Ortholithiation of Anisole by *n*-BuLi−TMEDA: Reaction via Disolvated Dimers

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The *n*-BuLi-mediated ortholithiation of substituted arenes is one of the most important reactions in organolithium chemistry.[1] Not surprisingly, the mechanism of ortholithiation has been the topic of considerable investigation and speculation as nicely summarized in a recent communication by Saà.[2] Of the many substrates available for investigation, anisole (**1**) has been the perennial favorite.[3−6] Schleyer and Bauer studied *n*-BuLi−anisole precomplexation using NMR spectroscopy.[3] Saà and co-workers as well as Schleyer and Bauer investigated the reaction coordinate with semiempirical calculations.[3,4] Slocum and co-workers described solvent-dependent metalation rates.[5] Most recently, Stratakis reported inter- and intramolecular kinetic isotope effects.[6] Amidst the extensive mechanistic discussions, *there has yet to emerge a combination of spectroscopic and rate studies verifying the stoichiometry of the rate-limiting transition structure(s)*.[7] We describe herein rate studies of the ortholithiation of anisole by *n*-BuLi/TMEDA.[8] In conjunction with previous spectroscopic studies showing *n*-BuLi/TMEDA[9−11] to be exclusively disolvated dimers (**2**),[12] the rate studies demonstrate that the ortholithiation proceeds via [(*n*-BuLi)$_2$(TMEDA)$_2$(anisole)]‡.[13]

The *n*-BuLi (Fisher) was twice recrystallized from concentrated pentane solutions at −94 °C.[14] The *n*-BuLi concentrations ([*n*-BuLi] = 0.05−1.2 *M*) were maintained high relative to **1** (0.004

(1) Reviews: Snieckus, V. *Chem. Rev.* **1990,** *90,* 879. Gschwend, H. W.; Rodriguez, H. R. *Organic React.* **1979,** *26,* 1.

(2) Saà, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996,** *61,* 5194.

(3) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989,** *111,* 7191.

(4) See ref 32 in Saà, J. M.; Deyà, P. M.; Suner, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992,** *114,* 9093.

(5) Slocum, D. W.; Moon, R.; Thompson, J.; Coffey, D. S.; Li, J.; Slocum, M. G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994,** *35,* 385. Slocum, D. W.; Thompson, J.; Friesen, C. *Tetrahedron Lett.* **1995,** *36,* 8171.

(6) Stratakis, M. *J. Org. Chem.* **1997,** *62,* 3024.

(7) (a) Fagley and co-workers[7b] reported that the ortholithiation of anisole by ethyllithium (EtLi) in benzene followed the rate law d[CH₃CH₃]/d*t* = *k′*-[EtLi]²[anisole]². Given the probability that EtLi is highly aggregated (tetrameric)[7c] under these conditions and the technical difficulties associated with the experiments, we are not quite sure how to interpret these results. (b) Fagley, T. F.; Klein, E. *J. Am. Chem. Soc.* **1955,** *77,* 786. (c) Kminek, I.; Kaspar, M.; Tvekoval, J. *Collect. Czech. Chem. Commun.* **1981,** *46,* 4, 1132.

(8) TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

(9) For spectroscopic studies of *n*-BuLi−TMEDA, see: Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989,** *111,* 7191. McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984,** *107,* 1805. Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983,** *66,* 308. Fraenkel, G. In *Lithium: Current Applications in Science, Medicine, and Technology*; Bach, R. O., Ed.; Wiley: New York, 1985. Baumann, W.; Oprunenko, Y.; Günther, H. *Z. Naturforsch. A* **1995,** *50,* 429. Also, see: Crassous, G.; Abadie, M.; Schue, F. *Eur. Polym. J.* **1979,** *15,* 747 and ref 2.

(10) Recent ¹⁵N labeling studies showed dimer **2** to be chelated as drawn. Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997,** *119,* 5479.

(11) Hoffmann, D.; Collum, D. B. unpublished.

(12) For crystallographic studies of *n*-BuLi−TMEDA, see: Williard, P. G.; Nichols, M. A. *J. Am. Chem. Soc.* **1993,** *115,* 1568. Barnett, N. D. R.; Mulvey, R. E.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993,** *115,* 1573.

