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Buttressing Effects on Haloarene Deprotonation: A Merely Kinetic or Also Thermodynamic Phenomenon?

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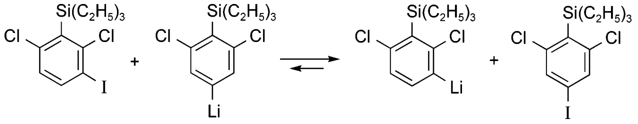
ABSTRACT

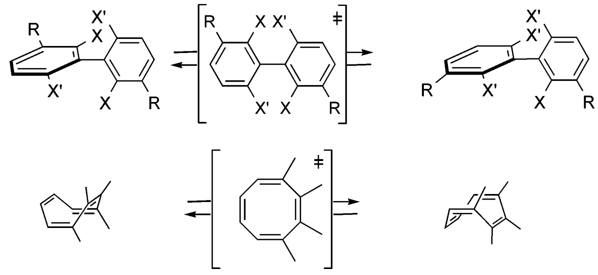


(2,6-Dichlorophenyl)- and (2,6-dibromophenyl)trialkylsilanes undergo hydrogen/metal interconversion preferentially at the 4- rather than 3-position. However, the organometallic species generated by such a "*meta* metalation" are thermodynamically less stable (i.e., more basic) than those that would result from an ordinary "*ortho* metalation". This was demonstrated by equilibration experiments based on permutational halogen/metal interconversion. A new buttressing effect can explain the unprecedented regioselectivity. It is supported by X-ray structures that reveal marked deformations of the benzene ring in halophenylsilanes.

Buttressing effects[1−5] have so far been invoked only in relation to molecular mobility. For example, the introduction of bulky groups R into the *meta* positions of biphenyls, carrying *ortho* substituents X and X′, compromises the flexibility of the latter and, by increasing the repulsive forces at the coplanar transition state, raises the torsional barrier.[1] Similar arguments were put forward to rationalize the unusually high (approximately 32 kcal/mol) inversion barrier of the 1,2,3,4-tetramethylcyclooctatetraene ring.[5,6] At the planar transition state, each methyl group is squeezed in by its neighbors and thus has been confined to rigidity (Scheme 1).

Buttressing effects on acid−base reactions,[7,8] in particular the proton transfer from haloarenes to strong bases such as lithium 2,2,6,6-tetramethylpiperidide (LITMP) or *sec*-butyllithium, were unprecedented until a short while ago. Although 1,3,5-tribromobenzene readily undergoes hydrogen/metal permutation at the 2-position,[9] (2,4,6-tribromophenyl)trimethylsilane proved to be completely inert toward LITMP, even when in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) and potassium *tert*-butoxide.[7] (2,6-Dibromophenyl)triethylsilane and its 2,6-dichloro analogue do experience deprotonation when treated with strong bases, but mainly, if not exclusively, at the

Scheme 1. Typical Buttressing Effects Restraining the Internal Molecular Mobility



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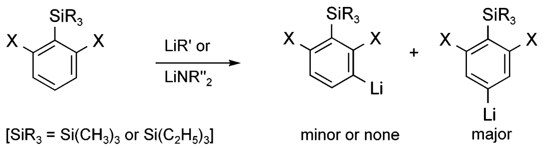
Scheme 2. Predominant or Exclusive "*meta* Metalation" Rather Than "*ortho* Metalation"



remote 5-position ("*meta* position") rather than at the halogen-adjacent position ("*ortho* position"; Scheme 2).[8]

