Mechanistic Evidence for Ortho-Directed Lithiations from One- and Two-Dimensional NMR Spectroscopy and MNDO Calculations†

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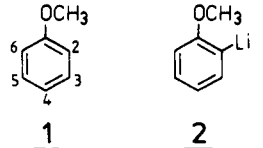
Abstract: The prototype directed lithiation reaction, the ortho metalation of anisole (**1**) with *n*-butyllithium (*n*-BuLi), is investigated by a combination of NMR spectroscopy and semiempirical MO calculations. Anisole forms a 1:1 complex with *n*-BuLi in toluene-d_8. This is shown by ^{13}C NMR to be a tetrameric aggregate. Two-dimensional $^6Li,^1H$-heteronuclear Overhauser effect spectroscopy (HOESY) demonstrates the solvation of *n*-BuLi by **1** by revealing close contacts between lithium and the OCH_3 and the ortho-hydrogen atoms of **1**. While these observations are in accord with the postulated directed metalation mechanism, this complex does not undergo ortho lithiation even at room temperature. When one equivalent of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) is added, anisole is completely displaced by the chelating ligand and dimeric *n*-BuLi solvated by TMEDA is formed preferentially. Despite the absence of a detectable anisole–*n*-BuLi complex, metalation of **1** now occurs readily even at low temperatures. The mechanism is suggested to involve a complex between *n*-BuLi *dimer* and **1** as the reactive intermediate, although this must be present in low concentration. An agostic metal–hydrogen interaction facilitates proton removal. This postulate is supported by MNDO calculations. Similar behavior is found by NMR for 1,3-dimethoxybenzene (**12**) and for *N,N*-dimethylaniline (**14**). Thioanisole (**8**) shows weaker interactions (shown by HOESY and ^{13}C NMR) with *n*-BuLi. No evidence for an initial complex formation involving fluorobenzene (**20**) could be detected. MNDO calculations provide explanations for the behavior reported in this paper.

The regiospecific introduction of lithium into aromatic rings often is facilitated by substituents with free electron pairs (Scheme I). This well-documented effect (often termed "ortho lithiation") is of great synthetic potential. First observed by Gilman[1] and Wittig,[2] such reactions have been reviewed extensively.[3-9] Analogous activation effects in nonaromatic compounds are well-known.[10] The efficiency of ortho lithiation was found to depend on the nature of the substituent and to decrease in the order[11a,b,e] $CONEt_2 > CH_2NMe_2 > OCH_3 > N(CH_3)_2 > F$.

Intra-[11c,d] and intermolecular[11e] competition experiments showed that the lithiation-directing ability of the tertiary carboxamide group is superior to that of other groups such as sulfonamide, oxazoline, methoxy, or chlorine.

However, acidity measurements on monosubstituted benzenes revealed only small differences in pK_a values in going from donor to acceptor substituents. This suggests that kinetic effects are predominantly responsible for the reactivity orders.[11f]

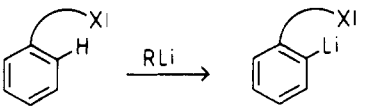
That ortho lithiation is favored also thermodynamically is predicted by ab initio calculations;[12] thus, the STO-3G stabilization energies vs phenyllithium were −7.1, −0,5, and 0.0 kcal/mol, respectively, for *o*-, *m*-, and *p*-lithiophenol. At the same calculational level *o*-, *m*-, and *p*-lithiofluorobenzene were stabilized by 8,4, 1.2, and 0.7 kcal/mol relative to phenyllithium. Favorable dipole or electrostatic interactions, rather than charge transfer, may be the main stabilizing influence for such ortho derivatives. Under thermodynamic product control conditions (4 h at +100 °C) anisole (**1**) reacts with phenyllithium to give *o*-lithioanisole (**2**).[2]



1 **2**

Recent thermochemical experiments[13] showed that quenching of *p*-anisyllithium with *sec*-butyl alcohol was 3.6 kcal/mol more exothermic than the analogous reaction of *o*-anisyllithium. Although somewhat smaller in magnitude than the (rather crude) theoretical calculation, this confirms the extra stabilization afforded by direct OCH_3–Li interaction. Such interactions are exhibited by the unusual crystal structure of **2**.[14] While **2** forms tetrameric units, two of the lithium atoms are coordinated to one oxygen atom, one lithium atom is coordinated to two oxygens, and the fourth lithium atom is linked via a TMEDA molecule acting as a monodentate ligand to a second tetrameric unit (TMEDA = *N,N,N',N'*-tetramethylethylenediamine).

Scheme I



The effectiveness of ortho lithiation was demonstrated impressively by a very early experiment: when *p*-bromoanisole reacted with phenyllithium, no halogen–metal exchange was found. Instead, the bromoether was lithiated ortho to the oxygen substituent exclusively.[2]

Despite the power of NMR, only a few direct observations pertinent to the mechanism of ortho lithiation have been reported. Ellison and Kotsonis[15] observed changes in the ^1H NMR spectrum

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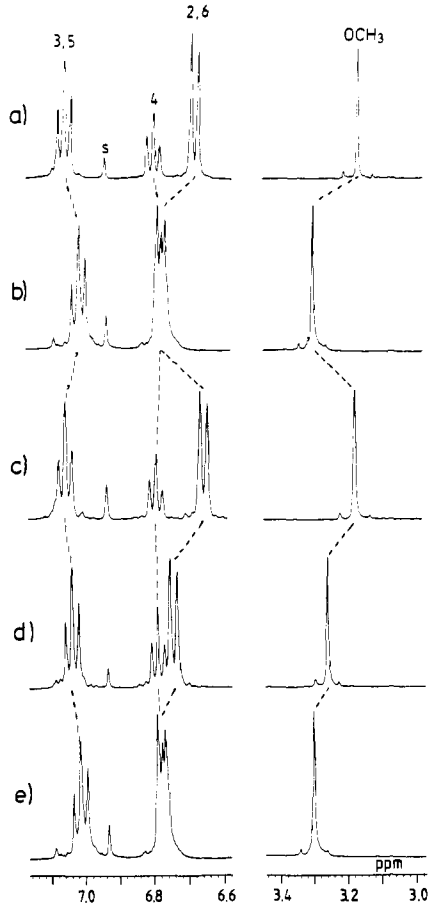

Figure 1. ^{1}H NMR spectrum (toluene-d_8, −64 °C) of (a) anisole (ca. 1.6 M anisole), (b) anisole + 1 equiv of *n*-BuLi (ca. 0.8 M anisole), (c) anisole + 1 equiv of *n*-BuLi + 1 equiv of TMEDA (ca. 0.8 M anisole), (d) anisole + 0.5 equiv of *n*-BuLi (ca. 1.6 M anisole), (e) anisole + 2 equiv of *n*-BuLi (ca. 0.8 M anisole), s = solvent signal.

of anisole (**1**) and of 1-methoxynaphthalene when *n*-butyllithium (*n*-BuLi) was added to their solutions in hexane. This was attributed to aryl ether–*n*-BuLi complex formation. Similar experiments indicating the formation of a complex between *n*-BuLi and alkyl aryl ethers were described earlier by Graybill and Shirley.[16] We have now reinvestigated and extended these early measurements by using modern NMR methods and semiempirical MNDO calculations,

