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Mechanisms of Competitive Ring-Directed and Side-Chain-Directed Metalations in Ortho-Substituted Toluenes

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Heteroatom-directed metalation reactions of aromatic compounds are complicated by the presence of an ortho CH_3 group or side chain as a second possible metalation site. We have employed *ab initio* calculations (Becke3LYP 6-311++G**//HF 6-31G* + ΔZPE (6-31G*) to study the preferred site of lithiation of three ortho-substituted toluenes (o-$CH_3C_6H_4OH$ (**13**), o-$CH_3C_6H_4NH_2$ (**21**), and o-$CH_3C_6H_4F$ (**28**)) with LiH as a model metalation reagent. The results are compared with the ring and side chain lithiations of toluene (**7**). The acidity of the hydrogen which undergoes exchange does not explain the regiochemistry. The preferred site for lithiation is governed by the stabilization of the transition state, rather than by the initial complexation: electrostatic dipole effects and enhanced intramolecular interaction of the metalating reagent with the substituent groups in the transition states are responsible. The complexation energies of lithium hydride with toluene, *o*-hydroxytoluene, *o*-aminotoluene, and *o*-fluorotoluene are −11.8 kcal/mol (**8**; $C_6H_5CH_3{-}LiH$ π-complex), −14.6 kcal/mol (**14**, o-$CH_3C_6H_4OH$-LiH, coordinated to O), −15.6 kcal/mol (**15**, o-$CH_3C_6H_4OH{-}LiH$, coordinated to O with agostic interaction to $-CH_3$), and −11.9 kcal/mol (**16**; o-$CH_3C_6H_4OH{-}LiH$ π-complex). We could only locate one type of σ complex, both for *o*-fluorotoluene and *o*-aminotoluene (*o*-toluidine). The binding energies are −15.9 kcal/mol (**22**; o-$CH_3C_6H_4NH_2{-}LiH$) and −10.8 kcal/mol (**29**; o-$CH_3C_6H_4F{-}LiH$), respectively. The related π complexes are less stable than the σ structures with energies of −14.1 kcal/mol (**23**; o-$CH_3C_6H_4NH_2{-}LiH$) and −9.2 kcal/mol (**30**; o-$CH_3C_6H_4F{-}LiH$). The activation barriers for toluene, relative to the separated species, are as follows: for ortho metalation (**9**), 15.5 kcal/mol; for methyl lithiation (**10**), 4.4 kcal/mol. When substituents are present, the activation barriers are reduced significantly: for X = OH, 4.4 kcal/mol (**17**; TS_{ortho}) and 1.3 kcal/mol (**18**; TS_{CH_3}); for X = NH_2, 6.6 kcal/mol (**24**; TS_{ortho}), and −1.3 kcal/mol (**25**; TS_{CH_3}); for X = F, 6.6 kcal/mol (**31**; TS_{ortho}) and 3.4 kcal/mol (**32**; TS_{CH_3}). Benzylic lithiation of toluene is calculated to be −2.0 kcal/mol exothermic (**12**); however, ortho metalation is 6.8 kcal/mol endothermic (**11**). Both ortho and side chain lithiations in substituted toluenes are exothermic: X = OH, ortho −5.9 kcal/mol (**19**), −6.7 kcal/mol (**20**; CH_3); X = NH_2, −3.8 kcal/mol (**26**; ortho), −8.9 kcal/mol (**27**; CH_3); X = F, −7.5 kcal/mol (**33**; ortho), −4.1 kcal/mol (**34**; CH_3). Since benzyl derivatives with different alkali metals have different structural preferences, substituent interactions vary. The effects of ortho substituents X (X = NH_2, OH, F) in benzyl and in phenyl alkali-metal compounds (M = Li, Na, K) were computed with the 6-31G* basis set for Li, Na, H, C, N, O, and F and the pseudopotential method (9 VE ECP) for K. Becke3LYP 6-311++G**//6-31G* +ΔZPE (6-31G*) calculations emphasize the importance of electrostatic interactions in phenyl alkali-metal compounds (the stabilization energies follow the electronegativity: N < O < F). The reverse order is calculated for the benzyl series, where the intramolecular interactions between the metal and X are most important.