(13) For leading references to the chemistry of TMEDA and related polyamines, see: Collum, D. B. *Acc. Chem. Res* **1992,** *25,* 448. *Polyamine-Chelated Alkali Metal Compounds*; Langer, A. W., Jr., Ed.; American Chemical Society: Washington, 1974. Szwarc, M. *Carbanions, Living Polymers, and Electron-Transfer Processes*; Interscience: New York, 1968. Morton, M. *Anionic Polymerization: Principles and Practice*; Academic Press: New York, 1983. *Anionic Polymerization: Kinetics, Mechanism, and Synthesis*; McGrath, J. E., Ed.; American Chemical Society: Washington, 1981; Chapters 1, 2 and 29.

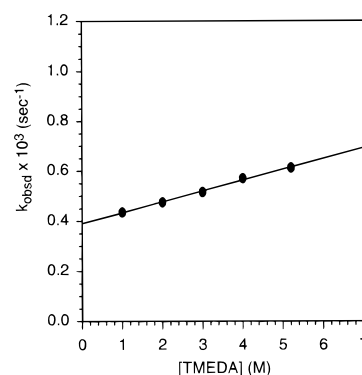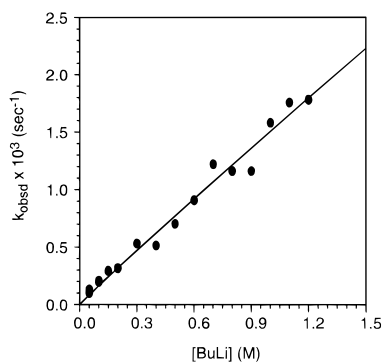(14) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993,** *32,* 580.

Figure 1. Plot of k_{obsd} versus [TMEDA] in pentane cosolvent for the disappearance of **1** (0.01 *M*) by *n*-BuLi (0.30 *M*) at 0 °C. Each point is the average of three runs with standard deviations (σ) of <±10%. The curve depicts the results of an unweighted least-squares fit to f(*x*) = *ax* + *b* (*a* = 4.3 ± 0.2 × 10⁻⁵, *b* = 3.90 ± 0.05 × 10⁻⁴).

or 0.01 *M*) to ensure pseudo-first-order conditions. These conditions also preclude the formation of substantial concentrations of mixed aggregates arising from incorporation of the ArLi product.[15,16] Decomposition of *n*-BuLi/TMEDA is not appreciable at 0 °C. The TMEDA concentrations ([TMEDA] = 1.0 M − neat) were adjusted using pentane as the cosolvent.[17] The rate of *n*-BuLi-mediated lithiation of anisole (**1**, eq 1) was determined

(1)
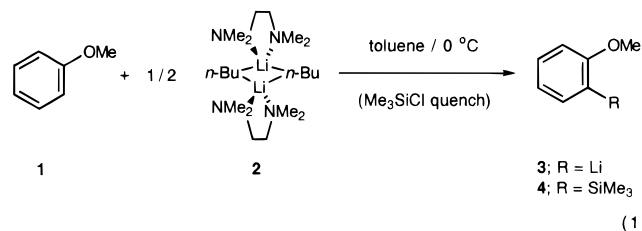
by quenching individual reactions with chlorotrimethylsilane/triethylamine[5] at different times and monitoring the decrease of anisole by GC relative to an internal dodecane standard.[18] The disappearance of **1** and appearance of **4** displayed first-order kinetics over >3 half-lives. The rate constants were nearly constant (±10%) over a 20-fold range of [anisole], confirming the first-order dependence on anisole. A substantial kinetic isotope effect ($k_{obsd(H)}/k_{obsd(D)} = 20 \pm 3$), determined by comparing **1** with **1**-*d*₈ (Aldrich), confirmed a rate-limiting proton abstraction.[19]

Figures 1 and 2 display plots of k_{obsd} vs [TMEDA] and k_{obsd} vs [*n*-BuLi], respectively. The slight dependence of the lithiation rate on the TMEDA concentration and the linear dependence on

(15) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988,** *27,* 1624. Caubere, P. In *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78−139.

(16) Lithiations in solutions containing preformed lithiated anisole **3** as well as solutions that had been aged for several hours afforded no significant change in the measured rate constants.

