3024 *J. Org. Chem.* **1997,** *62,* 3024−3025

On the Mechanism of the Ortho-Directed Metalation of Anisole by *n*-Butyllithium[†]

Manolis Stratakis[1]

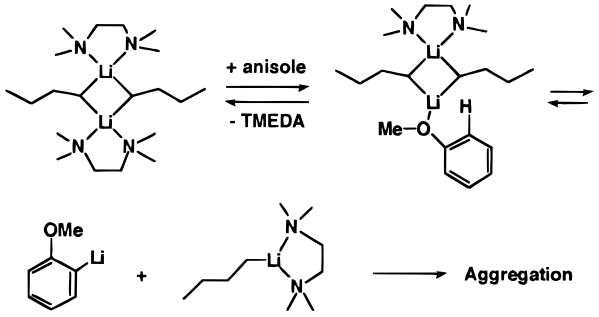
Department of Chemistry, University of Crete,
Iraklion 71409, Greece

Received December 30, 1996 (Revised Manuscript Received March 17, 1997)

The ortho-directed metalation of arenes[2] bearing an appropriate directing group (DMG), by alkyllithiums or lithium amides, is a powerful method for achieving a variety of functionalizations on the phenyl ring. Addition of stoichiometric amounts of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in hexane or ether increases both reaction rates and yields. Although TMEDA is frequently used as a cosolvent in metalations, its tendency to chelate lithium in the presence of THF—especially in the case of lithium amides—has been questioned by Collum.[3] Beak has proposed that complexation of the alkyllithiums with the DMG ("complex induced proximity effects")[2c,4] is the key feature of the metalation reactions. On the other hand, Schleyer considered the term "kinetically enhanced metalation", proposing that directing and activating effects are transition-state phenomena.[5]

The ortho-metalation of anisole was discovered by Wittig[6] and Gilman[7] independently almost 60 years ago. The yield of the reaction is remarkably high, especially with the aid of several additive cosolvents.[8] Roberts and Curtin were the first to suggest[9] that complexation of the alkyllithium to the methoxy group facilitates ortho-proton removal. Bauer and Schleyer,[10] using 1D and 2D heteronuclear NMR, provided direct spectroscopic evidence for the formation of an intermediate cubic aggregate between anisole and *n*-BuLi upon mixing in toluene-d_8 at −64 °C. The mixed aggregate does not give any further reaction even on prolonged standing. However, addition of 1 equiv of TMEDA causes the immediate liberation of "free" anisole, while dimeric *n*-BuLi solvated by TMEDA is formed. Under these conditions, *o*-anisyllithium can be gradually formed. It was suggested that dimeric *n*-BuLi partly solvated by anisole leads to the product (Scheme 1). The proposed mechanism was also supported by MNDO calculations.

Scheme 1



Similar theoretical calculations and experimental observations by Saa[11] and co-workers in the ortho-directed metalations of phenol, naphthols, and 1,3-disubstituted heteroaromatics indicated the significance of agostic hydrogen−metal interactions in the intermediate complexes.

Slocum and co-workers[12] found that even incremental amounts of TMEDA in diethyl ether (0.2 equiv per alkyllithium) can cause a significant rate acceleration and suggested a predictive model for the ortho-metalation. According to that model, formation of a complex between anisole and *n*-BuLi in ether occurs in the rate-determining step, followed by a faster metal−hydrogen exchange. Complex formation is necessary to reduce the tendency of methoxy group to delocalize, thus increasing the acidity of the ortho-protons. In the presence of TMEDA, coordination probably is not involved, and a simple "overriding base" reacts rapidly with the relatively acidic ortho protons.

In order to shed some light on the mechanistic discrepancy of the ortho-directed metalation, we report in this paper an isotope effect study in the lithiation of anisole by *n*-BuLi in diethyl ether with or without added TMEDA (Scheme 2). The combination[13] of intra- and intermolecular isotope effects is a powerful tool for distinguishing between stepwise and concerted reaction mechanisms. Recently, by applying this combination, it was found that the metalation of a benzylic urea[14] by *s*-BuLi/TMEDA proceeds through the prior formation of an alkyllithium−urea complex in the rate-determining step.

