate that this was occurring, at least in the reactions of lithiodithianes: see Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1984**, *49*, 935−939.

[7] Their monomeric nature in THF solution is supported by a variety of data, including cryoscopy in THF (for **5**[8b] and analogues of **7**[9]), the observation of single C−Li couplings (for **5**,[8c] and analogues of **3**,[8c] **4**[8c] and **5**[1d]) and the concentration independence of the 1, 2: 1, 4 ratio for several of the lithium reagents studied (including **3**[3a] and (2-pyridylthio)(isopropylthio)methyllithium[1e,10]).

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[11] The additions were performed at −120 °C. The Supporting Information contains a description of a simple device to facilitate mixing and temperature control during low-temperature additions.

[12] The simulations were performed with the computer program WINDNMR (Reich, H. J. *J. Chem. Educ. Software*, **1996**, 3D, 2).

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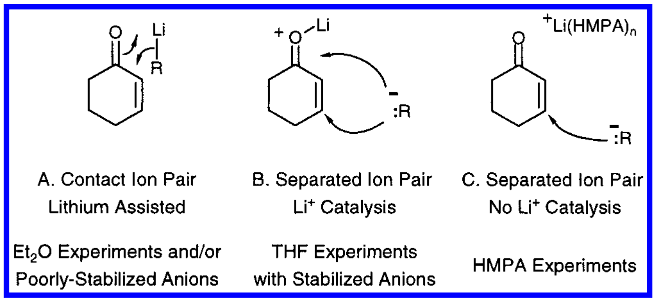
Scheme 1. Mechanistic Proposal



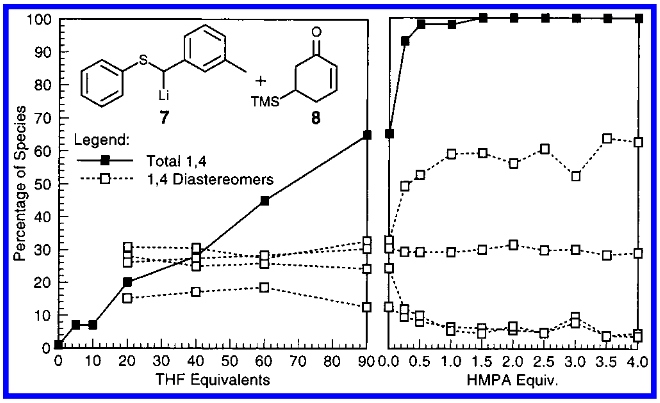


Figure 3. Changes in 1,4 addition and 1,4 diastereomer distribution as functions of the equivalents of THF in ether (left) and HMPA with 90 equiv of THF (right) for the reaction of **7** with **8** at −120 °C in Et_2O.

equiv. of HMPA, where the amount of 1,4 addition has already reached 90%. Compound **4** shows an intermediate behavior. The lack of a direct correlation between the CIP/SIP ratio and the 1,2:1,4 addition suggests that the reactions are governed by Curtin-Hammett kinetics. If the CIP and SIP interconvert more readily than they react with an enone, then the product ratio will not reflect the ground-state CIP/SIP ratio measured in the NMR experiments (equilibration is slow on the NMR time scale). Minute amounts of a more reactive SIP, not detected by NMR, can dominate the reaction, even though the CIP is unambiguously the dominant ground-state structure.

