3822 *J. Am. Chem. Soc.* **2001,** *123,* 3822−3823

Multiple Hydrogen/Lithium Interconversions at the Same Benzene Nucleus: Two at the Most

Manfred Schlosser,* Laurence Guio, and Frédéric Leroux

Section de Chimie (BCh), Université
CH-1015 Lausanne, Switzerland

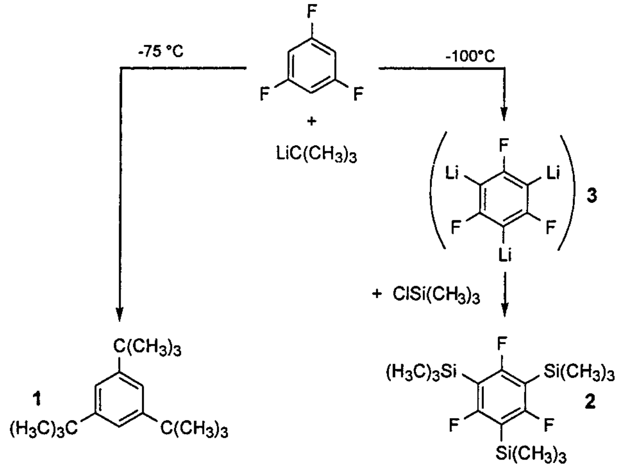
Received September 5, 2000

Every first-year student is advised not to draw formulas carrying two like charges in close vicinity. Electrostatic repulsion, so goes the argument, would make such structures energetically exorbitant and hence unrealistic. This plausible rule of thumb is confirmed by recent computational work at the MP2, MP4, and B3LYP levels of theory. Proton abstraction from a "naked" *phenyl anion* by another phenyl anion is a highly endothermal process, requiring reaction enthalpies of 112, 96, and 91 kcal/mol at *ortho*, *meta*, and *para* positions.[1] However, the situation changes profoundly when the phenyl anion-promoted deprotonation of *phenyllithium* is examined. This time the process is exothermal at *ortho* and *para* positions by approximately 10 and 5 kcal/mol, respectively.[1] In other words, the chelating and π-coordinating properties of the lithium atom render phenyllithium more acidic than benzene is!

With this as a background it should be intriguing to assess computationally (i.e., under gas phase conditions) and experimentally (in solution) the relative basicities of the three phenylenedilithiums which at least formally result when one phenyllithium cannibalizes another one. In this context recent work by Bickelhaupt et al.[2] deserves attention. 1,3,5-Trilithiobenzene proved to be too basic to be generated from 1,3,5-tribromobenzene by permutational halogen/metal exchange even when *tert*-butyllithium was employed as the reagent. 5-Bromo-1,3-phenylenedilithium was obtained almost exclusively under optimized conditions.[2] 1,3,5-Trilithiobenzene (79%) did form along with 1,3-phenylenedilithium (13%) and phenyllithium (7%) as byproducts when the halogen in 1,3,5-tribromobenzene was replaced reductively using the 4,4′-di-*tert*-butylbiphenyl/lithium "radical-anion".[2]

The reluctance of benzene nuclei to tolerate a total of three lithium substituents casts doubt on reports published by H. Gilman et al.[3,4] more than a quarter of a century ago and regularly quoted in the scientific literature since then. The authors claimed to have discovered an unprecedented temperature effect. If performed at −75 °C, the reaction between 1,3,5-trifluorobenzene and a slight excess of *tert*-butyllithium afforded 1,3,5-tri(*tert*-butyl)benzene (**1**) in up to 72% yield.[3,4] Under quite similar conditions, but at −115 °C and after subsequent treatment with chlorotrimethylsilane, 1,3,5-trifluoro-2,4,6-tris(trimethylsilyl)benzene (**2**) was isolated as the sole product (95−96%).[3,4] The trilithiated species **3** was assumed to be its direct precursor.

These results are mysterious for two reasons. The authors tacitly assume the fluoride displacement by *tert*-butyl groups to obey the standard nucleophilic addition/nucleofugal elimination mode although this mechanistic pattern is restricted to heavily strained[5] or acceptor-activated[6] haloarenes as substrates. Equally incomprehensible is how 1,3,5-trifluorobenzene could undergo smooth and fast trilithiation at a temperature as low as −115 °C, fluorine being known to act only as a moderately strong exchange-accelerating neighboring group.[7]



