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Metalations in hydrocarbon solvents; media effects on *n*-BuLi reactivity[☆]

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Abstract—The relative basicities of solutions of *n*-BuLi in cyclohexane as a function of the addition of increasing increments of THF or TMEDA (designer media) have been assessed. As the chloro DMG is incapable of complexing to *n*-BuLi, it can neither affect the *n*-BuLi oligomeric equilibrium nor exhibit a DoM mechanistic component involving prior-coordination (CIPE). Accordingly, by measuring the rates of loss of chlorobenzene in the varied media as well as by certain ^{7}Li NMR studies, a gradual, controlled increase in the basicity of *n*-BuLi in cyclohexane with increasing increments of THF or TMEDA was observed. Relationships of the basicity in the varied media to the three oligomeric forms of *n*-BuLi are proposed.

Two limiting mechanisms for the directed *ortho*-metalation (DoM) reaction are commonly subscribed to in the literature. The more prevalent complex-induced-proximity-effect (CIPE)[1] mechanism involves coordination of a directing metalation group (DMG) on an aryl substrate to an alkyllithium reagent prior to the rate-determining step. DMG's directing *ortho*-lithiation primarily via a CIPE pathway often contain a contribution from an enhanced acidity of the *ortho*-H's brought about by the electronic nature of the DMG, for example, $-OCH_3$, $-N(CH_3)_2$, $-C(O)N(CH_2CH_3)_2$. The overriding base mechanism,[2] the second limiting mechanism, possesses no prior-coordination component but rather depends solely upon the enhanced acidity of the *ortho*-H's resulting from the strong electronegativities of certain DMG's, for example, –F, –Cl, $-CF_3$, – CN. Stabilities of alkyllithiums in various media,[3] as well as the acidity afforded by several DMG's,[4] have been evaluated, but not the inherent basicities of promoted alkyllithium solutions. Since all DoM reactions fundamentally contain an acid/base component, greater insight into the inherent basicities of such media was desired.

To initiate this study, insight into our 'designer media', that is, equivalents of certain ethers or amines in hydrocarbon solvent, was sought. Such media commonly involve incremental amounts of either THF or TMEDA in a hydrocarbon solvent and are ideal for study of media modification affects on the basicity of the most useful alkyllithium reagent, *n*-BuLi.[5] Our working hypothesis has been that the oligomer equilibrium for *n*-BuLi (Eq. 1) is displaced to lower oligomeric, more basic, forms which are more effective in DoM reactions, that is, the basicity of these solutions is increased in proportion to the increase in the percent of either THF or TMEDA present. Both ^{7}Li NMR as well as media variation/reactivity studies indicate that these assumptions are correct.

$$2(\text{n-BuLi})_6 \xrightleftharpoons{\text{THF}} 3(\text{n-BuLi})_4 \bullet \text{THF}_s \xrightleftharpoons{\text{THF}} 6(\text{n-BuLi})_2 \bullet \text{THF}_s \tag{1}$$

s = 1-4; a similar formulation can be written for TMEDA

Required for this investigation was an aryl substrate possessing a DMG that would direct metalation solely by the 'overriding base' mechanism so that modulating effects brought about by prior-coordination (CIPE mechanism) could not contribute. The specific substrate chosen for study was chlorobenzene in a medium of cyclohexane containing an internal standard of dodecane. We had noted during an earlier study of the metalation of *p*-chloroanisole that in THF solvent a

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competing metalation took place *ortho*- to the –Cl substituent resulting in a smooth formation of a benzyne intermediate as evidenced by the products that were formed.[5b] Various chlorobenzenes have been successfully metalated and ortho-substitution products isolated, but this was accomplished at temperatures below −100 °C.[6] As basicity measurements at such low temperatures would be most difficult, the decision was reached to metalate chlorobenzene at 25 °C and track the extent of its disappearance (via initial benzyne intermediate formation) as a measure of the inherent basicity of the metalation medium. This necessitated the use of the internal standard, dodecane, so that the rate of disappearance of chlorobenzene could be followed by noting the decrease in the $C_6H_5Cl/C_{12}H_{26}$ ratio.[7]

The results of our studies involving increments of THF and increments of TMEDA are recorded in Figures 1 and 2, respectively.[8,9]

Remarkably, it was observed that over 6 h, no reaction whatsoever took place with 'unactivated' *n*-BuLi, that is, *n*-BuLi in bulk cyclohexane. This was observed not only in cyclohexane, but in *n*-hexane and in toluene as well. The clear nature of the solutions remained over the 6 h period, although there was some darkening of the solutions when the systems were allowed to run overnight. Our conclusion is that chlorobenzene does not react with hexameric *n*-BuLi, the least reactive of the oligomeric forms of *n*-BuLi.