Introduction

The regiospecific synthesis of polysubstituted aromatic compounds and their modification are important in preparative organic chemistry.[1] The classical electrophilic substitution reactions often must be carried out under relatively severe conditions and give mixtures of positional isomers. In contrast, metalation (*i.e.* the reaction of "acidic" hydrocarbons with organometallic compounds) provides a convenient method for introducing new functionalities at specific positions under mild conditions.[2] The organolithium intermediates react with a variety of electrophiles easily. In the late 1930s Wittig[3] and Gilman[4] discovered independently that metalation of anisole with *n*BuLi preferentially takes place at the ortho position. They pioneered the development of a new aromatic substitution chemistry ("neue

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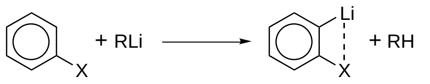
Aromatenchemie"),[5] based on the "ortho directed metalation reactions" (eq 1).



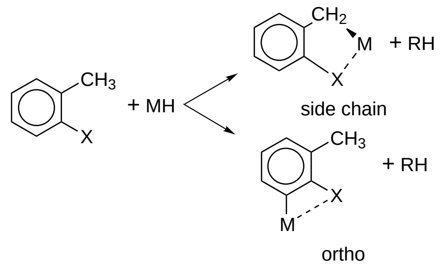
(1)

X = R_2NSO_2, $ArSO_2$, $CONR_2$, CH_2NMe_2, OAr, OMe, NMe_2, F, CF_3, etc.

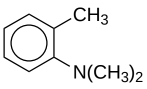
Fundamental reactivity studies by Gilman[6] and later by Hauser,[7] Slocum,[8] and Roberts and Curtin,[9] as well as by Beak[10] and Snieckus,[1a] extended the scope of the directing substituents X.[11] These substituents not only influence the regiochemistry but also accelerate the reaction. *o*-Lithioanisole forms readily with *n*BuLi and anisole under conditions where benzene is unreactive. The first mechanistic interpretation, by Roberts and Curtin,[9] suggested that complexation of the metal to a lone pair of the substituent would bring the metal in the vicinity of the ortho hydrogens and thus facilitate reaction with the carbanion moiety. Later, Beak and Meyers coined the term "complex induced proximity effect" for this phenomenon.[10] However, Roberts and Curtin already had admitted that their explanation "is not completely satisfactory".[9] For example, CF_3 groups activate ortho positions effectively but are unlikely to complex lithium reagents well. There also is a paradox: strong complexation should induce a high regioselectivity—but the complexation energy would have to be overcome in order to reach the transition state. Hence, low reactivity would be expected, but this does not agree with experimental observations.

NMR studies by Bauer showed that complexation between substrate and metalating reagent can indeed be counterproductive.[12] A complex of anisole with *n*BuLi in toluene-d_8 is demonstrated by HOESY, but this complex is unreactive, even at room temperature. Reaction occurs readily, even at low temperatures, in the presence of TMEDA, but anisole complexation could not be detected under these conditions. On the basis of Bauer's NMR studies and on *ab initio* calculations, van Eikema Hommes and Schleyer stressed an alternative explanation for ortho-directed metalations. To emphasize the importance of transition state stabilization rather than initial complexation, they proposed the term "kinetically enhanced metalation" instead of "complex induced proximity effects".[13]

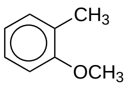
The presence of benzylic hydrogens in a methyl group ortho to the metalation-directing substituent introduces an alternative reactive site for metalation.[11] Depending on the nature of X and the actual metalating reagent, ortho- or benzylic-metalated products may dominate (eq 2).



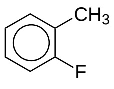
Side chain directed metalations have found useful applications in the synthesis of condensed heterocyclic compounds.[2,11] The predominating site of metalation, however, cannot be predicted easily. Different metalating conditions must be applied to obtain the desired regiochemistry. The substituted toluenes **A** (X = $N(CH_3)_2$), **B** (X = OCH_3), and **C** (X = F) are especially intriguing literature examples.



