

π -Arene/Metal Binding: An Issue Not Only of Structure but Also of Reactivity

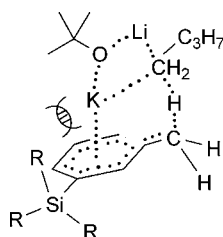
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ABSTRACT

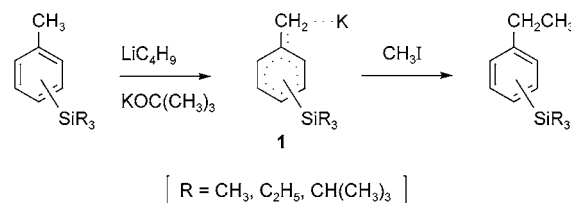


A trimethyl-, triethyl-, or triisopropylsilyl group attached to the meta position of toluene retards the rate of permutational hydrogen/metal interconversion with butyllithium in the presence of potassium *tert*-butoxide by factors of 1.7, 3, and 7, respectively. Although remote from the reaction center, the substituents sterically impede the coordination of potassium to the arene electron sextet. π -Arene/metal bonding may play a major role in modulating chemical and, by extension, biochemical reactivity.

To rationalize and even predict chemical reactivity requires detailed knowledge about the involved transition states. As part of our continuing efforts to probe the composition and geometry of such elusive species in the context of organo-metallic reactions,^{1a,2} we have carried out a new series of competition kinetic experiments.³ In this way, we have measured the rates of the permutational hydrogen/metal interconversion (“metalation”) between trimethylsilyl- and triethylsilyl-substituted toluenes and butyllithium in the presence of potassium *tert*-butoxide relative to that of the

toluene parent compound. In addition, triisopropyl-3-tolyl-silane was included in the study. The superbasic mixed-metal (“LIC-KOR”) reagent is known to produce benzylmetal species that retain most of the potassium, whereas most of the lithium, although not all, combines with *tert*-butoxide (the alcoholate thus formed being removable by extraction of the residue with toluene).⁴ The organometallic intermediates **1** (see Scheme 1) were trapped with iodomethane. The

Scheme 1. Metalation of Trialkylsilyl-Substituted Toluenes with the Superbasic Mixed-Metal LIC-KOR Reagent



kinetically relevant substrate concentrations before and after the reaction and, as a check, the product concentrations were determined by high-accuracy gas chromatography.^{2c,3e,5}

(1) (a) Schlosser, M. In *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, 2002; pp 45–84; (b) pp 249–251.

(2) (a) Schlosser, M.; Franzini, L.; Bauer, C.; Leroux, F. *Chem. Eur. J.* **2001**, *7*, 1909–1914. (b) Baston, E.; Maggi, R.; Friedrich, K.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3985–3989. (c) Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* **2002**, *8*, 799–804. (d) Heiss, C.; Schlosser, M. Manuscript in preparation. (e) Lefebvre, O.; Marull, M.; Cottet, F.; Schlosser, M. Manuscript in preparation. (f) Gorecka, J.; Heiss, C.; Scopelliti, R.; Schlosser, M. *Org. Lett.* **2004**, *6*, 4591–4593.

(3) (a) Büker, H. H.; Nibbering, N. M. M.; Espinosa, D.; Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997**, *38*, 8519–8522. (b) Schlosser, M.; Mongin, F.; Porwisiak, J.; Dmowski, W.; Büker, H. H.; Nibbering, N. M. M. *Chem. Eur. J.* **1998**, *4*, 1281–1286. (c) Baston, E.; Wang, Q.; Schlosser, M. *Tetrahedron Lett.* **2000**, *41*, 667–700. (d) Faigl, F.; Marzi, E.; Schlosser, M. *Chem. Eur. J.* **2000**, *6*, 771–777. (e) Schlosser, M.; Marzi, E.; Cottet, F.; Büker, H. H.; Nibbering, N. M. M. *Chem. Eur. J.* **2001**, *7*, 3511–3516.