In bulk THF solvent, quite a different response to *n*-BuLi was observed; the solution turned black upon addition of the base. GC analysis of the resulting solution after treatment with chlorotrimethylsilane (ClTMS) and aqueous workup afforded products emanating from the formation of benzyne. Noted in the GC spectra were signals possessing masses and fragments reflecting the formation of $C_6H_5C_4H_9$, $C_6H_4(C_4H_9)Si(CH_3)_3$, $C_6H_4(C_4H_9)–C_6H_5$, and $C_6H_4(C_4H_9)–C_6H_4Si(CH_3)_3$. Trace amounts of other products were also noted in the GC spectra. Formation of the –TMS products permits us to qualitatively explain the observation that only about 75% of the chlorobenzene reacted. As can be discerned from the relative intensities of these products in the GC spectra, about 0.25 equiv of the *n*-BuLi is 'captured' by further reaction with the benzyne intermediate, resulting in a deficiency of *n*-BuLi at the end of the reaction. The two hydrocarbon products principally formed, $C_6H_5C_4H_9$ and $C_6H_4(C_4H_9)–C_6H_5$ represent not only 'capture' products but also products that have carried on the reaction as they have extracted a proton from, most likely, chlorobenzene.

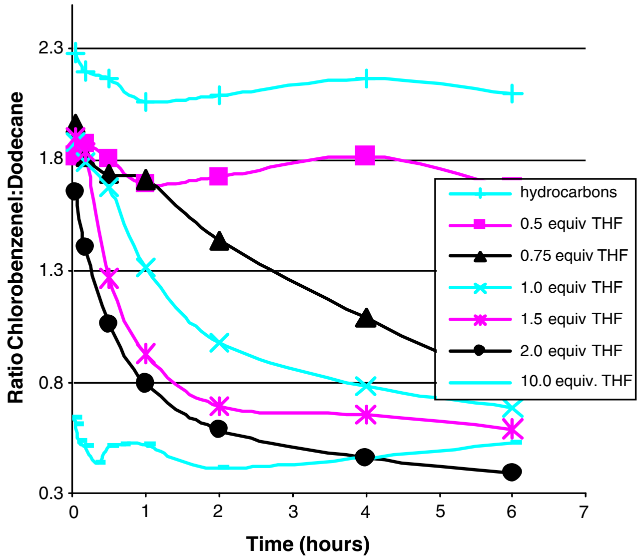

Figure 1. Disappearance of chlorobenzene (relative to $C_{12}H_{26}$) initiated by *n*-BuLi and promoted by THF. Each curve represents an average of at least two runs of 1.0 M chlorobenzene and *n*-BuLi in cyclohexane at 25 °C.

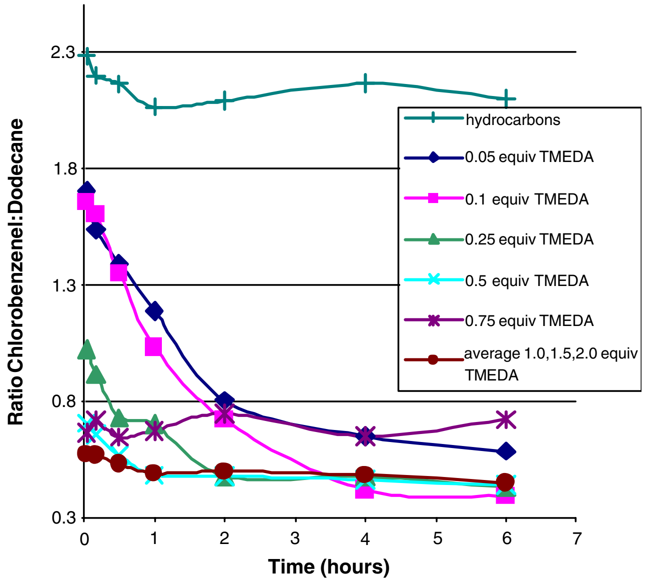

Figure 2. Disappearance of chlorobenzene (relative to $C_{12}H_{26}$) initiated by *n*-BuLi and catalyzed by TMEDA. Each curve represents averaged data for two runs of 1.0 M chlorobenzene and *n*-BuLi in cyclohexane at 25 °C.