Results and Discussions

Anisole (1). Anisole has long been known to react with strong lithioorganic bases in ether solution to give 2-lithioanisole (**2**).[4,17] In agreement with the observations in hexane,[15,16] when 1 equiv of *n*-BuLi[18] is added to a solution of **1** in toluene-d_8, pronounced changes in the ^{1}H NMR spectrum (Figure 1) are observed. The resonances of the OCH_3 group and of the ortho-hydrogen atoms are shifted downfield by 0.13 and 0.10 ppm, respectively, whereas the meta- and para-proton signals undergo an upfield shift. These downfield shifts seem to be typical for organolithium compounds and have now many precedents (e.g., phenyllithium,[19] mesityllithium,[20] and 1-naphthyllithium[21]). This deshielding effect may be explained by the electric field of the lithium cation, which polarizes the σ-electrons of the C–H bond.[22]

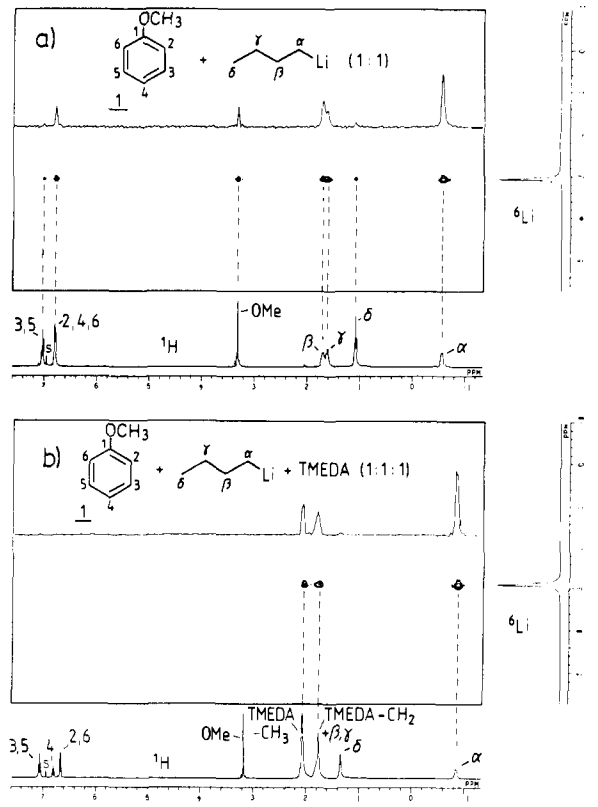

Figure 2. Phase-sensitive ^{6}Li,^{1}H HOESY (toluene-d_8, −64 °C) (a) of a 1:1 anisole (**1**)–*n*-BuLi mixture; (b) of a 1:1:1 anisole (**1**)–*n*-BuLi–TMEDA mixture (ca. 0.8 M **1**). Inserts: f_1 – traces of the ^{6}Li signals; spectral parameters, see Experimental Section; s = solvent signal.

Table I. ^{13}C NMR Chemical Shifts of *n*-BuLi in Different Aggregates (δ, ppm)

C	hexamer	tetramer	dimer
α	12.0	10.5	12.8
β	31.9	33.9	35.8
γ	32.1	35.4	37.3
δ	14.5	14.7	14.9
solvt	toluene-d_8	THF-d_8	THF-d_8
temp., °C	−64	−96	−96
ref	this work	21	21, 39

The observed spectra suggest that anisole is ligated to *n*-BuLi. The OCH_3– and ortho protons are in close proximity to lithium. This can be demonstrated independently by ^{6}Li,^{1}H two-dimensional heteronuclear Overhauser effect spectroscopy (HOESY). We have employed this new tool for the detection of short lithium–hydrogen contacts.[20,21,23-26] HOESY cross peaks appear between ^{6}Li and ^{1}H signals due to dipolar relaxation processes. The HOESY spectrum of an equimolar **1**–*n*-BuLi mixture shows the expected cross peaks betwen the ^{6}Li signal and the ^{1}H resonances of *n*-BuLi (Figure 2a). In addition, cross peaks are observed between ^{6}Li and the OCH_3 and the ortho-proton resonances. This demonstrates the close proximity of these hydrogens to lithium and corroborates the existence of a tight anisole–*n*-BuLi complex.

Both ^{13}C,^{6,7}Li coupling constants and multiplicities can be used to determine the aggregation states of organolithium compounds.[27,28] These line-splitting patterns characterize dimeric[28]

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Table II. ^{13}C NMR Chemical Shifts of Anisole (**1**)–*n*-BuLi Mixtures in Different Ratios and with Added TMEDA (δ, ppm)[a]

C	**1**	**1** + *n*-BuLi (1:1)	**1** + *n*-BuLi + TMEDA (1:1:1)	**1** + *n*-BuLi (2:1)	**1** + *n*-BuLi (1:2)
OCH_3	54.3	56.5	54.3	55.6	57.3
1	159.8	158.7	159.7	159.2	158.3
2,6	113.9	115.4	113.9	114.8	115.9
3,5	129.8	129.7	129.7	129.7	129.7
4	120.7	122.3	120.7	121.6	122.8
α		9.6	13.2	9.9	9.5/11.8[b]
β		33.5	35.9	33.6	33.4/32.2
γ		33.7	37.5	33.8	33.5/32.3
δ		14.5	15.0	14.5	14.5/14.5
$TMEDA-CH_3$			46.3		
$TMEDA-CH_2$			56.6		

[a] In toluene-d_8 at −64 °C; numbering, see formula in text and Scheme II; concentrations, see corresponding spectra in Figure 1. [b] Values on the left of the slash = *n*-BuLi tetramer–anisole solvate. Values on the right = *n*-BuLi hexamer.

and tetrameric[21] *n*-BuLi. While no line splitting is observed due to rapid fluxional exchange in benzene-d_6 and even at low temperatures in toluene-d_8, *n*-BuLi is known by colligative measurements to be hexameric in hydrocarbon solvents.[29]

Table I summarizes the ^{13}C NMR chemical shifts of dimeric, tetrameric, and hexameric *n*-BuLi. These differ significantly from each other and thus may also be used to diagnose the degree of aggregation. In the ^{13}C NMR spectrum of an equimolar anisole **1**–*n*-BuLi mixture in toluene-d_8 at −64 °C, the α-C atom signal of *n*-BuLi does not show $^{13}C,^6Li$ coupling. However, the chemical shifts of the *n*-butyl group (Table II) are compatible only with those of *n*-BuLi *tetramer* (cf. Table I). Thus, anisole must disrupt the hexameric *n*-BuLi aggregate to give a tetramer **3** (Scheme II), peripherally solvated with anisole. This is analogous to the known THF solvate.[28]

