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).1,2 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).3 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

Bryson3b and Cohen3a 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 (SSIP) give predominantly 1,4 addition. This hypothesis was based on the observations that the addition of HMPA3d and colder temperatures2a,3a (conditions which favor SIP formation) kinetically favor 1,4 addition.3 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 technique1b to quantify the amount of separated ion in solution and correlate this with changes in regioisomeric and diastereomeric product ratios to test this hypothesis.5


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


(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.; J. J. J. Org. Chem. 1984, 49, 935–939.

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

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/Et₂O at −120 °C.

(7) Their mononeric nature in THF solution is supported by a variety of data, including cryoscopy in THF (for 5a and analogues of 7), the observation of single C–Li couplings (for 5a and analogues of 3, 4, 5, and 5a) and the concentration independence of the 1, 2: 1, 4 ratio for several of the lithium reagents studied (including 3a and (2-pyridylthio)isopropylmethylmethyl-lithium10b).


(9) 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.

(10) The simulations were performed with the computer program WINNMR (Reich, H. J.; J. Chem. Educ. Software 1996, 30, 2).
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-Hammet 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 is that the tetrakis(trifluoromethyl) analogue of 3 (bis(3,5-bis(trifluoromethyl)phenylthio)methyl lithium, 6), which is almost fully separated in THF, actually gave a predominance 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 8 were performed in Et₂O 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 Et₂O 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...