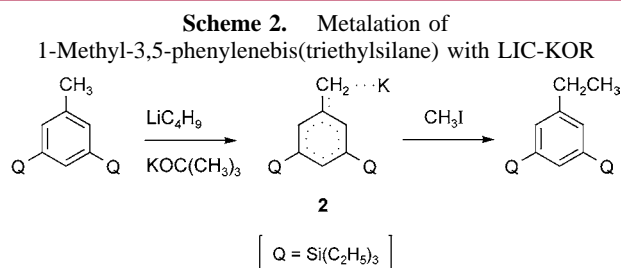
Table 1. Metalation of Trialkyltolylsilanes with Butyllithium in the Presence of Potassium *tert*-Butoxide^a or, as Indicated by Values in Brackets, with Butyllithium in the Presence of *N,N,N',N'',N'''*-Pentamethyldiethylenetriamine (PMDTA):^b Rates Relative to Toluene ($k_{\text{rel}} = 1.0$)

isomer	R = CH ₃	R = C ₂ H ₅	R = CH(CH ₃)
ortho	0.70 [0.50]	0.26 [0.33]	
meta	0.60 [1.3]	0.34 [1.0]	0.14 [–]
para	3.5 [4.3]	2.5 [4.1]	

^a In tetrahydrofuran (THF) at –75 °C. ^b In THF at 0 °C.

The results compiled in Table 1 are remarkable in several aspects. They reveal a rate enhancement brought about by para-positioned trialkylsilyl groups but also a strong rate retardation if such substituents are located at the meta position. However, the latter effect is restricted to the potassium-containing mixed-metal reagent, being absent when the similarly polar butyllithium/PMDTA (*N,N,N',N'',N'''*-pentamethyldiethylenetriamine) complex is employed (Table 1).

The reaction-inhibiting action of the *meta*-trialkylsilyl groups proved to be cumulative. 1-Methyl-3,5-phenylenebis-(triethylsilane) was found to undergo the LIC-KOR-promoted metalation, generating intermediate **2**, 0.14 (= 0.37²) times as rapidly as toluene (Scheme 2).



The rate decrease caused by *meta*-trialkylsilyl is too large to be attributed to an electronic interaction. Actually, the average σ_m of –0.05⁶ would require an unreasonably high reaction constant ρ of +4.4 to support the hypothesis of a simple inductive effect [$\log 0.60 = 4.4(-0.05)$]. Moreover, this ρ value would have to grow to +9.4 and +17 when *meta*-triethylsilyl and *meta*-triisopropylsilyl are considered, respectively. On the other hand, how could one evoke a steric effect if the silyl substituent occupies the meta position, which is distant from the exocyclic reaction center? In our opinion, the only plausible explanation has to be based on

(4) Schlosser, M.; Hartmann, J. *Angew. Chem.* **1973**, *85*, 544–545; *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 508–509.

(5) Schlosser, M.; Marzi, E. *Chem. Eur J.*, in press, published online March 30, 2005.

(6) (a) Roberts, J. D.; McElhill, E. A.; Armstrong, R. *J. Am. Chem. Soc.* **1949**, *71*, 2923–2926. (b) Benkeser, R. A.; Krysiak, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 2421–2425. (c) Bassindale, A. R.; Taylor, P. G. In *The Chemistry of Organosilicon Compounds*; Patai S.; Rappoport, Z., Eds.; Wiley: Chichester, 1989; Part II, pp 893–963, spec. pp 893–903.

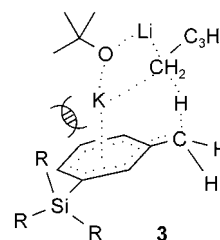


Figure 1. Metalation of toluenes with butyllithium/potassium *tert*-butoxide: π -arene/potassium interaction at the transition state.

the assumption of an η^6 -type coordination of potassium by the arene π -electrons at the transition state **3** (Figure 1). Under such circumstances, the bulky trialkylsilyl substituents will inevitably become repulsive.

Potassium/ π -arene interactions have been postulated for the first time in an attempt to rationalize why the crowded *endo*-4,4,4-triphenyl-2-butenylpotassium can compete with its unstrained *exo* isomer at the conformational equilibrium on equal terms.⁷ Later, several X-ray structures of organopotassiums,⁸ organosodiums,⁹ and even alkali metal amides¹⁰ have been published that feature η^6 -metal coordination as a key factor modeling the crystallographic architecture. In contrast, evidence for η^6 -lithium coordination is scarce¹¹ if one disregards “radical-anions”¹² and “arene-dianions”.^{12c,13} It can only manifest itself if no better donor components are

(7) Moret, E.; Furrer, J.; Schlosser, M. *Tetrahedron* **1988**, *44*, 3539–3550.