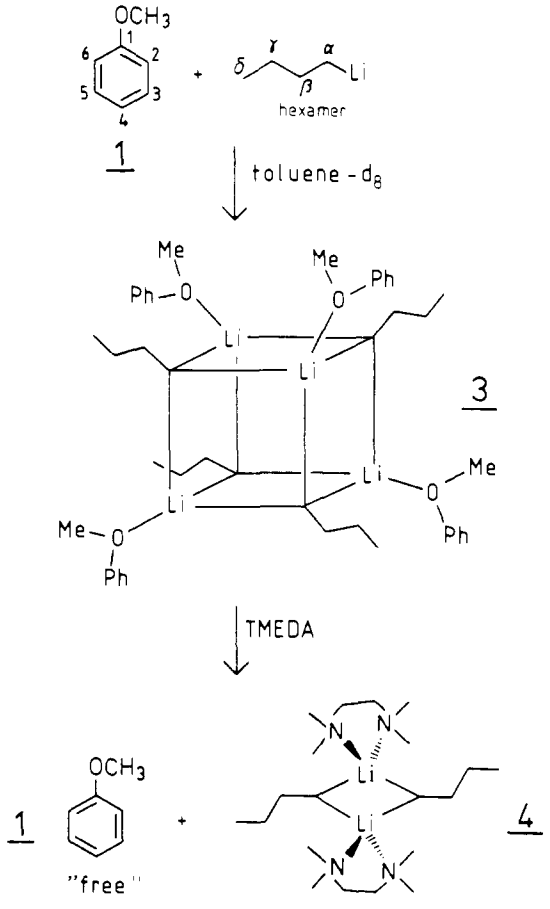
The rapid exchange (NMR time scale) between free anisole and anisole bound to the *n*-BuLi tetramer **3** can be demonstrated by using a 2:1 mixture of **1** and *n*-BuLi in toluene-d_8: only averaged signals for **1** are obtained in the ^1H NMR spectrum, and the chemical shifts lie between those of free and of complexed anisole (Figure 1). This also holds for the ^{13}C NMR spectrum of this mixture: whereas the resonance lines of *n*-BuLi are not affected as compared to the 1:1 mixture (i.e., the fully coordinated *n*-BuLi tetramer is still observed) the chemical shifts of anisole are between those of free and of complexed anisole (Table II).

In contrast, the ^1H NMR spectrum of anisole in a 1:2 mixture with *n*-BuLi is the same as that with a 1:1 ratio (Figure 1). This observation suggests that the binding of anisole to *n*-BuLi in the 1:1 mixture is essentially complete. The ^{13}C NMR spectrum (Table II) is in agreement: the anisole chemical shifts in the 1:1 and the 1:2 **1**–*n*-BuLi ratio are essentially identical. When excess *n*-BuLi is present, a second set of signals due to *n*-BuLi hexamer (cf. Table I) is found in addition to the signals of the *n*-BuLi tetramer. Hence, interaggregate *n*-BuLi exchange is slow on the NMR time scale under these conditions.

Due to the close contacts between anisole and the lithiating reagent in a **1**–*n*-BuLi mixture in toluene-d_8, it would seem reasonable to expect facile metalation of anisole. *Strikingly, this is not observed under these conditions.* The **1**-*n*-BuLi 1:1 solution does *not* undergo any NMR-detectable formation of the ortholithio product **2** after an hour at room temperature. Even the 2:1 **1**-*n*-BuLi solution shows the same behavior.

The situation changes completely when 1 equiv of TMEDA is added to the 1:1 anisole–*n*-BuLi mixture in toluene-d_8. Under these conditions the ^1H NMR spectrum of anisole at −64 °C is completely identical with that of anisole *without* added *n*-BuLi (Figure 1), i.e., TMEDA has replaced anisole as the complexing agent to *n*-BuLi. This is confirmed by $^6Li,^1H$ HOESY (Figure 2b): besides the expected cross peaks to the *n*-butyl group, the ^6Li nuclei now exhibit interactions with the TMEDA protons. However, no HOESY interactions are found between lithium and anisole. Anisole is now "free"! The ^{13}C NMR spectrum (Table II) agrees: the shifts of anisole are completely identical with those of anisole *without* added *n*-BuLi and differ from those of the **1**-*n*-BuLi mixture without added TMEDA.[30] Interestingly, the ^{13}C NMR chemical shifts of *n*-BuLi are now compatible with those found for *n*-BuLi *dimer*, i.e., the addition of TMEDA leads to deaggregation of the tetramer. Scheme II summarizes these findings.

Scheme II



However, despite its "free" character in the presence of *n*-BuLi/TMEDA, *anisole is readily metalated even at temperatures below 0 °C under these conditions.*[31] This process must involve a reactive intermediate, undetectable by NMR, with low stationary concentration. We propose the mechanism shown in Scheme III. A TMEDA chelate of *n*-BuLi opens and—as TMEDA is a relatively poor *monohapto* ligand[26]—one TMEDA dissociates from *n*-BuLi, leaving two coordination sites at lithium open. These could be coordinated by the anisole oxygen *and* by agostic Li···H interactions.[32] Thus, anisole could behave as a *chelating* ligand. The lithium-activated ortho proton is removed subsequently by

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(28) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.

(29) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. The disruption of hexameric *n*-BuLi to a tetrameric solvate on addition of electron donors has also been found by these authors.

(30) These findings are consistent with those of a calorimetric study; the addition of TMEDA to *n*-BuLi was found to be more exothermic by a factor of 12 than the heat released upon addition to anisole to *n*-BuLi: Kminek, I.; Kaspar, M.; Trekoval, J. *Coll. Czech. Chem. Commun.* **1981**, *46*, 1124.

(31) Even when kept at −78 °C, anisole is metalated quantitatively in the ortho position after 3 months by *n*-BuLi/TMEDA.

(32) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395. Koga, N.; Obara, S.; Morokuma, K. *J. Am. Chem. Soc.* **1984**, *106*, 4625. Erker, G.; Frömberg, W.; Angermund, K.; Schlund, R.; Krüger, C. *Chem. Commun.* **1986**, 372.