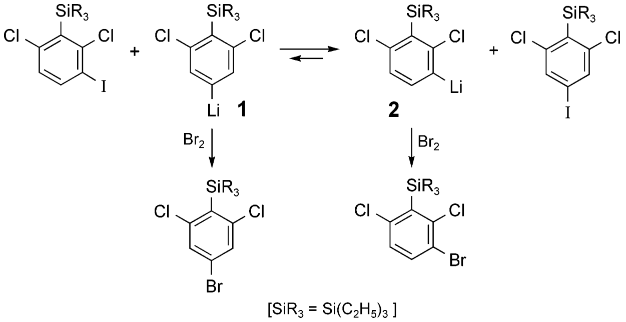
To gain insight we embarked on a systematic investigation. One of the key questions to be asked was whether the preference for *meta* rather than *ortho* lithiation is a kinetic or thermodynamic phenomenon. To this end, we have determined the relative stabilities of our metalation products by heavy halogen/metal permutational equilibration. This method has been first applied to probe the basicity of 4-tolyllithium relative to phenyllithium by allowing one organolithium Li-R to react with the other bromoarene Br-R′ in diethyl ether at 0 °C until the proportions of the four components did not change any more and by repeating the experiment starting from the counterpart combination of reagents Br-R and Li-R′.[10] The carbon−halogen bond strengths being tacitly assumed to depend little or not at all on the nature of the organic parts R and R′, the equilibrium positions must mirror the relative thermodynamic stabilities (or, in other words, basicities) of the organolithium species involved. Later, the relative basicities of two more aryllithiums were assessed in this way.[11,12]

$$R'{-}I + Li{-}R \overset{K}{\rightleftarrows} Li{-}R' + R{-}I$$

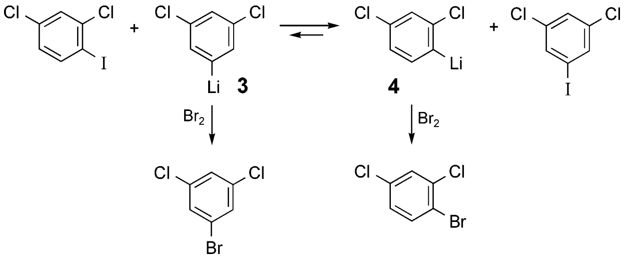
When applying this technique to the couples (2,6-dichloro-3-iodophenyl)triethylsilane/3,5-dichloro-4-(triethylsilyl)phenyllithium (**1**) and (2,6-dichloro-4-iodophenyl)triethylsilane/2,4-dichloro-3-(triethylsilyl)phenyllithium (**2**), the equilibrium, approached from both sides, was attained in tetrahydrofuran at −100 °C after a few minutes (Scheme 3). The aryllithium species were converted with elemental bromine into (4-bromo-2,6-dichlorophenyl)triethylsilane and (3-bromo-2,6-dichlorophenyl)triethylsilane, which were quantified together with the corresponding iodo compounds by gas chromatographic analysis. The monitored 13:87 equilibrium composition in favor of the kinetically disadvantaged aryllithium species **2** translates into a difference in thermodynamic stability, $\Delta G_{\mathrm{eq}}^{173}$, of 1.31 kcal/mol.

Most instructive was also the comparison with the non-silylated analogues. The couples 2,4-dichloro-1-iodobenzene/3,5-dichlorophenyllithium (**3**) and 1,3-dichloro-5-iodobenzene/2,4-dichlorophenyllithium (**4**) converged to an equilibrium position that was virtually the same as the previously observed one. The 14:86 proportions correspond to a basicity difference of 1.25 kcal/mol. This is the amount of energy gained when one moves a chloro substituent in an aryllithium from a *meta* to an *ortho* position and simultaneously another one from a *meta* to the *para* position. The quantitative agreement with model studies is remarkably good. The iodoarene-mediated equilibration between 3- and 2-chlorophenyllithium produces a 5:95 mixture at −100 °C and between 2- and 4-chlorophenyllithium a 70:30 mixture at −75 °C (Scheme 4). This corresponds to basicity increments of −2.03 and +0.67 kcal/mol, the sum of −1.36 being an excellent approximation to the previously found number of −1.25 kcal/mol.

Scheme 3. Equilibration between Two Dichloro(triethylsilyl)phenyllithiums and the Corresponding Iodoarenes by Permutational Halogen/Metal Interconversion



Scheme 4. Equilibration between 2,4- and 3,5-Dichlorophenyllithium and the Corresponding Dichloroiodobenzenes



The conclusion is clear. The buttressing effect encountered with the metalation of (2,6-dichlorophenyl)- or (2,6-dibromophenyl)trialkylsilane does not manifest itself at the ground state level but represents a merely kinetic and hence transition state phenomenon. To elucidate all details associated with it, more scrutinity will be required. All that we can do at the moment is to present a working hypothesis that can be subjected to accordingly devised tests in the future.