(8) (a) Hoffmann, D.; Bauer, W.; Schleyer, P. V. R.; Pieper, U.; Stalke, D. *Organometallics* **1993**, *12*, 1193–1200. (b) Hoffmann, D.; Bauer, W.; Hampel, F.; van Eikema Hommes, N. J. R.; Schleyer, P. V. R.; Otto, P.; Pieper, U.; Stalke, D.; Wright, D. S.; Snaith, R. *J. Am. Chem. Soc.* **1994**, *116*, 528–536. (c) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **1994**, *13*, 755–756. (d) Schön, J. C. *Angew. Chem.* **1995**, *107*, 1183–1185; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1081–1083.

(9) (a) Bock, H.; Ruppert, K.; Fenske, D. *Angew. Chem.* **1989**, *101*, 1717–1720; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1685–1688. (b) Bock, H.; Ruppert, K.; Havlas, Z.; Fenske, D. *Angew. Chem.* **1990**, *102*, 1095–1097; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1042–1044. (c) Corbelin, S.; Kopf, J.; Lorenzen, N. P.; Weiss, E. *Angew. Chem.* **1991**, *103*, 875–876; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 825–826. (d) Bock, H.; Ruppert, K.; Havlas, Z.; Bensch, W.; Hönle, W.; von Schnering, H. G. *Angew. Chem.* **1991**, *103*, 1197–1200; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1183–1186. (e) Jost, W.; Adam, M.; Enkelmann, V.; Müllen, K. *Angew. Chem.* **1992**, *104*, 883–884; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 878–879. (f) Bock, H.; Näther, C.; Ruppert, K.; Havlas, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6907–6908. (g) Bock, H.; Ruppert, K.; Herdtweck, E.; Herrmann, W. A. *Helv. Chim. Acta* **1992**, *75*, 1816–1824.

(10) Kennedy, A. R.; MacLellan, J. G.; Mulvey, R. E. *Angew. Chem.* **2001**, *113*, 3345–3347; *Angew. Chem., Int. Ed.* **2001**, *40*, 3245–3247.

(11) (a) Bladauski, D.; Dietrich, H.; Hecht, H. J.; Rewicki, D. *Angew. Chem.* **1977**, *89*, 490–491; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 474–475. (b) Bladauski, D.; Rewicki, D. *Chem. Ber.* **1977**, *110*, 3920–3929. (c) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1987**, 716–718. (d) Ruhlandt-Senge, K.; Ellison, J. J.; Wehmschulte, R. J.; Pauer, F.; Power, P. P. *J. Am. Chem. Soc.* **1993**, *115*, 11353–11357. (e) Schiemenz, B.; Power, P. P. *Angew. Chem.* **1996**, *108*, 2288–2290; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2150–2152. (f) Dinnebier, R. E.; Behrens, U.; Obrich, F. *J. Am. Chem. Soc.* **1998**, *120*, 1430–1433.

(12) (a) DeBoer, E. *Adv. Organomet. Chem.* **1964**, *2*, 115–155. (b) Manceron, L.; Andrews, L. *J. Am. Chem. Soc.* **1988**, *110*, 3840–3846.

(13) Benken, R.; Günther, H. *Helv. Chim. Acta* **1988**, *71*, 694–702. (b) Renken, B.; Andres, W.; Günther, H. *Angew. Chem.* **1988**, *100*, 1212–1213; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1182–1183.

available. The solvation provided by ether- or amine-type donors is strong enough to override any π -complex interaction and favor the formation of coordinatively saturated monomers or μ -bound dimers and tetramers. Thus, it becomes intelligible why the butyllithium/PMDTA-mediated metalation of toluenes does not mirror adverse *meta*-trialkylsilyl effects.