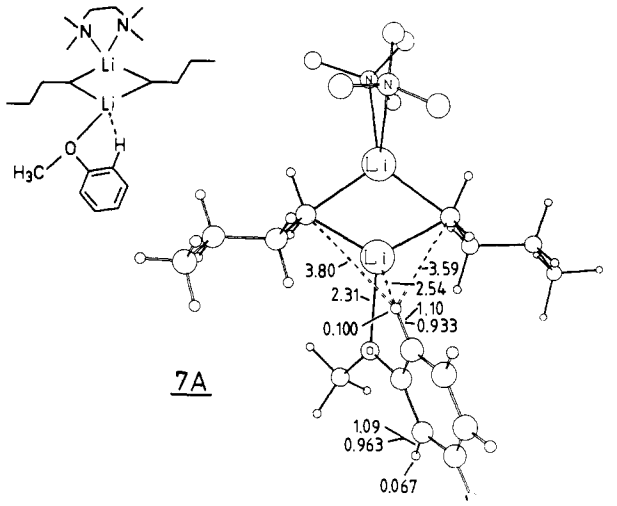
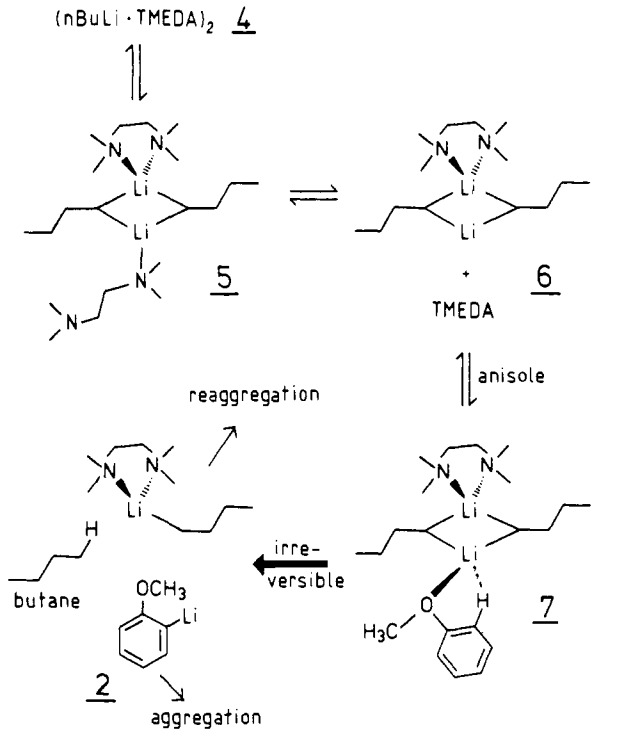


Figure 3. MNDO structure **7A** of intermediate **7** (Scheme III). For clarity, the TMEDA hydrogen atoms are omitted. Numbers at bonds: bond lengths (Å, single or upper values) and bond orders (lower values); numbers at hydrogen atoms: charges; ΔH_f° = −116.1 kcal/mol.

Scheme III



the adjacent strongly basic α-carbon atom of *n*-BuLi.

On the basis of kinetic ("rapid injection NMR") experiments, McGarrity observed earlier that *n*-BuLi dimer is at least 10 times more reactive than the tetramer.[33] We propose the following explanation: in *n*-BuLi tetramer there is only *one* accessible coordination site per lithium. This precludes the simultaneous chelation and hydrogen activation described above. In contrast, in the dimer each lithium atom may be *2-fold* coordinated. We consider this to facilitate ortho-lithiation reactions.

The proposed *n*-BuLi dimer/TMEDA/anisole intermediate **7** (Scheme III) was calculated by using MNDO. In structure **7A** (Figure 3) one hydrogen atom clearly shows the assumed agostic lithium–hydrogen interaction; compared to the corresponding nonactivated ortho proton, the Li–H distance is 2.40 Å shorter,

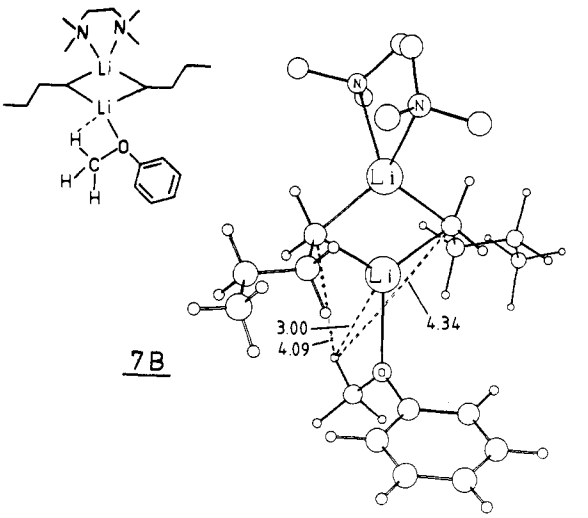


Figure 4. MNDO structure **7B** of intermediate **7** (Scheme III). For explanation of numbers, see Figure 3; ΔH_f° = −116.2 kcal/mol. In the starting geometry, one OCH_3 hydrogen atom was positioned near lithium.

the positive charge at H is higher, the C–H bond order is reduced, and the C–H bond is elongated. Thus, a favorable Li–O–C–C–H five-membered ring is formed. This might explain the selective activation of an ortho position over other possible metalation sites (apart from inductive or hydridization effects).

Similar activation of an OCH_3 proton requires a less favorable four-membered Li–O–C–H ring. This has been verified by MNDO. When a different starting geometry with one OCH_3 proton already in vicinity to lithium was used, structure **7B** resulted (Figure 4). This is 0.1 kcal/mol more stable than **7A**. However, in **7B** the activation of an OCH_3 proton by lithium is far less pronounced than in **7A** as is indicated, e.g., by the larger Li–H separation (3.00 Å in **7B** vs 2.54 Å in **7A**) as well as by the charges at the OCH_3 hydrogen atoms and the C,H bond lengths and bond orders of the OCH_3 group of **7B**: these parameters are essentially identical with those of **7A**. In addition, the mean distance between the "activated" hydrogen atom and the α-C atoms of *n*-BuLi is 0.53 Å larger in **7B** than in **7A**.

Ortho metalation has been postulated to proceed via a six-membered cyclic transition state.[4] This is closely related to structure **7A** of Figure 3. If the dashed line between lithium and the activated ortho hydrogen atom is ignored, a favorable six-membered ring consisting of Li, α-C (BuLi), ortho-H, ortho-C, ipso-C, and O can be discerned. In this sense, **7A** can be taken to represent a local minimum structure not far from the transition state of the proton-transfer reaction.

We stress that the work in the present paper does not address the mechanism of the metalation step directly. A referee claims that "radical anions" and "one electron transfer" are involved. Our ab initio model studies of several metalation reactions[34] (e.g., $CH_3Li + HC{\equiv}CH \rightarrow LiC{\equiv}CH + CH_4$[34b] show that low barriers can be associated with singlet processes. The transition states have considerable ionic but little radical character.

Scheme III does not account for some of the known experimental results involving ortho metalation, e.g.: (i) heavier alkali-organometallic compounds (e.g., RNa, RK) also give ortho metalation in the same manner as organolithium compounds.[35] These species are probably monomeric in donor solvents, e.g., THF,[36] and metal complexation and hydrogen activation analogous to Scheme III is less likely. (ii) In some cases [e.g., (trifluoromethyl)benzene[37]] ortho lithiation can be rationalized by inductive

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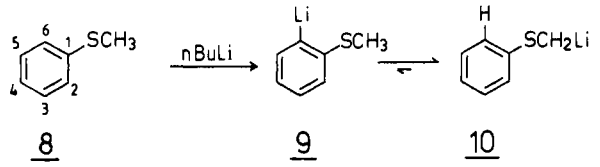
Scheme IV



8 9 10

Table III. ^{13}C NMR Chemical Shifts of Thioanisole (**8**)–*n*-BuLi–TMEDA Mixtures (δ, ppm)[a]

C	**8**[b]	**8** + *n*-BuLi[c] (1:1)	**8** + *n*-BuLi[c] + TMEDA (1:1:1)
SCH_3	14.1	14.3	14.2
1	139.1	138.1	139.1
2,6	125.3	125.7	125.4
3,5	129.1	129,1	129.1
4	124.5	124.9	124.5
α		12.0/10.2[d]	13.2
β		32.3/33.2	35.9
γ		32.5/33.4	37.5
δ		14.5/14,5	15.0
TMEDA-CH_3			46.3
TMEDA-CH_2			56.6

[a] In toluene-d_8 at −64 °C; numbering, see Scheme IV. [b] Ca. 3.2 M **8**. [c] Ca. 1.4 M **8**. [d] Values on the left of the slash; major isomer (unsolvated *n*-BuLi hexamer).

rather than by agostic effects. This agrees with the calculational results found for fluorobenzene (see below).