Plots of the extent of disappearance of chlorobenzene with time for differing equivalents of THF present in the solution of *n*-BuLi in cyclohexane are presented in Figure 1.[8] Little reaction was noted with 0.5 equiv THF, but as little as 0.75 equiv of THF brought about a gradual darkening of the solution and a very gradual loss of chlorobenzene. The rate of loss and the rate of darkening of the solution both increased as the equivalent of THF added were increased from 1.0 to 1.5 to 2.0 equiv. No significant change in the array of products resulting from the formation of the benzyne intermediate was noted. Significant loss of chlorobenzene was routinely found even after 2 m, indicating a possible concentration dependence on the reaction.

Although THF and TMEDA are known as the most reactive 'catalysts' for metalation reactions, the former as solvent and the latter as an additive, notable differences in their ability to provide effective metalation have been described in the literature. This difference is reflected in this assessment of the basicity of *n*-BuLi containing increments of TMEDA (Fig. 2). As little as 0.05 equiv of TMEDA provides a chlorobenzene loss curve approximating that afforded by the 1.0 equiv THF system.[8] Fractional equivalent of TMEDA of 0.25 and greater generate more rapid loss of chlorobenzene and provide systems as aggressive as bulk THF solvent. These systems all rapidly darkened upon addition of *n*-BuLi. Arrays of benzyne products little different from those found for the THF systems were produced.

Interpretation of these reactivity data (Figs. 1 and 2) is as follows; upon progressive addition of either THF or TMEDA to the hydrocarbon media, the hexamer, tetramer, dimer equilibrium of *n*-BuLi (Eq. 1) is shifted toward the more reactive forms, the tetramer and dimer. In this study these forms are revealed as possessing greater basicity than the hexamer, the oligomer form chiefly present in pure hydrocarbon solvent. To provide further insight into these equilibria, ^{13}C and ^{7}Li NMR examination of *n*-BuLi in THF/cyclohexane and TMEDA/cyclohexane were initiated. These studies have proven to be more complicated than anticipated, but some interesting observations have been made nonetheless.

Since *n*-BuLi deoligomerization (Eq. 1) is accompanied by progressive ligation of the tetramer and dimer, respectively, evidence of this increasing ligation was sought. As a consequence, ^{13}C NMR spectral examinations of 1.0 M *n*-BuLi solutions containing equivalents of THF and increments of TMEDA in cyclohexane were initiated. In each system ^{13}C spectra afforded little evidence of secondary signals that might be associated with liganding THF or TMEDA.[9] Neither did examination of these same spectra at −40 °C.

^{7}Li examination of 1.0 M solutions of *n*-BuLi in cyclohexane at 25 °C exhibited a broad signal at 5.13 ppm and a second set of overlapping signals at 4.25 and 4.18 ppm.[10] This second set of signals was present to the extent of about 6%. Arguments can be made that these upfield ^{7}Li signals should be assigned to the presence of lower oligomeric forms of *n*-BuLi.[11,12] The 4.25/4.18 ppm signals possess a shift quite similar to the principal ^{7}Li shift of *t*-BuLi in cyclopentane. *t*-BuLi in hydrocarbon. Solvent exists principally in the tetramer oligomeric form.[13]

Addition of sequentially increased equivalents of THF to 1.0 M *n*-BuLi in cyclohexane brought a steady upfield shift in the principal ^{7}Li signal ultimately reaching 3.15 ppm for neat THF.[14] In contrast, addition of 0.05, 0.1, 0.2, 0.5, and 1.0 equiv of TMEDA to separate 1.0 M solutions of *n*-BuLi in cyclohexane afforded an ^{7}Li signal at 5.00 ± 0.02 ppm. In other words, only a consistent −0.13 ppm shift was produced for all concentrations of TMEDA versus the 5.13 ppm signal observed in the absence of TMEDA. Deoligomerization of *n*-BuLi cannot be inferred from these ^{7}Li room temperature NMR studies involving TMEDA. As for the THF studies our conclusion is that the increasing upfield shifts with increasing equivalents of THF are to be attributed chiefly to the increasing polarity of the medium, which mask any potential effects due to deoligomerization.