A reinvestigation conformed our suspicion. When we attempted to trap the trilithiated 1,3,5-trifluorobenzene (**3**) at −115 °C with electrophiles other than chlorotrimethylsilane (e.g., dimethyl sulfate and carbon dioxide), only monosubstituted derivatives **4** were obtained. After consecutive treatment of 1,3,5-trifluorobenzene in tetrahydrofuran at −100 °C, in the absence or presence of potassium *tert*-butoxide and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA), with *tert*-butyllithium (3 equiv, 2 h) and with phenylacetylene-ω-*d* the recovered substrate contained mainly (≥90%) a single deuterium atom and had incorporated a second or third isotopic label in trace amounts at best (≤3 and ≤1%, respectively). Repetition of this reaction at −75 °C, using 3.0 or 6.0 equiv of *tert*-butyllithium, afforded 1,3,5-tri-*tert*-butylbenzene (**1**) in 37 and 72%. Both samples of the hydrocarbon were essentially dideuterated. When the reaction mixture (made with 6.0 equiv of *tert*-butyllithium) was poured on dry ice rather

---

* Author for correspondence. Telephone: ++41/21/692 39 51. Fax: ++41/21/692 39 65. E-mail: manfred.schlosser@ico.unil.ch.

(1) Bachrach, S. M.; Hare, M.; Kass, S. R. *J. Am. Chem. Soc.* **1998**, *120*, 12646−12649.

(2) Rot, N.; Bickelhaupt, F. *Organometallics* **1997**, *16*, 5027−5031.

(3) Dua, S. S.; Gilman, H. *J. Organomet. Chem.* **1974**, *64*, C1 − C2.

(4) Howells, R. D.; Gilman, H. *Tetrahedron Lett.* **1974**, *15*, 1319−1320.

(5) Bickelhaupt, F.; Jenneskens, L. W.; Klamer, J. C.; de Wolf, W. H. *J. Chem. Soc., Chem. Commun.* **1984**, 733−735.

(6) Nucleophilic displacement of *p*-fluorine atoms from cyano or oxazoline substituted arenes: Richtzenhain, H. *Ber. Dtsch. Chem. Ges.* **1944/46**, *77/79*, 1−6; *Chem. Ber.* **1948**, *81*, 92−97; Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383−7385.

(7) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(8) The structural assignment is supported by ^{1}H- and ^{13}C NMR spectra and elementary analysis.

(9) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155−6157; see also: House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324−2336.

(10) Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, *36*, 4385−4388.

(11) We have monitored the reaction between chlorotrimethylsilane (0.5 M) and butyllithium (0.5 M in diethyl ether at −75 °C and in tetrahydrofuran at −100 °C) and chlorotrimethylsilane (0.5 M) and *tert*-butyllithium (0.5 M in tetrahydrofuran at −100 °C) in the time interval ranging from 0 to 720 min and found approximate half-lives of 1 h, ≤1 min, and ≫1 day, respectively.

(12) Authentic material[7] prepared by consecutive treatment of 1-bromo-3,5-difluorobenzene in tetrahydrofuran with *tert*-butyllithium, cuprous iodide tributylphosphine complex, again *tert*-butyllithium and 1-nitronaphthalene [method: Bergbreiter, E. D.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 4937−4944; Bergbreiter, E. D.; Reichert, O. M. *J. Organomet. Chem.* **1977**, *125*, 119−124].

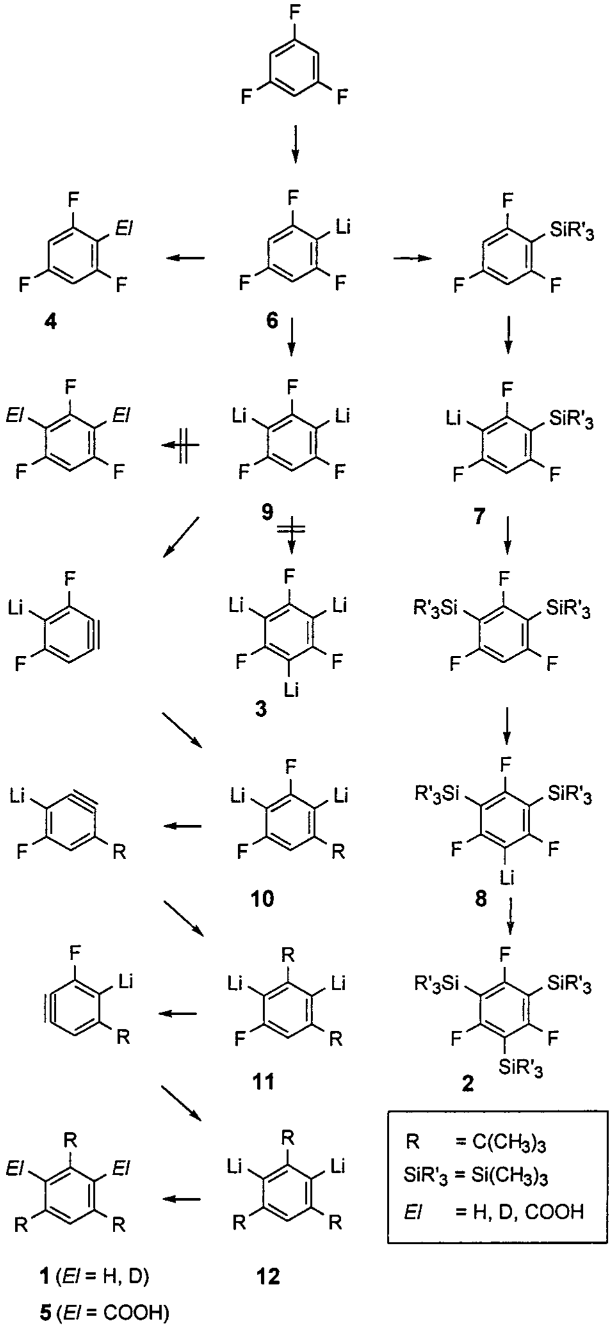
(13) Authentic material prepared from 3,5-di-*tert*-butylaniline [Burgers, J.; van Hartingsveldt, W.; van Keulen, J.; Verkade, P. E.; Visser, H.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 1327−1342] by the Balz-Schiemann reaction [method: Roe, A. *Org. React.* **1949**, *5*, 193−228].