Metalation of anisole-*2-d*[15] was achieved by addition of 0.5−2 equiv of *n*-BuLi.[16] The anions were quenched by TMSCl; the resulting 2-(trimethylsilyl)anisoles were purified by preparative GC (SE-30, T_{col} = 120 °C) and then analyzed by ^{1}H NMR. The isotope effects found

---

[†] Dedicated to Professor Andrew Streitwieser on the occasion of his 70th birthday.

(1) Permanent address after summer 1997: Department of Natural Sciences, University of Cyprus, Nicosia 1678, Cyprus.

(2) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306−15. (b) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957−86. (c) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356-64. (d) Klumpp, G W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1−21. (e) Brandsma, L.; Verkuisjsse, H. *Preparative Polar Organometallic Chemistry*; Springer: Berlin, 1987; Vol. I. (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (g) Qeuguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−304.

(3) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−54.

(4) (a) Hay, D.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145−53. (b) Warmus, J. S.; Rodkin, M. A.; Barkley, R.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1993**, 1357−59. (c) Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628−36.

(5) (a) van Eikema-Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755−58. (b) van Eikema-Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903−16. (c) Kremer, T.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 3345−59.

(6) Wittig, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 1197−218.

(7) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109−12.

(8) For the highest yield ever observed (80%), using a 1/1 mixture of *n*-BuLi/anisole in a solution containing 14% (v/v) THF in hexane, see: Slocum, D. W.; Reed, D.; Jackson, F., III; Friesen, C. *J. Organomet. Chem.* **1996**, *512*, 265−67. Higher yields (>95%) have been achieved by using 2 equiv of *n*-BuLi/TMEDA in ether (ref 12a).

(9) Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658−60.

(10) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191−98.

(11) (a) Saà, J. M.; Deyà, P. M.; Suner, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093−100. (b) Saà, J. M.; Morey, J.; Frontera, A.; Deyà, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 1105−16. (c) Saà, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194−95.

(12) (a) Slocum, D. W.; Moon, R.; Thompson, J.; Coffey, D. S.; Li, J. D.; Slocum, M. G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994**, *35*, 385−88. (b) Slocum, D. W.; Thompson, J.; Friesen, C. *Tetrahedron Lett.* **1995**, *36*, 8171−74.

(13) (a) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126−34. (b) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607−14.

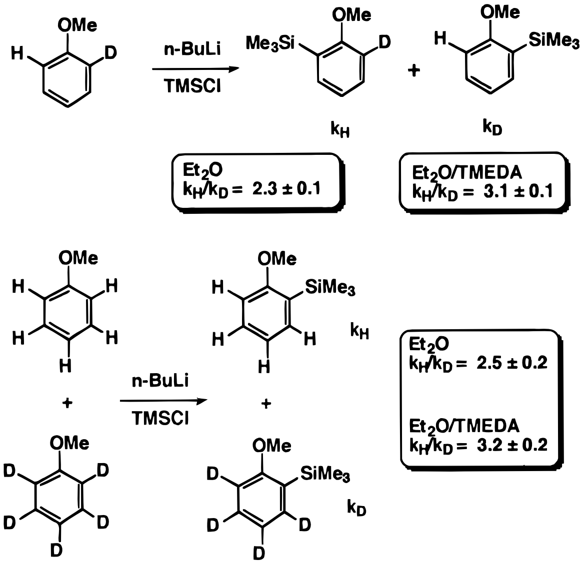
(14) Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 405−06.

(15) Anisole-*2-d* was prepared by quenching the Grignard reagent of 2-bromoanisole with D_2O. It was purified by distillation. $M^+ = 109$.

(16) The values of the intermolecular isotope effect are the same when using 0.5, 1, 1.5, or 2 equiv of *n*-BuLi/TMEDA per 1 equiv of anisole-*2-d*.