A

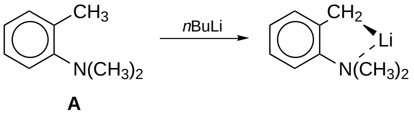


B

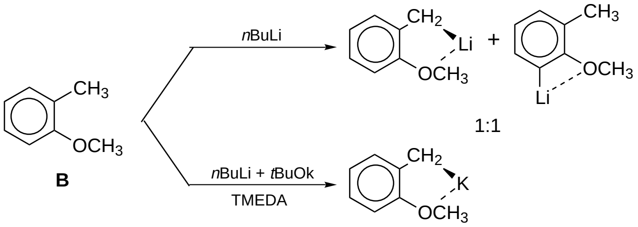


C

The methyl group of **A** is metalated regiospecifically under various conditions, e.g. by *n*BuLi/TMEDA in hexane.[14] Manzer showed that benzylic metalation is also possible in the absence of TMEDA, but at 20 °C in a mixture of hexane and Et_2O the reaction time requires about 2 days.[15] Brandsma reported that the benzylic metalation of **A** is considerably faster than the ortho metalation of *N*,*N*-dimethylaniline and that a equimolar mixture of *n*BuLi, *t*BuOK, and TMEDA in hexane leads to complete potassiation at the CH_3 group in only 1 h.[16]



In contrast to the case for **A**, the metalation of **B** gives a variety of results. Schinzer reacted **B** with *n*BuLi in ether and found ortho and side chain carboxylation products in "equal amounts".[17] Treatment of **B** with *n*BuLi and TMEDA in hexane gave about 75% ortho and 25% benzylic lithiation. Prolonged refluxing decreases



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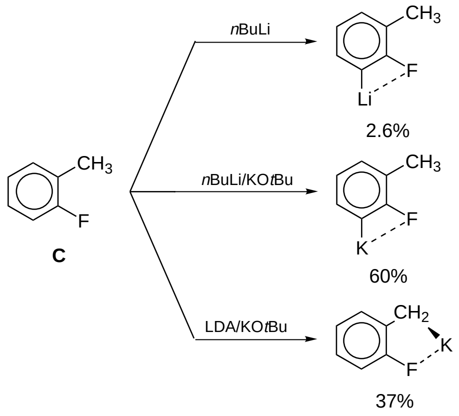
the ratio of ring to side chain metalated products. Using *t*BuLi in alkane solvents gave both isomers in about equal amounts.[18] However, a predominantly benzylic-metalated product was reported, with superbasic mixtures of *n*BuLi, *t*BuOK, and TMEDA.[16c] The ratio of ortho to benzylic product is sensitive to the actual base employed.

The tendency of ortho-lithiated phenyl fluorides to eliminate LiF above −45 °C, to form benzyne (which gives rise to a number of subsequent side products), necessitates handling *o*-(alkali-metal)phenyl fluorides at lower temperatures.[16] Consequently, this complicates direct comparisons of the metalations of **A**−**C**.



Nevertheless, trends are obvious. Gilman reacted **C** with *n*BuLi in THF for 7 h at −50 °C. After quenching with CO_2, the only product was 3-methyl-2-fluorobenzoic acid (i.e. via the ortho-lithiated intermediate). However, the yield was only 2.6%.[19] Schlosser improved the yield of the ortho-lithiated species: at −75 °C superbasic mixtures of *n*BuLi and KO*t*Bu yield 60% acid after carboxylation.[20] Schlosser also was able to deprotonate the benzylic protons selectively by employing a stoichiometric mixture of lithium diisopropylamide and KO*t*Bu. After trapping with carbon dioxide, the only product was *o*-(fluorophenyl)acetic acid (37% yield).[20]

The difference in metalations of **A**−**C** cannot be explained easily. Experimental mechanistic studies are complicated by the tendency of alkali-metal compounds to aggregate to solvate, as well as by their high reactivity and extreme oxygen and moisture sensitivity. Only a few semiempirical mechanistic studies of the regioselectivity of lithiating reactions have been reported.[21,22b] The recent PM3[23] and MNDO[24] calculations of Anders and co-workers on competitive reactions involving two differently hybridized carbon centers (*e.g.* on the lithiation of toluene) gave results contrary to experiment and our *ab initio* calculations.[22b]

Ab initio methods[25] should be more reliable for model mechanistic and structural studies of alkali-metal organic compounds.[26] The present paper extends our earlier investigations on directed lithiations[13] to the problem of regioselectivity. We used three different, experimentally well examined model substrates: *o*-hydroxytoluene (as the model for *o*-methoxytoluene **B)**, *o*-aminotoluene (as the model for *N*,*N*-dimethyl-*o*-toluidine **A**), and *o*-fluorotoluene (**C**). As a metalating agent we employed LiH (as a monomer model organolithium reagent). Of course, geometries were employed so that the OH and NH groups did not "react" with the metalating reagents.

As acidity also may be important in the regiochemistry of hydrogen abstraction, the relative acidities of ortho-substituted benzenes (C_6H_5X; X = H, NH_2, OH, F) and ortho-substituted toluenes (*o*-$CH_3C_6H_4X$; X= H, NH_2, OH, F) were computed.