(14) Crowther, G. P.; Sundberg, R. J.; Sarpeshkar, A. M. *J. Org. Chem.* **1984**, *49*, 4657−4663; Slocum, D. W.; Hayes, G.; Kline, N. *Tetrahedron Lett.* **1995**, *36*, 8175−8178.

(15) Cabiddu, S.; Contini, L.;. Fattuani, C.; Floris, C.; Gelli, G. *Tetrahedron* **1991**, *47*, 9279−9288.

(16) Maercker, A. In *Houben-Weyl: Methoden der organischen Chemie*; Hanack, M., Ed.; Thieme: Stuttgart, 1993; Vol. E 19d, pp 448−566, see pp 462−466.

10.1021/ja0032733 CCC: $20.00



than quenched with phenylacetylene-*ω*-*d*, pure 2,4,6-tri-*tert*-butylbenzene-1,3-dicarboxylic acid (**5**) (mp > 250 °C dec)[8] was isolated in 68% yield.

On the basis of these findings, a consistent picture of the events at −100 and −75 °C can be drawn. Chlorotrimethylsilane is a treacherous electrophile since it reacts very slowly with bulky bases such as lithium diisopropyl amide and lithium 2,2,6,6-tetramethylpiperidide, coexisting with them at low temperatures over hours.[9,10] The same is the case with *tert*-butyllithium and, to some extent, even butyllithium as we have realized now.[11] Thus, a silylation step can and must be interposed between the first, second, and third hydrogen/lithium interconversion or, in other words, the threefold electrophilic substitution is mediated by nothing but monometalated intermediates (**6** − **8**). At −75 °C, the dilithiated trifluorobenzene **9** gradually begins to emerge but does not survive. A cascade of alternating lithium fluoride eliminations and *tert*-butyllithium additions to the thus generated dehydroarenes is instantaneously unleashed. Each dilithiated intermediate being less stable than its precursor (**12** < **11** < **10** < **9**), the sequence does not stop before all three fluorine atoms are displaced, that is the dilithiated tri-*tert*-butylbenzene (**12**) is attained. No trace of 1-*tert*-butyl-3,5-difluorobenzene[12] nor of 1,3-di-*tert*-butyl-5-fluorobenzene[13] was detected in the neutralized reaction mixture.

One should beware of unwarranted generalizations. If not trilithiated species, dilithiated ones can be generated and characterized by electrophilic substitution provided that the metalation-promoting neighboring groups are solidly attached to the aromatic ring and not nucleofugally as labile as halogens. The double lithiation of 1,4-dimethoxybenzene[14] and 1,3,5-trimethoxybenzene[15,16] does indeed occur quite effectively.

Acknowledgment. This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (Grant 20-55′303-98) and the Bundesamt für Bildung und Wissenschaft, Bern (Grant 97.0083 linked to the TMR project FMRXCT970129). This publication is dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday (in June, 2000). He has taught intellectual and experimental rigor to generations of scholars.

Supporting Information Available: Preparation and characterization of authentic samples for comparison [trimethyl(2,4-trifluorophenyl)silane; (2,4,6-trifluoro-1,3-benzenediyl)-1,3-bis(trimethylsilane); (2,4,6-trifluoro-1,3,5-benzenetriyl)-1,3,5-tris(trimethylsilane), **2**; 1-*tert*-butyl-3,5-difluorobenzene; 1,3-di(*tert*-butyl)-5-fluorobenzene; 1,3,5-tri(*tert*-butyl)benzene, **1**; 2,4,6-trifluorobenzoic acid, **4**; 2,4,6-tri(*tert*-butyl)isophthalic acid, **5**]; details concerning the reactions between 1,3,5-trifluorobenzene and *tert*-butyllithium; kinetic investigation of the condensation between chlorotrimethylsilane and butyllithium or *tert*-butyllithium (PDF). This material is made available free of charge via the Internet at http://pubs.acs.org.

JA0032733