Our deductions proceeded stepwise. We ruled out repulsive interactions between lithium and any halogen on the basis of their opposite polarities (which hardly will create attractive forces) and the distance (approximately 2.3 Å in the case of bromine). Moreover, the "*meta*-orienting" effect was found to be particularly pronounced when the deprotonation was

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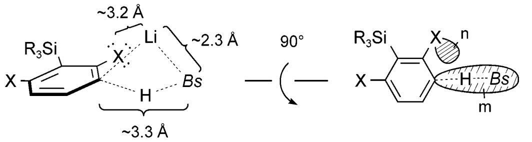
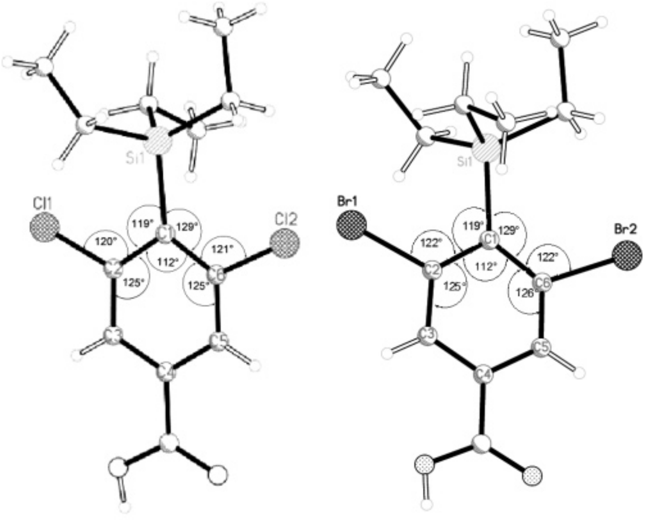


Figure 1. Postulated transition state of the (disfavored) metalation of (2,6-dichlorophenyl)- or (2,6-dibromophenyl)trialkylsilanes at the 3-position (*ortho*-metalation).

accomplished with potassium rather than lithium bases. On the other hand, we had recognized a marked increase in deprotonation-related buttressing effects when the transmitter halogen was varied from fluorine through chlorine and bromine to iodine. The heavier the halogen, the longer is its atomic distance but also its van der Waals radius and the looseness of its nonbonding electrons. One of these nonbonding doublets collides with the two delocalized electrons confined in the molecular orbital (m) within which the proton is transferred from the aromatic carbon to the base, i.e. from its former to its future binding partner, in an almost linear C•••H•••*Bs* array (Figure 1). The in-plane proximity of two times two loosely bound electrons must give rise to repulsive forces.

But why then do other 2-substituted 1,3-dihalobenzenes such as 1,3-dichloro-2-fluorobenzene undergo lithiation at the 4-position rapidly and cleanly? The halogen n-electrons overlap with the proton-transfer-mediating m-electrons only when the C(2),C(3),X valence angle is widened beyond the standard 120°. If there is no bulky substituent attached to the 2-position, the X,H distance is presumable large enough to avoid any repulsive orbital interference. Moreover, if not impeded by buttressing, the halogen X may swing to the other side and thus facilitate the protophilic attack of the base. In other words, the key argument for explaining the different behavior of 1,3-dichloro-2-fluorobenzene and (2,3-dichlorophenyl)trialkylsilanes centers around the facile in-plane deformability of the bond angles established between chlorine, bromine, or iodine atoms and the carbon skeleton.



5 **6**

Figure 2. X-ray crystallographic structures of 3,5-dichloro- and 3,5-dibromo-4-triethylsilylbenzoic acids (**5** and **6**) revealing marked deformations of the C(2)C(1)C(6), (C(1)C(2)X, and C(1)C(6)X angles (X = Cl or Br).

This deformability is illustrated impressively by the X-ray structures of the 3,5-dichloro- and 3,5-dibromo-4-(triethylsilyl)benzoic acid (**5** and **6**, respectively; Figure 2).[8]

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Supporting Information Available: Experimental procedures and characterization data for the new compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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