Observations have been made that ^{7}Li spectra of *n*-BuLi solutions of equivalents of THF in cyclohexane and fractional equivalents of TMEDA in cyclohexane are time dependent. For example, 1.0 M *n*-BuLi in cyclohexane containing 2.0 equivalents of THF exhibited an ^{7}Li shift of 4.3 ppm after 30 m and a shift of 3.7 ppm after 24 h. Since only marginal decomposition of THF under these conditions is detectable after 24 h,[9] it is unlikely that the change in shift can be attributed to the small amount of lithium enolate generated. Moreover, a similar upfield shift was found for a solution of 0.2 equiv of TMEDA in cyclohexane where, after 24 h, a shift of 4.26 ppm was observed. Since no solvent/reagent decomposition is possible in the TMEDA solutions, the observed upfield movements can be associated with changes in oligomer/ligand distribution, likely involving formation of lower MW oligomers but with greater ligation.[15] This also is likely true for the THF solutions with the awareness that THF decomposition may play a role.[16]

Both sequentially increased equivalents of THF and sequentially increased increments of TMEDA in hydrocarbon solvent provide increasingly basic solutions as revealed by the augmented disappearance of PhCl. ^{13}C Spectra of *n*-BuLi in THF/hydrocarbon solutions reveal that these solutions are much more resistant to attack by base than solutions of *n*-BuLi in pure THF. The dynamic behavior of the solutions is further demonstrated by the migrations of the ^{7}Li chemical shifts but exact interpretation of these migrations awaits further study. Overall, our observations support our contention that THF/hydrocarbon and TMEDA/hydrocarbon media are ideal systems for metalation reactions in that a wide range of basicity and reactivity[5] can be accessed. Moreover, these systems exhibit much greater stability towards *n*-BuLi than do systems involving this reagent in pure ether solvent.[9] As suggested recently, the chief role of the media in *n*-BuLi reactions is to manipulate to advantage the oligomeric equilibrium (Eq. 1).[17]

Acknowledgements

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7. A standard solution was prepared of 2.0 M chlorobenzene in cyclohexane (*n*-hexane, toluene) containing 0.5 M $C_{12}H_{26}$. These solutions afforded baselines with a $C_6H_5Cl/C_{12}H_{26}$ ratio of 2.2, essentially the same line as that for the unreactive C_6H_5Cl/*n*-BuLi in hydrocarbon solvent line in Figures 1 and 2.
8. Experimental: GC/MS and GC spectra were obtained on an Agilent 5973 MSD instrument with 6890N Network GC system. NMR studies were conducted on a JEOL Eclipse ECA 500 MHz unit possessing broadband and low temperature capabilities. All reagents were purchased from Aldrich Chemical Company. Solvents were dried over molecular sieves, 4 Å, 4–8 mesh. To 15 mL of the standard 2.0 M chlorobenzene in cyclohexane solution in a sealed nitrogen-purged flask was added the requisite equivalent(s) of THF or TMEDA followed by 15 mL of 2 M *n*-BuLi in cyclohexane. After the indicated periods of time, 1 mL samples of the solutions were extracted via syringe, quenched with chlorotrimethylsilane ($ClSi(CH_3)_3$), followed by aqueous $NaHCO_3$ workup. Samples were then subjected to GC analysis.
9. No evidence of decomposition of THF in the *n*-BuLi, THF/cyclohexane systems at 25 °C was noted in a 1 h ^{13}C spectrum. Such might have been anticipated based on the published half-life of *n*-BuLi in pure THF of 1.78 h (see Ref. 3). To check our ability to detect such decomposition, a 1 h ^{13}C spectrum of *n*-BuLi in pure THF at 25 °C was examined. (The known fragmentation of THF by *n*-BuLi affords ethylene and the lithium enolate of acetaldehyde.) After 1 h, two new ^{13}C signals were evident, one at 158.16 ppm, the other at 81.32 ppm. The 158.16 ppm signal was assigned to the carbonyl carbon of the enolate and the upfield signal to the remaining carbon. After 2 h, these signals became more pronounced and the C_1–C_4 signals of *n*-BuLi became significantly attenuated along with the appearance of several new minor signals in the hydrocarbon region of the ^{13}C spectrum.