As the metal employed may determine the observed regiochemistry,[16] we computed the stabilization energies of ortho-substituted phenyl Li, Na, and K compounds. The results were compared with the stabilization of *o*-NH_2, *o*-OH, and *o*-F-substituted benzyl alkali-metal species.

Density functional theory includes electron correlation effects to some extent and is now widely used.[27] Consequently, we also examined the metalations of benzene and toluene, both of which have been calculated at the MP2 level,[13,22a] using the Becke3LYP functional for comparison and reference purposes.

Computational Methods

All calculations were performed using the Gaussian 92 DFT and Gaussian 94 program packages.[28] Geometries were first optimized at the RHF/6-31G* level using standard gradient

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techniques and were characterized as minima (NIMAG 0) or transition structures (NIMAG 1) by calculation of the vibrational frequencies. Corrections for zero point vibrational energy differences were scaled by 0.89.[25] Electron correlation effects were included in MP2-FC/6-31+G*, Becke3LYP/6-311+G*, and Becke3LYP/6-311++G** single-point calculations on the RHF-optimized geometries.[27] Atomic charges and bond orders were calculated using the Natural Population (NPA) and Natural Bond Orbital (NBO) analysis methods developed by Reed and Weinhold.[29]

As diffuse function augmented basis sets are essential to obtain reliable results on free anions,[25,30] all molecules in the study of acidity effects were optimized at RHF/6-31+G*. Again, the stationary points were established to be minima by frequency calculations at the RHF level. Becke3LYP single points using the 6-311++G** basis set at the RHF-optimized geometries and zero point energy correction gave the final energy estimates, which include electron correlation.

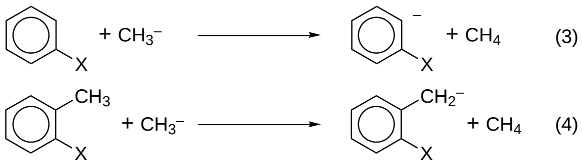
Compared to all-electron calculations, the use of pseudopotentials to replace core electrons for compounds of the heavier elements (e.g. K) diminishes the computational costs considerably.[31,32] In contrast to the lighter alkali metals, core polarizability is significant for the heavier alkali metals K−Cs.[33] Thus, for the comparative study of the metal effects we employed quasirelativistic nine-valence-electron (valence plus $n-1$ shell) effective core potentials (9-VE ECP) for K, as the larger frozen-core approximation leads to large errors in a 1-VE ECP treatment. The 6-31G* general basis set was used for Li, Na, H, C, O, N, and F (basis A). More flexible (3111/3111/1) (basis A) and (21111/21111/11) (basis B) valence basis sets optimized with pseudopotentials,[34a] including a single or a double set of uncontracted d functions from Huzinaga *et al*,[34b] were employed for K. All molecules were optimized at RHF basis A level and characterized as minima by frequency analysis. Electron correlation effects were considered by DFT single-point calculations on the RHF-optimized geometries. We used the 6-311++G** basis set for Li, Na, H, C, O, N, and F (basis B) and K pseudopotentials together with the (21111/21111/11) (basis B) valence basis set. The energies discussed in the text at the highest level of theory (Becke3LYP/basis B//RHF/basis A + ΔZPE (basis A, scaled by 0.89)) are our final estimates.

Results and Discussion

Relative Acidities. Since directed metalations proceed by metal−hydrogen exchange, the acidity of the substituted hydrogen might be significant (thermodynamic considerations). Fraser's pK_a values of some monosubstituted benzenes in THF provide evidence for the acidifying effect of an substituent on the ortho proton.[35] However, the lack of correspondence between these pK_a values and the substituent reactivity order (toward an alkyllithium reagent in ether) documents the predominant importance of kinetic factors in ortho-directed metalations. The effect of an ortho substituent on the acidity of toluene has not yet been determined experimentally. Hence, we calculated *ab initio* the relative acidities of ortho-substituted (X = H, NH_2, OH, F) benzenes and toluenes and evaluated the intrinsic stabilizing effects of X (eqs 3 and 4 and Table 1).

