

Preliminary communication

Media effects in directed *ortho* metalation¹

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Abstract

Rates and extents of directed *ortho* metalation (DoM) of anisole and *p*-methylanisole (*p*-MA) with *n*-BuLi have been measured in THF/*n*-hexane. About a 14% (v/v) solution of THF in the hydrocarbon provides an extent of metalation which exceeds that in neat THF at the same concentration. Impressive regioselectivity results from the DoM of *p*-MA in this solvent system; virtually no metalation of the lateral methyl group occurs.

Keywords: Lithium; Metalation

In spite of the vast number of studies over the past 50 years on the use and efficacy of the directed *ortho* metalation (DoM) reaction, questions regarding the mechanism of this reaction still abound [1]. The data and insights gained from crystal structures, NMR studies and colligative property investigations have not as yet been successfully related to reactivity [2]. Likewise, only modest understanding exists of media effects on reactivity in DoM. Beyond the knowledge of hexamer, tetramer, dimer equilibria for the various alkyl- and aryl-lithiums, little quantitative data are available which relate these structures to reactivity. The seminal study by McGarrity and coworkers [3] has remained proprietary in this regard as it is the only citation used when the question of alkyllithium structure vs. reactivity is raised.

The solvent tetrahydrofuran (THF) is well-known to be the most supportive of all the ether and hydrocarbon solvents for DoM. In general, both rates and extents of metalation are unmatched in any other solvent unless an additive such as tetramethylethylenediamine (TMEDA) is present. There are drawbacks, however, to the use of THF. The solvent is troublesome to purify (peroxides)

and to dry. Secondary metalations seem to occur more often in THF. Lastly, THF is known to be attacked by alkyllithiums [4].

We report herein some preliminary observations on the metalation of anisole and *p*-methylanisole (*p*-MA) in a mixed solvent system of THF/*n*-hexane. If THF is so effective in supporting reactivity of alkyllithium reagents, then increments of THF in a hydrocarbon solvent (usually non-supportive of metalation chemistry without an additive such as TMEDA) should bring about DoM. Such a solvent mixture containing relatively small amounts of THF in bulk hydrocarbon solvent would avoid some of bulk THF's aforementioned shortcomings.

Fig. 1 illustrates the effect of increments of THF in 30 ml *n*-hexane on the rate and extent of metalation of anisole. As little as 1.0 equiv. of THF in *n*-hexane dramatically increases the efficacy of this metalation [5]. Fig. 1 reveals that 3.0 equiv. (4.9 ml) of THF in this system provides the maximum extent of metalation of anisole, an extent of metalation greater than the extent of metalation in THF alone [6]. However, as can be seen in Fig. 1, the rates of metalation (initial portion of the reaction plot) are slower for all the THF/*n*-hexane systems than for THF alone. These rates appear to exhibit a dependency on the concentration of added THF.

For anisole the maximum achievable extent of metalation is found at 3.0 equiv. of THF, as illustrated by the

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¹ Dedicated to the occasion of Professor Marvin Rausch's 65th birthday.

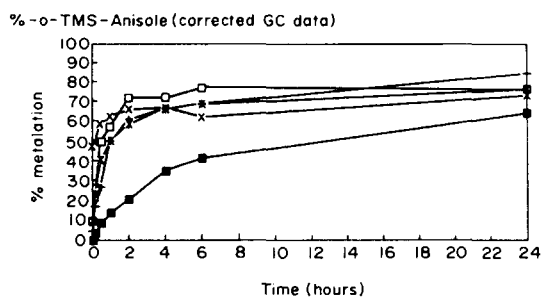


Fig. 1. Metalation of anisole in *n*-hexane containing increments of THF.

chart depicted in Fig. 2. In this chart the maximum extents of metalation are plotted for 1.0 to 8.0 equiv. of THF (average 2–4 runs each). The effect of dilution can also be seen. The plot of an identical study, except that the final volume of *n*-hexane was 60 ml, reveals that somewhat lesser extents of metalation are achieved at every increment of THF and that there is no maximum at a low number of increments of THF. The appearance of a maximum extent of metalation at 3.0 equiv. of THF in the more concentrated system suggests the possibility that we have maximized in some way the equilibria among THF, *n*-BuLi and anisole to form the complex leading to the transition state.

Demonstration of the necessity of THF in *n*-BuLi/*n*-hexane is shown in Fig. 3. In these runs THF (0.04 mol) was not added to the otherwise normal reaction mixture until 24 h had elapsed. The remarkable change in reaction rate brought about by this addition strongly suggests that THF reorganizes the *n*-BuLi hexamer into a more reactive form, perhaps the dimer, although some subtle solvation of a transition state structure cannot be ruled out. Again a dependence of the reaction rate upon the concentration is revealed.

Some generality of this phenomenon has been demonstrated in the metalation of *p*-MA in THF/*n*-hexane. Fig. 4 illustrates the dependence of equivalents of THF on the rate and extent of *ortho* metalation of *p*-MA. For the *p*-MA substrate our preliminary findings

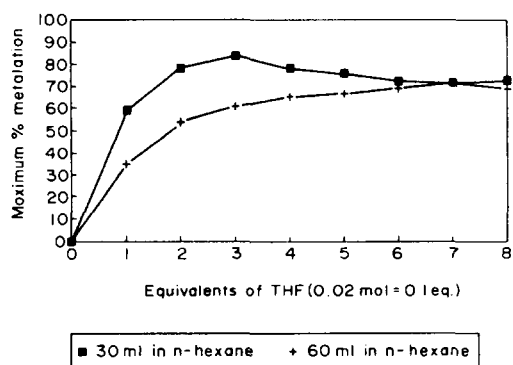


Fig. 2. Metalation of anisole in *n*-hexane, effect of increments of THF.