Besides hydrogen activation by lithium, the enhanced reactivity of the *n*-BuLi dimer over the tetramer also may be rationalized by the shielding of the negatively polarized α-carbon atom by the surrounding lithium atoms. This is more pronounced in the tetramer with three lithium contacts to the anionic center, than in the dimer, which has only two.

Very recently, Reich et al.[38] found that phenyllithium is much more effective in ortho lithiations in THF and in presence of the trihapto ligand *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDTA) than in THF alone, Under these conditions phenyllithium is monomeric,[20] whereas in THF without added PMDTA a dimer–monomer equilibrium is present.[20] Thus, the large enhancement of ortho lithiation of anisole in toluene-d_8 in the presence of TMEDA must also take into account a possible *n*-BuLi monomer, However, it has been found that the monomer–dimer equilibrium of phenyllithium in THF is shifted completely toward the *dimer* side when 1 equiv of TMEDA is added.[39] *n*-BuLi does not form monomers exclusively even in THF in the presence of stoichiometric amounts of PMDTA.[20] In presence of TMEDA and in apolar solvents the existence of even small amounts of monomeric *n*-BuLi seems unlikely. Hence, we believe that monomeric *n*-BuLi is not involved in the results we have described. Our model studies of metalation mechanisms have indicated that monomer and dimer reactions have comparable activation energies.[34a]

Thioanisole (8). In contrast to anisole, thioanisole is known to be lithiated by *n*-BuLi at the methyl group to give **10** rather than at the ortho position. In contrast, ortho metalation is found with Grignard reagents.[3,40] However, the formation of **10** was shown to proceed via initial ortho lithiation and subsequent trans metalation[41] (Scheme IV). The crystal structure of **10** has been reported.[42]

As noted for anisole, drastic changes are observed in the ^1H NMR spectrum when 1 equiv of *n*-BuLi is added to thioanisole

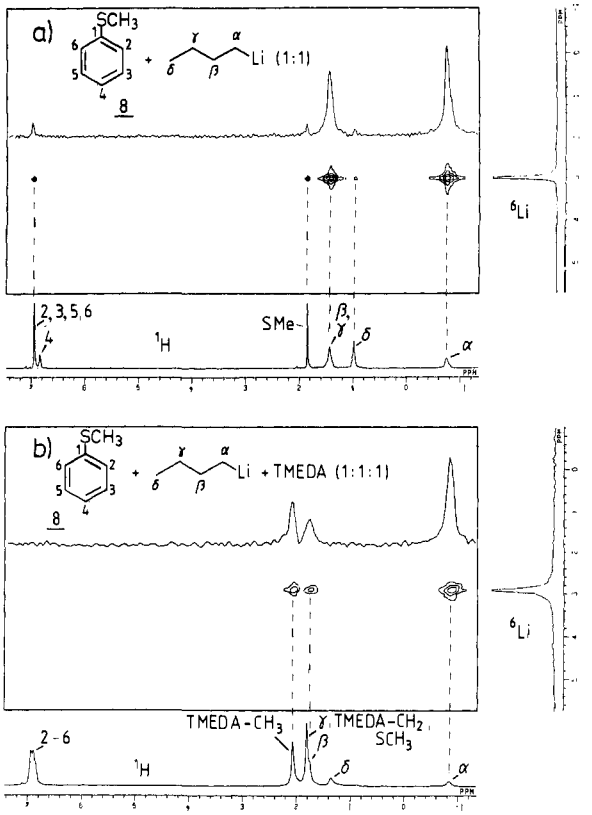
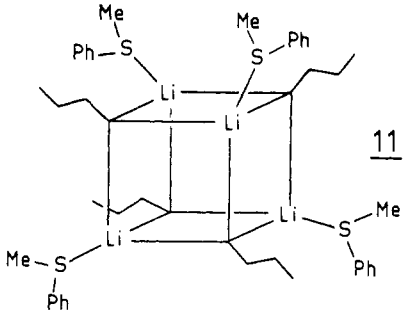


Figure 5. $^6Li,^1H$ HOESY (absolute value mode) (a) of a thioanisole (**8**)–*n*-BuLi 1:1 mixture and (b) of a thioanisole (**8**)–*n*-BuLi–TMEDA 1:1;1 mixture in toluene-d_8 at −64 °C (ca. 1.4 M **8**). Inserts: f_1 – traces of the ^6Li signals; spectral parameters, see Experimental Section; s = solvent signal.

in toluene-d_8, The ortho and SCH_3 proton resonances of **8** are shifted downfield by 0.4 and 0,2 ppm, respectively.[43] The $^6Li,^1H$ HOESY experiment (Figure 5a) reveals close contacts between lithium and the ortho and the SCH_3 protons, However, the cross-peak intensities are reduced as compared to those for the analogous cross peaks of anisole (cf, Figure 2), This indicates that the *average* distances between thioanisole and *n*-BuLi are longer, This is supported by the ^{13}C NMR spectrum (Table III). As was observed for anisole, the chemical shifts of **8** change in the presence of *n*-BuLi, but these changes are less pronounced in magnitude. For the *n*-butyl resonances, two signal sets with an approximate intensity ratio of 4;1 are found, The values of the major isomer correspond well with the data for *n*-BuLi hexamer (cf. Table I), whereas the values of the minor isomer are in agreement with those for tetrameric *n*-BuLi (analogous to **3**, Scheme II), Thus, thioanisole only partly deaggregates *n*-BuLi hexamer to give a solvate **11**. The addition of 1 equiv of TMEDA



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to a 1:1 thioanisole–*n*-BuLi solution produces changes similar to

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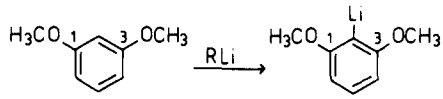
(43) The changes in the ^1H NMR spectrum of **8** after addition of *n*-BuLi are even more drastic than for anisole under similar conditions. However, some care has to be taken in interpreting ^1H NMR chemical shifts due to concomitent solvent and concentration effects; also see ref 15.

Scheme V



those found for anisole. The ^{6}Li,^{1}H HOESY cross peaks between ^{6}Li and the ^{1}H resonances of **8** disappeared whereas new cross peaks involving the hydrogen positions of TMEDA are evident[44] (Figure 5b). The ^{13}C NMR resonances of free **8** also are present (Table III). As with anisole, the shifts of the *n*-butyl residue correspond to those of *dimeric n*-BuLi.