Table 1. Relative Acidities of Ortho-Substituted Benzene (eq 3) and Toluene (eq 4) Derivatives (kcal/mol)

	//RHF 6-31+G*	Becke3LYP 6-311++G** //6-31+G*	Becke3LYP 6-311++G** //6-31+G* + ΔZPE	exptl[36]
		Equation 3		
X = H	−19.5	−16.5	−15.6	−15.8
X = NH_2	−23.1	−21.1	−19.7	
X = OH	−21.8	−20.5	−19.5	
X = F	−31.4	−29.8	−28.7	−28.9
		Equation 4		
X = H	−31.3	−35.6	−35.2	−35.9
X = NH_2	−29.4	−34.7	−34.2	
X = OH	−34.5	−39.9	−39.4	
X = F	−34.7	−40.5	−39.5	



In contrast to the σ-phenyl carbanion, the benzyl anion is stabilized by π-electron delocalization to the aromatic ring and is about 20 kcal/mol more stable than the phenyl anion. Hence, toluene is more acidic than benzene. The calculated stabilization energies (Table 1) for both toluene and benzene reproduce the experimental values.[36] The ortho benzene substituent X stabilizes the related anion by inductive interactions. This is best for the substituent with the highest electronegativity (X = F), which results in the highest relative acidity. The influence of an ortho X substituent on toluene is less pronounced (see eq 4 and Table 1). The NH_2 group is destabilizing by about 1 kcal/mol relative to the unsubstituted benzyl anion. Both OH and F result in a stabilization of about 4 kcal/mol. Nevertheless, all *o*-X benzylic anions are more stable than the corresponding *o*-X phenyl anions.

According to the relative acidities in Table 1, directed metalations of ortho-donor-substituted toluenes always should take place at the side chain. However, this prediction is contrary to experiment. The relative directing ability of the various X groups also is different from the acidities. Fluorine should be a strong directing substituent. However, if both fluorine and oxygen directing groups are present in the same molecule (e.g. in *p*-fluoroanisole), lithiation takes place mainly ortho to the oxygen substituent.[37] The discrepancy between

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(36) (a) Wenthold, P. G.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 6401. (b) Lias, S. G.; Bartmess, J. E.; Liebmann, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1.

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Table 2. Energies, Relative to the Separated Reactants (kcal/mol)

species	//RHF 6-31G*	RMP2(FC) 6-31+G*//6-31G*	Becke3LYP 6-311+G*//6-31G*	Becke3LYP 6-311++G**//6-31G*	Becke3LYP 6-311++G**//6-31G* + ΔZPE
4, Cpx$_\pi$ C_6H_6−LiH	−15.7	−17.2	−10.0	−9.6	−8.2
5, TS C_6H_6/LiH	35.6	19.8	17.8	16.2	15.1
6, $C_6H_5Li + H_2$	16.4	4.7	9.6	9.1	6.4
X = H					
8, Cpx$_\pi$ $C_6H_5CH_3$−LiH	−16.5	−21.0	−13.6	−13.2	−11.8
9, TS$_{ortho}$ $C_6H_5CH_3$/LiH	36.2	20.9	18.0	16.4	15.5
10, TS$_{CH_3}$ $C_6H_5CH_3$/LiH	27.9	11.0	7.5	5.6	4.4
11, *o*-$C_6H_4LiCH_3 + H_2$	16.6	6.4	10.0	9.5	6.8
12, $C_6H_5CH_2Li + H_2$	12.8	1.1	2.2	0.8	−2.0
X = OH					
14, Cpx$_{ortho}$ $C_6H_4CH_3OH$−LiH	−19.6	−19.0	−16.8	−15.8	−14.6
15, Cpx$_{CH_3}$ $C_6H_4CH_3OH$−LiH	−19.9	−20.0	−18.0	−17.0	−15.6
16, Cpx$_\pi$ $C_6H_4CH_3NH_2$−LiH	−16.1	−18.2	−13.6	−13.3	−11.9
17, TS$_{ortho}$ $C_6H_4CH_3OH$/LiH	22.7	6.7	6.2	5.3	4.4
18, TS$_{CH_3}$ $C_6H_4CH_3OH$/LiH	21.2	5.5	3.6	2.1	1.3
19, $C_6H_3LiOHCH_3 + H_2$	2.7	−9.5	−3.7	−3.4	−5.9
20, $C_6H_4OHCH_2Li + H_2$	5.3	−6.6	−3.2	−3.8	−6.7
X = NH_2					
22, Cpx $C_6H_4CH_3NH_2$−LiH	−21.8	−21.7	−18.5	−17.7	−15.9
23, Cpx$_\pi$ $C_6H_4CH_3NH_2$−LiH	−18.4	−20.6	−15.9	−15.5	−14.1
24, TS$_{ortho}$ $C_6H_4CH_3NH_2$/LiH	22.0	7.4	7.7	6.9	6.6
25, TS$_{CH_3}$ $C_6H_4CH_3NH_2$/LiH	18.0	1.7	0.5	−0.8	−1.3
26, $C_6H_3LiNH_2CH_3 + H_2$	2.0	−8.1	−1.9	−1.5	−3.8
27, $C_6H_4NH_2CH_2Li + H_2$	2.0	−10.8	−6.0	−6.6	−8.9
X = F					
29, Cpx $C_6H_4CH_3F$−LiH	−15.1	−13.6	−11.9	−11.8	−10.8
30, Cpx$_\pi$ $C_6H_4CH_3F$−LiH	−13.6	−15.3	−10.8	−10.5	−9.2
31, TS$_{ortho}$ $C_6H_4CH_3F$/LiH	23.4	7.6	9.2	7.6	6.6
32, TS$_{CH_3}$ $C_6H_4CH_3F$/LiH	24.7	10.0	6.8	4.6	3.4
33, $C_6H_3LiFCH_3 + H_2$	1.8	−10.4	−4.5	−4.9	−7.5
34, $C_6H_4FCH_2Li + H_2$	7.5	−3.1	0.3	−1.0	−4.1