S0022-3263(96)02418-8 CCC: $14.00

Scheme 2



are $k_H/k_D = 2.3 \pm 0.1$ in ether (in a typical experiment using 1.5 equiv of base per 1 equiv of anisole, conversion to products was achieved in 50% yield after 16 h) and $k_H/k_D = 3.1 \pm 0.1$ in the presence of TMEDA (95% conversion in 20 min using again 1.5 equiv of *n*-BuLi). In all experiments, the amount of added TMEDA was equimolar with respect to the amount of base.

The intermolecular isotope effects[17] in neat ether ($k_H/k_D = 2.5 \pm 0.2$) and in ether with added TMEDA ($k_H/k_D = 3.2 \pm 0.2$) are identical within experimental error, to the intramolecular isotope effects in the same solvent systems. This indicates that the ortho-hydrogen abstraction of anisole by the base in both cases occurs in the rate-determining step.

For the case of added TMEDA in ether, if we assume that the dimeric intermediate complex between anisole and *n*-BuLi exists,[10] its formation undoubtedly occurs in a faster step compared to the step leading to the formation of the *o*-anisyllithium. The activation energy for its formation must be substantially lower compared to the second deprotonation step; otherwise, a significant decrease in the overall calculated isotope effect would be expected.[13a] The identical intra- and intermolecular isotope effects are also in accordance with a single-step mechanism where a highly reactive low *n*-BuLi aggregate that is formed by the action of TMEDA deprotonates anisole without any precoordination as postulated earlier.[12a] It is difficult to distinguish between the two mechanisms on the basis of the kinetic isotope effects.

In neat diethyl ether, *n*-butyllithium exists as a tetramer.[18] According to the isotope effects found in this solvent, we propose the following mechanistic possibilities: (i) Products are formed in a slow step via a transition state achieved from an intermediate containing *n*-BuLi and anisole. The intermediate may be either a tetrameric or a dimeric aggregate. In both cases, the rate of the reaction is expected to be significantly retarded as occurs, indeed because in the transition state of hydrogen abstraction achieved through the tetrameric aggregate severe steric repulsions are existing or, on the other hand, the concentration of a reactive dimeric aggregate[19] is expected to be very low. (ii) The possibility that no precomplexation occurs and deprotonation occurs in a single step cannot be ruled out. Although further experimental work is neccesary to delineate the metalation mechanism in neat ether, it is clear that a previously proposed mechanism[12a] (formation of an intermediate complex in the rate-limiting step) is not consonant with the observed isotope effects.

In conclusion, it is important to emphasize that the current results *neither require nor exclude the existence of a preequilibrium complex.* They establish the abstraction of hydrogen as the rate-determining step and are consistent with transition-state phenomena, as predicted by theoretical calculations.[5]

Acknowledgment. The author is grateful to Professors G. J. Karabatsos and M. Orfanopoulos for valuable discussions and comments and to Professor M. Orfanopoulos for a generous hospitality in his laboratory.

Supporting Information Available: Copies of proton NMR spectra (9 pages).

JO962418E

---

[17] Anisole-d_5 was prepared by methylation of the Na salt of phenol-d_6 (Aldrich, 99% D) with dimethylsulfate. $M^+ = 113$. Kinetic competition between anisole-d_0 versus anisole-d_5 was accomplished by adding a limited amount of *n*-BuLi to an equimolar mixture of anisoles-d_0 and -d_5 (20−25% conversion to the trimethylsilyl adducts). The observed values of the intramolecular isotope effects were also obtained, in addition to ^1H NMR integration, by GC analysis of the reaction mixture on a 5% phenyl methyl silicone capillary column, where anisole-d_0 and anisole-d_5 have different retention times.

[18] Bergander, K.; He, R.; Chandrakumar, N.; Eppers, O.; Günther, H. *Tetrahedron* **1994**, *50*, 5861−68.

[19] The possibility that the reactive intermediate is a dimeric aggregate, despite the fact that *n*-BuLi in ether is a tetramer, cannot be excluded. Athough most of the organoalkali compounds exist as high aggregates, usually many of their reactions proceed through spectroscopically undetectable lower aggregates or even monomers. For some representative examples, see: (a) Waack, R.; Doran, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 2456−61. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810−15. (c) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772−80. (d) Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688−89. (f) Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136−37.