The chemical properties of the 1:1 thioanisole–*n*-BuLi mixture in toluene-d_8 are comparable to those of anisole: without added TMEDA no metalation products are found by NMR even after several hours at +30 °C whereas in presence of TMEDA rapid lithiation takes place even below 0 °C.

The conclusions concerning the lithiation mechanism of **8** are similar to those of anisole, i.e., an intermediate with low stationary concentration must be the lithiation-directing species (cf. Scheme III).

1,3-Dimethoxybenzene (12). The lithiation of 1,3-dimethoxybenzene (resorcinol dimethyl ether) has long been known to be directed exclusively to the 2-position by the two ortho-directing OCH_3 groups[3,45,46] (Scheme V), The X-ray structure of the lithiated product **13** (which is remarkable due to the presence of the nearly planar tetracoordinate lithiated carbon atom) has been described recently in two independent investigations.[47]

In the presence of 1 equiv of *n*-BuLi (both with and without TMEDA), the NMR spectral behavior closely resembles that of anisole. In the ^{1}H NMR spectrum under conditions identical with those of anisole (cf. Figure 1), the chemical shift differences $\Delta\delta$ = [δ(**12** + *n*-BuLi) − δ(**12**)] are 0.07, 0.04, 0.12, and −0.03 ppm for OCH_3, H4,6, H2, and H5, respectively. The ^{6}Li,^{1}H HOESY spectrum of a **12**-*n*-BuLi mixture (1;1) reveals close contacts (indicated by intense cross peaks) between ^{6}Li and OCH_3, H2, and H4,6,

In the ^{13}C NMR spectrum (Table IV) changes are found similar to those for anisole: in the presence of 1 equiv of *n*-BuLi, the chemical shifts of **12** differ from those that characterize the free species. As for anisole, the ^{13}C NMR chemical shifts of the *n*-butyl group are compatible with those for *tetrameric n*-BuLi. The conclusions drawn are similar to those for anisole, i.e., **12** disrupts the *n*-BuLi hexamer to give a tetrasolvated tetramer analogous to **3** (Scheme III). Only one signal is observed for each of the degenerate OCH_3, 1,3, and 4,6 positions in **12** in the presence of *n*-BuLi, Thus, if **12** complexes lithium in an η^1 mode, the ligand exchange at lithium must be rapid on the NMR time scale.

When 1 equiv of TMEDA is added, the observations are similar to those for anisole: the ^{1}H NMR, ^{6}Li,^{1}H HOESY, and the ^{13}C NMR spectra (Table IV) indicate the presence of "free" **12**. However, the ^{6}Li,^{1}H HOESY spectrum shows cross peaks between ^{6}Li and the hydrogen positions of the chelating ligand, TMEDA. The ^{13}C NMR data of the *n*-butyl residue are in agreement with the presence of dimeric *n*-BuLi.

The chemical behavior of **12**–*n*-BuLi mixtures in toluene-d_8 resembles that of anisole: only very slow metalation is found even at room temperature without added TMEDA. But even very careful addition of TMEDA at −78 °C results in partial (ca. 30%) lithiation at C2. The conclusions drawn concerning the lithiation mechanism are similar to those summarized in Scheme III, i.e., a low stationary concentration of a highly reactive intermediate, analogous to **7**, is indicated,

Table IV. ^{13}C NMR Chemical Shifts of 1,3-Dimethoxybenzene (**12**) and 2-Lithio-1,3-dimethoxybenzene (**13**) in the Presence of *n*-BuLi and TMEDA[a]

C	**12**[b]	**12** + *n*-BuLi[c] (1:1)	**12** + *n*-BuLi + TMEDA[c]	**13**[d]	**13**[e]
OCH_3	54.5	55.4	54.4	53.6	54.1
1,3	161.2	160.6	161.2	168.2	168.8
2	100.3	101.4	100.3	143.8	147.9
4,6	106.0	107.2	106.0	101.4	101.5
5	130.3	130.2	130.2	129.2	126.4
α		10.2	13.2		
β		33.7	35.9		
γ		33.9	37.5		
δ		14.5	14.9		
TMEDA-CH_3			46.2		
TMEDA-CH_2			57.4		

[a] In toluene-d_8 at −64 °C; numbering, see Scheme V. [b] Ca. 2.8 M **12**. [c] Ca. 1.1 M **12**. [d] Partially formed after addition of 1 equiv of TMEDA to the 1:1 **12**–*n*-BuLi solution in toluene-d_8; cf. values in ref 47. [e] In THF-d_8 at −90 °C; cf. ref 47.

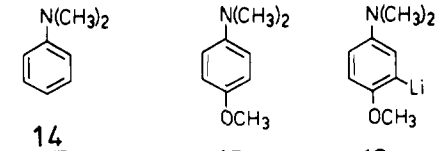
Table V, ^{13}C NMR Chemical Shifts of *N*,*N*-Dimethylaniline (**14**)–*n*-BuLi–TMEDA Mixtures[a]

C	**14**[b]	**14** + *n*-BuLi[c] (1:1)	**14** + *n*-BuLi + TMEDA[c] (1:1:1)
$N(CH_3)_2$	40.1	41.9	40.1
1	150.5	151.0	150.5
2,6	112.6	115.6	112.5
3,5	129.4	129.2	129.3
4	116.7	119.6	116.7
α		8.8	13.3
β		33.3	35.9
γ		33.6	37.6
δ		14.5	15.0
TMEDA-CH_3			46.3
TMEDA-CH_2			56.6

[a] In toluene-d_8 at −64 °C; numbering, see formula in text. [b] Ca. 1.3 M **14**. [c] Ca. 0.5 M **14**.

The ^{13}C NMR chemical shifts of the partially formed lithioproduct **13** agree well with those found for crystals of **13** dissolved in toluene-d_8,[47] i.e., the structure in solution seems to be the same. In contrast, the data for **13** in THF-d_8 (where the aggregation state is lower than in toluene-d_8) are quite different (c,f. Table IV and ref 47).

***N*,*N*-Dimethylaniline (14).** The ortho-directing effect of nitrogen in dialkylarylamines is known to be less pronounced than that of oxygen in alkyl aryl ethers and of sulfur in alkyl aryl thioethers.[4,11] This is demonstrated by a direct competition: *N*,*N*-dimethyl-*p*-anisidine (**15**) is lithiated nearly exclusively ortho to the methoxy group to give **16**.[11]



When 1 equiv of *n*-BuLi is added to a toluene-d_8 solution of *N*,*N*-dimethylaniline (**14**), a pronounced downfield shift ($\Delta\delta$ 0.2) is observed for the ortho protons. The other hydrogen resonances remain essentially unchanged. As in the former examples, ^{6}Li,^{1}H HOESY shows cross peaks (and, hence, close contacts) between ^{6}Li and the ortho and the NMe_2 protons (Figure 6a). In the ^{13}C-NMR spectrum effects similar to those found for anisole are observed. The *n*-butyl data are those expected for a *n*-BuLi tetramer (Table V). This suggests the presence of a 4-fold

(44) The ^{1}H NMR chemical shifts of the aromatic protons in this 1:1:1 thioanisole (**8**)–*n*-BuLi–TMEDA mixture (cf. Figure 5b) are somewhat different from those of pure **8** and are less well resolved. However, the ^{13}C NMR spectrum clearly indicates the presence of free **8** and shows no detectable amount of metalation products.