   A solution of 1.0 M *n*-BuLi containing 1.0 equiv of THF in cyclohexane after 24 h exhibited both signals of attack of THF by *n*-BuLi, but only in minor amounts. Little effect on the C_1–C_4 signals of *n*-BuLi was noted. No attempt was made to quantify these observations.
10. On JEOL 500 MHz instruments the ^7Li reference requires a correction factor. To reference against 1.0 M LiCl at 27 °C, a 2.92 ppm downfield shift was determined. The signal appears at 2.92 ppm against the instruments' internal standard. The literature (Elschenbroich, Ch.; Salzer, A. *Organometallics*, 2nd ed.; Weinheim, 1992; pp 20–27) records that *n*-BuLi/cyclopentane possesses an ^7Li shift of 1.6 ppm versus a LiBr standard. Correction of this shift to our standard leads to a shift of ca. 4.5 ppm. The remaining discrepancies are likely accounted for by the different salt standards, LiCl versus LiBr, as well as the different solvents, cyclopentane versus cyclohexane, involved.
11. 1.0 M solutions of *n*-BuLi in cyclohexane prepared by diluting 2.0 M *n*-BuLi in cyclohexane with an equal volume of cyclohexane and by diluting 10 M *n*-BuLi with 9 vol of cyclohexane as well as by diluting 1.6 M *n*-BuLi in hexanes with 0.6 vol of cyclohexane afford identical ^7Li spectra. The intensity of the integrated 4.25/4.18 ppm signal was temperature dependent, falling in intensity from approximately 6.1% at 25 °C to 3.3% at −60 °C. Additionally, the 4.25/4.18 ppm signal was found to be concentration dependent with greater intensities being observed upon dilution. Octamers and nonamers have been inferred as being present along with the greatly predominant hexamer in hydrocarbon solutions of *n*-BuLi (Thomas, R. D.; Jensen, R. M.; Young, T. C. *Organometallics*, **1987**, *6*, 565–571). The presence of lower oligomeric forms, to our knowledge, has never been proposed With the principal signal at 5.13 ppm being assigned to the *n*-BuLi hexamer, the upfield signals most likely are attributable to lower oligomeric forms. Applying our correction factor of 2.92 ppm to these values, afforded shifts of 1.33 and 1.25 ppm. These shifts are close to those noted for the dimer and tetramer of *n*-BuLi recorded in THF: (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1805–1810; (b) Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228–10229.
12. A 1.0 M solutions of *n*-BuLi containing 1.0 M PhCl exhibited an ^7Li spectrum after standing for 1 h at 25 °C identical to the 1 h ^7Li spectra observed in the absence of PhCl.
13. The ^7Li shift for *t*-BuLi in cyclopentane is recorded as 0.70 ppm (Elschenbroich and Salzer[10]). Application of the correction factor results in a corrected shift of about 3.6 ppm for the principal ^7Li shift in *t*-BuLi. This shift has been traditionally assigned to the tetramer oligomeric form. This value is about 0.6 ppm lower than our observed value for the putative tetramer of *n*-BuLi. Interestingly, this is the same discrepancy as between our observed and literature values of the ^7Li shift for the hexamer of *n*-BuLi.[10]
14. Prepared by adding appropriate volumes of dry THF (molecular sieves) and dry cyclohexane to 10 M *n*-BuLi. The signal initially at 4.25/4.18 ppm is sequentially diminished and shifted upfield with increasing equivalents of THF. This separate signal disappears when two or more equivalents of THF are present.
15. Examination of two carefully sealed (N_2) 1.0 M solutions of *n*-BuLi containing 2.0 equiv of THF, one that had stood for 1 h, the other for 24 h, was made. The PhCl/$C_{12}H_{26}$ disappearance method was utilized. The results indicate that the 24 h solution is *less* basic than the 1 h solution. These results are preliminary. Further studies will be forthcoming.
16. This decrease of reactivity over time has been noted for several vinyl-type organolithiums. An intriguing variation on our ‘greater ligation’ theme is the observation of the greatest reactivity when these lithium reagents were generated in situ from their respective tetrasubstituted stannane precursors. Speculations by the authors include the possibility that monomeric organolithium reagents are being generated (a) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611–4624; (b) Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107–3118.
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