Our first observation inconsistent with a simple CIP−SIP dichotomy to rationalize the 1,2:1,4 addition was that the tetrakis(trifluoromethyl) analogue of **3** (bis(3,5-bis(trifluoromethyl)phenylthio)methyllithium, **6**), *which is almost fully separated in THF*, actually gave a preponderance of 1,2 addition (61%) in 3:2 THF/ether. Addition of 4 equiv. of HMPA switched this to 88% 1,4 addition. Thus, if we assume as above that the SIP is more reactive than the CIP, *simple ion separation is not solely responsible for the conjugate addition*. It is very significant that the reaction, which is 34% complete in 30 s at −120 °C in THF-ether, proceeded to less than 3% in 1 h when 4 equiv. of HMPA were present, an HMPA-induced reduction in rate by a factor of 1800. We hypothesize that the rate-retarding and conjugate-addition-enhancing effects of HMPA for **6** arise from the suppression of a lithium-catalyzed process. Scheme 1 presents the three processes we postulate for the reaction: (A) the CIP gives 1,2 addition; (B) reaction of the lithium-complexed enone with the free carbanion gives a mixture of products, and (C) the uncatalyzed SIP process gives only 1,4 addition.

These conclusions are supported by the use of diastereomeric product ratios as “fingerprints” to track the involvement of the CIP and SIP species. Reactions of phenylthio(3-methyl)benzyllithium (**7**), which is similar to **3** in its ion pair behavior, with 5-trimethylsilyl-2-cyclohexen-1-one[13] (**8**) were performed in Et_2O with incremental amounts of THF added, followed by incremental amounts of HMPA. The total amount of 1,4 addition and the diastereomer distribution within the 1,4 products are shown in Figure 3.

The most significant result from Figure 3 is that the distribution of 1,4 diastereomers was essentially invariant as THF was added to ether, despite a change in the total amount of 1,4 addition from 0 to 65%. This suggests that the 1,4 products are being produced by the same mechanism throughout. In the absence of THF, only 1,2 addition is observed, and we propose that a CIP (A in Scheme 1) is the only reactive species. The addition of THF to the Et_2O solution increases the solvent strength and stabilizes small amounts of an SIP species which produces the 1,4 product principally through path B. Separated ions are not detectable in the NMR experiment in the absence of HMPA.

The addition of HMPA causes a dramatic change in the 1,4 diastereomer distribution. Thus HMPA affects the reaction beyond simply causing more of it to proceed through SIPs. Calculations predict that Lewis acid complexation of the carbonyl group favors 1,2 addition;[14] removal of Li^+ should lead to more 1,4 addition, as observed. We propose that the change in diastereomer ratios signals the onset of an uncatalyzed addition (path C, Scheme 1). A mechanism in which the lithium cation is inactive (path C) is also supported by the observation that the same final diastereomer ratio was achieved with several equiv. of N,N′-dimethylpropyleneurea (DMPU),[8a] as well as when 1 equiv. of crypt[2.1.1] was added.[15] These facts argue against inhibition of 1,2 addition by a sterically encumbered HMPA-coordinated catalyst (a behavior analogous to Yamamoto's bulky aluminum catalysts[2c]).

In summary, at least three mechanisms are required to explain these data. The CIP produces exclusively 1,2 addition, as hypothesized.[3a,16a] However, the situation with the SIP is more complicated. In the presence of HMPA, only 1,4 addition by the SIP is observed for **3**, **4**, **5**, **7** and a number of other anions.[10] We propose that the absence of Li catalysis is an important factor in achieving clean 1,4 addition. For well-stabilized anions in the absence of HMPA, when lithium catalysis is possible and SIPs are energetically accessible reactive intermediates, mixtures of 1,2 and 1,4 addition are observed (**3**, **6**, and **7**, for example).[16]

We find that many sulfur-substituted lithium reagents can be induced to cleanly add either 1,2 or 1,4 to enones. Figure 3 is a representative example. Lower temperatures and the addition of HMPA favor 1,4 addition kinetically,[4] only occasionally is there an advantage to the use of more than 2 equiv. of HMPA. Conversely, the use of pure Et_2O as a solvent, particularly at higher temperatures such as 0 °C (which also improves solubility of the lithium reagent), leads to clean 1,2 addition (although with strongly contact ions such as dithianyllithium, exclusive 1,2 addition is achieved even at −78 °C in THF).

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Supporting Information Available: Experimental procedures, characterization data, and ^7Li and ^{31}P spectra of HMPA titrations of **3**−**7** (18 pages).

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