Although of unusual magnitude, the rate-enhancing effect of *para*-trialkylsilyl is in perfect agreement with the electron-withdrawing capacity of this substituent. It is irrelevant in the present context whether the stabilization of electron excess by adjacent second-row (or heavier) elements is described by the arguably misleading concepts of d-orbital resonance^{6,14} or hyperconjugation^{6,15} or by "polarization" (in the sense of an $n \rightarrow \sigma^*$ mixing).^{1b} Whatever the exact nature of the phenomenon may be, it lowers the activation energy for the LIC-KOR-promoted metalation of trimethyl-4-tolylsilane and triethyl-4-tolylsilane. If the potassium was placed perfectly over the middle of the arene ring, the steric hindrance exhibited by a *meta*- or *para*-trialkylsilyl group should be identical. In this case, the electronic bonus provided by a *para*-trimethylsilyl and *para*-triethylsilyl substituent would represent the difference ($\Delta\Delta G^\ddagger -0.69$ and -0.78 kcal/mol relative to the toluene parent compound) between the compensated steric hindrance ($\Delta\Delta G^\ddagger +0.20$ and $+0.42$ kcal/mol) and the experimentally observed net rate enhancement of 3.5-fold and 2.5-fold ($\Delta\Delta G^\ddagger -0.49$ and -0.36 kcal/mol). However, as testified by X-ray structures,^{11e,f} the metal may prefer to reside somewhat outside of the arene center in order to minimize steric repulsion while still maintaining an η^6 -coordination.¹⁶ We assume the potassium to choose indeed such an asymmetric location at the transition state **3**, staying closer to the ipso and more distant from the *para* carbon atom. Therefore, we believe that the steric hindrance is diminished when the trimethylsilyl or triethylsilyl substituent is moved from the *meta* to the *para* position (say, for the sake of argument, to one-half of the *meta* values: $\Delta\Delta G^\ddagger +0.10$ and $+0.21$ kcal/mol). Thus, the lowering of the metalation barrier due to the electronic effect of a *para*-

trimethylsilyl and *para*-triethylsilyl group falls in the 0.6 kcal/mol range ($\Delta\Delta G^\ddagger -0.59$ and -0.57 kcal/mol).

If an *ortho*-trialkylsilyl group stabilizes charge excess to the same extent as a *para*-trialkylsilyl, we can evaluate the steric hindrance affecting the metalation of trimethyl-2-tolylsilane and triethyl-2-tolylsilane. The numbers obtained by adding 0.59 and 0.57 kcal/mol (see the preceding paragraph) to the experimental relative activation energies ($\Delta\Delta G^\ddagger +0.14$ and $+0.53$ kcal/mol) are amazingly moderate (0.73–1.1 kcal/mol). This may be attributed at least in part to the extreme in-plane deformability of C–Si bonds.^{2f}

A seminal review by G. W. Gokel et al.¹⁸ culminated in the conclusion that "Future studies in molecular recognition and supramolecular chemistry must include cation– π interactions in the panoply of feeble forces. The consequences of this interaction are potentially profound for biology." While fully endorsing this statement, we feel tempted to add "... and for synthesis-oriented mechanistic investigations as well."

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Supporting Information Available: Experimental procedures and characterization data for silane-type starting materials and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) (a) Pitt, C. G. *J. Organomet. Chem.* **1973**, *61*, 49–70. (b) Traylor, T. G.; Hanstein, W.; Berwin, H. J.; Clinton, N. A.; Brown, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 5715–5725.

(16) It is of course a matter of semantics whether the term η^6 -coordination is still appropriate when the distances of the metal to the *para* and *ipso* positions are not equal but differ slightly (by 5–20%^{11e,f}). This will have to be decided from case to case. For example, there are model structures such as the KCl, RbCl, and CsCl complexes of uranyl-salophen "receptors"¹⁷ that keep the metal relatively remote from the benzyl ligand. As a consequence, the mode of interaction is no longer η^6 - but rather η^1 - or η^2 -like, thus marking the other extreme of the π -arene coordination continuum.

(17) Cametti, M.; Nissinen, M.; Dalla Cort, A.; Mandolini, L.; Rissanen, K. *J. Am. Chem. Soc.* **2005**, *127*, 3831–3837.

(18) Gokel, G. W.; Barbour, L. J.; Ferdani, R.; Hu, J. *Acc. Chem. Res.* **2002**, *35*, 878–886.

(14) (a) Cason, L. F.; Brooks, H. G. *J. Org. Chem.* **1954**, *19*, 1278–1282. (b) Peterson, D. J. *J. Organomet. Chem.* **1967**, *8*, 199–208. (c) Peterson, D. J. *J. Organomet. Chem.* **1967**, *9*, 373–374. (d) Doering, W. V. E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1955**, *77*, 521–526.