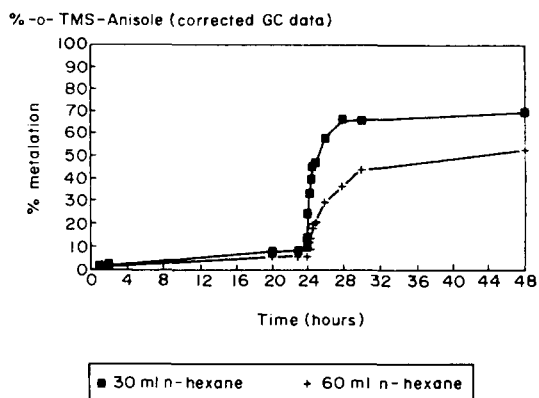


Fig. 3. Metalation of anisole in *n*-hexane, effect of delayed THF addition.

are that 8.0 equiv. of THF in *n*-hexane provide the maximum rate and extent of metalation. This number of equivalents of THF is significantly larger than that observed for anisole itself (3.0). No explanation for this phenomenon occurs to us, but the observation does suggest that individual substrates may each require different numbers of equivalents of THF in *n*-hexane to achieve the maximum effect.

One other feature of the *p*-MA system deserves comment. Unlike the pattern of metalation of *p*-MA in ether and ether/incremental TMEDA or ether/TMEDA [7], very little lateral metalation was observed. In the ether studies 2–3% yield of a second product ($M^+ = 194$) was found in the GC-MS spectrum under all conditions. This product is undoubtedly the product of lateral metalation (*p*-MeOC₆H₄CH₂SiMe₃). DoM of *p*-MA under most THF/*n*-hexane conditions produced no evidence of lateral metalation.

It is tempting, but early, to ascribe the effect of incremental amounts of THF in *n*-hexane on the metalation of anisole as a result of solvation of the *n*-BuLi dimer in the same manner as occurs in neat THF. The increased concentrations of the *n*-BuLi dimer thereby produced could lead to increased rates of metalation.

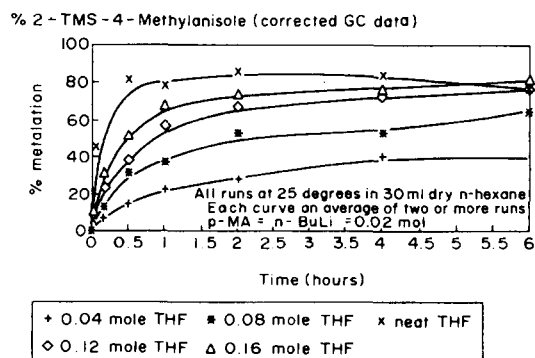


Fig. 4. Metalation of *p*-MA in *n*-hexane containing increments of THF.

Initial attempts to detect the dimer in THF/*n*-hexane by NMR have not met with success. Whatever the case, increments of THF in *n*-hexane appears to offer a novel milieu for the support of metalation reactions and possibly for the support of a wider range of carbanion reactions.

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- [5] *Reaction conditions*. 0.02 mol of anisole (*p*-MA) and 1.63 ml (0.02 mol, 1.0 equiv.) of THF dried over molecular sieves (Aldrich, 4A, 4–8 mesh) are added to 17.5 ml (47.5 ml) of dry hexane in a one-neck flask purged with N₂ and sealed with a septum. To this solution is added 12.5 ml (0.02 mol) of 1.6 M *n*-BuLi in *n*-hexane (FMC Corp.) to bring the volume of *n*-hexane to 30 ml (60 ml). Other runs use exactly the same procedure except that 0.04 mol (2.0 equiv.), 0.06 mol (3.0 equiv.), etc. of THF are utilized. The flask is placed in a constant temperature bath maintained at 25°C. The plots of percentage metalation vs. time are constructed by extracting about 1 ml samples with a syringe from the reaction solution after 2, 10, 30 min, 1, 2, 4, 6, 24 h, or other periods as necessary, and quenching with a solution of chlorotrimethylsilane (CITMS) in *n*-hexane. After aqueous workup each sample is subjected to GC analysis (HP 5890A with OV-17 packed glass column). Identities of products are checked by GC-MS analysis (HP 5890A gas chromatograph coupled with an HP 5970 series mass selective detector). Analysis of the corrected spectra of *o*-TMS anisole provides an estimate of the extent of metalation as measured by the *o*-lithioanisole's capture by the TMS moiety.
- [6] We can find no other report in the literature where anisole has been metalated in more than 80% yield using a 1.0 to 1.0 equivalency of anisole and *n*-BuLi. Higher extents of metalation have been reported using 2.0 equiv. of *n*-BuLi and incremental or stoichiometric TMEDA (D.W. Slocum, R. Moon, J. Thomson, D.S. Coffey, J.D. Li, M.G. Slocum, R. Gayton-Garcia and A. Siegel, *Tetrahedron Lett.*, 35 (1994) 385).
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