(17) (a) TMEDA was purified by recrystallizing TMEDA·2HCl[15b] two times from MeOH/H₂O. The ammonium salts were mixed in the solid phase with solid KOH. The resulting liquid was decanted, sequentially distilled from CaH₂/KH, Na/benzophenone, and Na/Pb. (b) Freund, M.; Michaels, H. *Ber.* **1897,** *30,* 1374.

(18) Following the increase of 2-(trimethylsilyl)anisole (**4**) concentration as a function of time afforded analogous rate constants (±10%).

(19) The kinetic isotope effect differs substantially from the k_H/k_D values of approximately 3 obtained previously.[6] The rate constants for the metalation of 0.01 M anisole and anisole-*d*₈ using 0.3 M *n*-BuLi and 2.3 M TMEDA are 53.0 ± 0.30 × 10⁻⁵ and 2.58 ± 0.34 × 10⁻⁵ sec⁻¹, respectively. While the methods we employed to determine the isotope effects are different, we cannot explain the discrepancy at this time. The methods we employed are described in Supporting Information.

Figure 2. Plot of k_{obsd} versus [*n*-BuLi] in pentane cosolvent for the disappearance of **1** (0.01 *M*) with an excess of TMEDA (2.0 *M*) at 0 °C. The curve depicts the results of an unweighted least-squares fit to f(x) = ax^b (a = 1.51 ± 0.04 × 10^{-3}, b = 0.97 ± 0.06).

the *n*-BuLi concentration (k_{obsd} = k'[*n*-BuLi]$^{0.97+0.06}$) are consistent with the idealized rate law in eq 2 and the general lithiation mechanism described by eq 3.

$$-d[\mathbf{1}]/dt = k'[\mathbf{1}]^1[\text{TMEDA}]^0[(n\text{-BuLi})_2(\text{TMEDA})_2]^1 \quad (2)$$

$$(n\text{-BuLi})_2(\text{TMEDA})_2 + \mathbf{1} \rightarrow [(n\text{-BuLi})_2(\text{TMEDA})_2 \cdot \mathbf{1}]^{\ddagger} \rightarrow \mathbf{3} \tag{3}$$
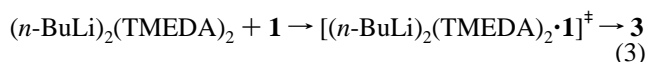
Implication of a dimer-based mechanism is interesting given the recent discussions of open dimers (e.g., **5**)[20] and triple ions (e.g., **6**)[21] as possible reactive intermediates. If one subscribes to the notion that precomplexation is important,[2-4,22] there exists

(20) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. Nakamura, E.; Nakamura, M.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016. For additional leading references to open dimers, see: Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, in press.

(21) Leading references to triple ions: Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707.

(22) Beak, P.; Meyers, A. I. *Acc. Chem. Res* **1986**, *19*, 356. Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

a number of mechanisms involving either Li−O or (C=C)-Li (π) interactions (**7** and **8**, respectively). In fact, we infer from
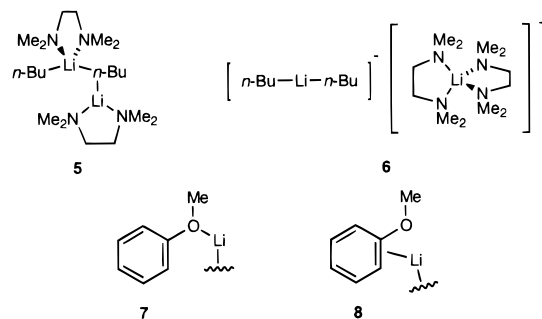
recent reports of Shimano and Meyers as well as Maggi and Schlosser the existence of at least two fundamentally different ortholithiation mechanisms.[23] Recent computational studies predicted a dimer-based lithiation to be plausible.[2-4] However, none of the computations include the stoichiometry implicated by the rate law. This illustrates an important synergism of theory and experiment: theory can provide experimentally elusive details while experiment places certain constraints on the theory.

We are currently investigating metalations mediated by other *n*-BuLi−diamine combinations as well as *n*-BuLi in mixtures of two diamines. NMR spectroscopic studies revealed a substantial cooperativity in the solvation of the disolvated *n*-BuLi reactant;[11] we are hoping that ortholithiations of anisole will shed light on cooperative solvation in the *disolvated* transition structures as well.

(23) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815. Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430.