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(47) Dietrich, H.; Mahdi, W.: Storck, W. *J. Organomet. Chem.* **1988**, *349*, 1. Harder, S.; Boersma, J.; Brandsma, L.; van Heteren, A.; Kanters, J. A.; Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 7802.

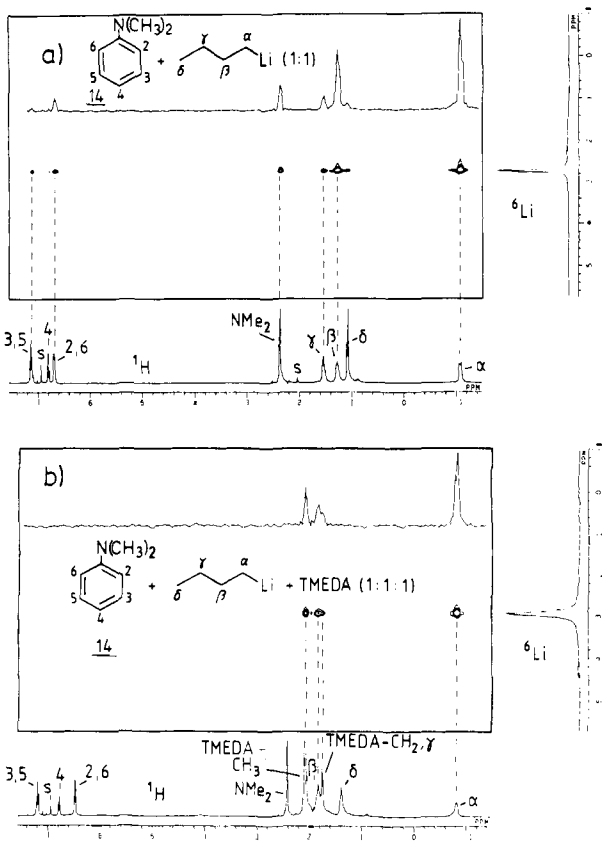


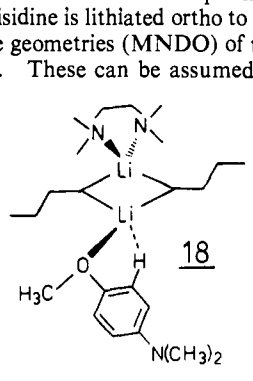
Figure 6. Phase-sensitive $^6Li,^1H$ HOESY (toluene-d_8, −64 °C) (a) of a *N,N*-dimethylaniline (**14**)–*n*-BuLi 1:1 mixture and (b) of a *N,N*-dimethylaniline (**14**)–*n*-BuLi–TMEDA 1:1:1 mixture (ca. 0.5 M **14**). Inserts: f_1 – traces of the ^6Li signals; spectral parameters, see Experimental Section; s = solvent signal.

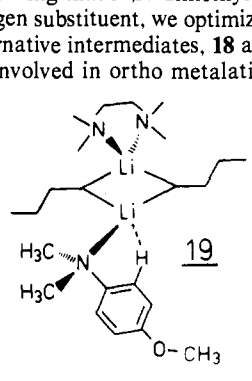
tetracoordinate species analogous to **3** (Scheme II).

After addition of 1 equiv of TMEDA, the ^1H NMR, the $^6Li,^1H$ HOESY (Figure 6b), and the ^{13}C NMR spectra (Table V) indicate "free" **14**. The *n*-BuLi ^{13}C NMR chemical shifts agree with those for dimeric *n*-BuLi. Hence, we conclude that the lithiation of *N,N*-dimethylaniline (**14**) with *n*-BuLi in the presence of TMEDA also follows the mechanism proposed in Scheme III.

The assumed reactive intermediate **17** for the lithiation of **14** was calculated by using MNDO (Figure 7). The "activation" of one ortho-hydrogen atom that is in vicinity of lithium is even stronger than that in the analogous anisole–*n*-BuLi complex (cf. Figure 4): the distance between the activated proton and Li is shorter, the charge at hydrogen is higher, the corresponding C–H bond is longer, and the C–H bond order is lower in **17** as compared to **3**.

To rationalize the experimental finding that *N,N*-dimethyl-*p*-anisidine is lithiated ortho to the oxygen substituent, we optimized the geometries (MNDO) of the alternative intermediates, **18** and **19**. These can be assumed to be involved in ortho metalation





and are analogous to **7** (Scheme III). One hydrogen atom is activated similarly in both **18** and **19** (shorter hydrogen–lithium distance, higher charge at hydrogen, lower C–H bond order, and a larger C–H distance of the activated hydrogen atom as compared

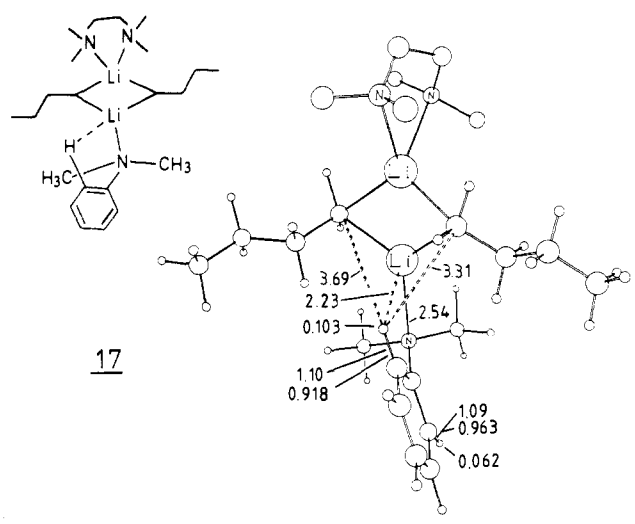
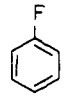


Figure 7. MNDO structure **17** of the hypothetical intermediate $(n\text{-BuLi})_2$–TMEDA–$PhNMe_2$. For explanation, see Figure 3; $\Delta H_f° = -67.03$ kcal/mol.

to its nonactivated ortho counterpart). However, intermediate **18** (in which an oxygen is bound to lithium) was found to be 3,05 kcal/mol more stable than **19**. The dipolar interaction of oxygen with lithium in **18** is more favorable than the dipolar interaction between nitrogen and lithium in **19**.

Fluorobenzene (20). Fluorobenzene is known to undergo facile ortho lithiation.[4,48,49] However, this has been ascribed more to



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the inductive effect of fluorine rather than to its complexing abilities.[11a,b] When both fluorine and oxygen are present as metalation directing groups in the same molecule (e.g., *p*-fluoroanisole), lithiation takes place mainly ortho to the oxygen substituent.[11a,b]

After addition of 1 equiv of *n*-BuLi to a toluene-d_8 solution of **20**, the ^1H NMR spectrum of the aromatic ring remains completely unchanged. The $^6Li,^1H$ HOESY experiment shows no trace of cross peaks between ^6Li and hydrogens of **20**. The ^{13}C NMR spectrum reveals the signals of free fluorobenzene and the presence of *hexameric n*-BuLi. This is expected for *n*-BuLi in apolar solvents without any ligand, Thus, fluorobenzene does not form a detectable amount of a complex with BuLi; the weak donor properties of **20** are confirmed. When 1 equiv of TMEDA is added, the ^1H and ^{13}C NMR spectra at −64 °C still show the presence of free fluorobenzene. Consistent with the experiments described above, dimeric *n*-BuLi is present under these conditions. However, even when kept at low temperature, this mixture metalates fluorobenzene slowly (ca. 50% conversion after 6 h at −54 °C).

The MNDO calculation of a possible lithiation intermediate (**21**) analogous to **7** (Scheme III) is shown in Figure 8. In contrast to the analogous calculations of Figures 3 and 7, the ortho-hydrogen atoms of fluorobenzene do not show evidence for activation. Both ortho protons are quite remote from lithium. The C-(ipso)-F-Li arrangement is essentially linear, i.e., neither hydrogen atom bends toward lithium. Thus, the MNDO calculations confirm that the directed ortho lithiation of fluorobenzene may

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(51) Thiel, W.; Clark, T. Unpublished (see the MNDOC Program: Thiel, W. Quantum Chemistry Program Exchange, No. 438).

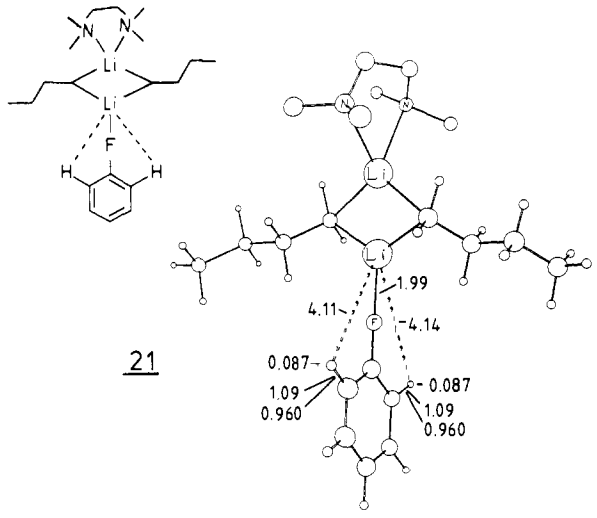

Figure 8. MNDO structure **21** of the hypothetical intermediate (n-BuLi)$_2$–TMEDA–PhF. For explanation, see Figure 3; $\Delta H_f°$ = −144.46 kcal/mol. All distances between ortho hydrogen atoms and α-carbon atoms of n-BuLi are larger than 5.2 Å.

be dominated by the strong inductive effect of fluorine.

Conclusions

Strongly bound complexes have been demonstrated to exist between n-BuLi and the ortho-directing groups of some aryl compounds in toluene solutions. However, ortho lithiation does not take place simply because of the close proximity of n-BuLi and the educts in these complexes. Rather, dimeric n-BuLi (formed in the presence of TMEDA) is found to be much more reactive than tetrameric n-BuLi. Under these conditions facile ortho lithiation occurs although no detectable amounts of complexes between dimeric n-BuLi and the educts are found. We believe that lithium with *more than one* accessible coordination site (as in dimeric n-BuLi) is an important prerequisite for effective lithiation. Under these conditions additional hydrogen activation by lithium may facilitate the reaction. This postulate is supported by MNDO calculations. However, an additional factor that may become dominant is the strong inductive effect of electronegative groups such as F and CF_3.

The extra stabilization of the ortho-lithiated products over their meta and para analogues (see the introduction) provides an additional driving force. Hence, both kinetic and thermodynamic factors are believed to facilitate ortho lithiation of aromatic compounds with appropriate substituents.

Experimental Section

All NMR spectra were recorded on a JEOL GX400 spectrometer using 5-mm sample tubes and a 10-mm mutinuclear probe head. Measuring frequencies were 399.8 MHz (^{1}H), 100.6 MHz (^{13}C), and 58.8 MHz (^{6}Li). ^{1}H and ^{13}C spectra were referenced to the solvent (toluene-d_8) signals: δ 2.03 (^{1}H, –CHD_2) and δ 125.2 (^{13}C, para carbon). ^{6}Li spectra are referenced to external 1 M LiBr (anhydrous) in THF; the reference measurements were carried out separately before the individual measurements at the reported temperatures. No corrections for different magnetic susceptibilities were made.

One-dimensional proton, carbon, and lithium spectra were recorded with the instrumental parameters described elsewhere.[21,26] Typical parameters of ^{6}Li,^{1}H HOESY experiments were spectral width 400 Hz (f_2 = ^{6}Li) and 3590 Hz (f_1 = ^{1}H), 128 increments in t_1 with 16 scans per increment, one times zero filling in t_1, mixing time 2.0 s, and either exponential line broadening in both dimensions for phase-sensitive spectra or exponential line broadening in t_2 and Gaussian window in t_1 for absolute value spectra. For a more detailed description of absolute value and phase-sensitive ^{6}Li,^{1}H HOESY, see ref 25.

All manipulations involving lithioorganic compounds were carried out in flame-dried glassware. Solvents and reagents (Aldrich, usually highest available purity) were distilled from calcium hydride (TMEDA) or used without further purification and were dried over sodium–lead alloy or calcium hydride.

Typical Sample Preparation. Anisole (75.8 mg, 0.7 mmol) is introduced into a 5-mm NMR tube fitted with a serum cap. Toluene-d_8 (0.35 mL) is added. In a separate small flask, 0.3 mL (0.75 mmol, 2.49 M in hexane) of n-Bu^{6}Li[28] is placed, and the solvent is removed. The residual oil is dissolved in 0.3 mL of toluene-d_8 and transfered to the cooled (−78 °C) anisole solution. After completion of the NMR measurements 0.076 mL (0.7 mmol) of TMEDA is added slowly at −78 °C by means of a syringe and the solution is then mixed carefully at low temperatures.

MNDO calculations were carried out on a CONVEX C120 computer using the VAMP (vectorized AMPAC[50]) program. For the lithium parameterization, see ref 51.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, by the Fonds der Chemischen Industrie, by the Volkswagenstiftung, and by the Convex Computer Corp. We thank A. Streitwieser, P. Beak, and G. Fraenkel for helpful discussions and T. Clark for the vectorized MNDO program (VAMP). We are indebted to the referees for helpful comments.

Registry No. 1, 100-66-3; **8**, 100-68-5; **12**, 151-10-0; **14**, 121-69-7; **20**, 462-06-6; TMEDA, 110-18-9; n-BuLi, 109-72-8; n-BuLi hexamer, 15036-82-5.