the acidities and experimentally observed metalation sites emphasizes the importance of kinetic factors both in ortho-directed and in side-chain-directed metalations.

Mechanisms of Directed Metalations. Deeper insights into the mechanisms of directed metalations would extend the practical applications of this reaction. The reaction pathway in directed metalations begins with the initial complexes (see Table 2 for the energies relative to the separated species). The structures of the initial complexes are shown in Figure 1; the transition states are depicted in Figure 2. The relative energies of the reactions discussed in the text are summarized in Figures 3−6.

Initial Complexes. LiH forms η^6 complexes both with benzene (**3**) and with toluene (**7**); the binding energies are −8.2 kcal/mol (**4**) and −11.8 kcal/mol (**8**), respectively. The previously reported MP2 bonding energies for such η^6 complexes[13] are systematically too negative (due, perhaps, to basis set superposition errors, BSSE). Becke3LYP data, however, seem to describe the bonding more reliably.

We optimized two different complexes for the ortho-substituted toluenes: (a) σ-complexes between lithium and a lone pair on X and (b) π-complexes between the aromatic ring and the metal. For *o*-hydroxytoluene (**13**), we located two different σ-complexes, **14** and **15**. The latter is 1 kcal/mol more stable and shows an agostic interaction of lithium with the benzylic hydrogens (indicated by the relatively short Li−H distance of 2.531 Å). A rotation of the CO bond interconverts **15** into **14**, which has no agostic interaction with the ortho hydrogen (r(Li···H) = 3.185 Å). If complex-induced proximity effects were important in the directed metalation of methylanisole, one would expect, contrary to experiment, mainly a side-chain-lithiated product. For both X = NH_2 (**21**) and X = F (**28**) we could only locate one type of σ-complex, **22** and **29**, which show no agostic interactions at all. The amino group has the largest complexation energy of all the molecules in our study; amines generally complex somewhat better than ethers.[38] The interaction of LiH with *o*-fluorotoluene is only exothermic by −10.8 kcal/mol, due to the low complexing ability of fluorine. The almost linear C−F−Li−H arrangement in **29** suggests a predominately electrostatic interaction.

All the HLi-X σ-complexes are more stable than the alternative π-bound HLi-aromatic structures. MP2 overestimates the π-interaction. At the MP2/6-31+G*//RHF 6-31G* level the π-bonded structure **30** is −1.7 kcal/mol more stable than the σ alternative **29** (see Table 2); the RHF and Becke3LYP levels give the opposite ordering.

Transition Structures. The activation barrier for benzene lithiation (**5**) is 15.1 kcal/mol, relative to the separated reagents (see Table 2). For toluene, the energies are 15.5 kcal for ring metalation (**9**) and 4.4 kcal/mol for benzylic metalation (**10**). A substituent ortho to the methyl group reduces the transition state energy for ring metalation dramatically; for the side-chain reaction, this reduction occurs to a smaller extent. The activation energies are as follows: for X = OH, 4.4 kcal/mol (**17**; TS$_{ortho}$) and 1.3 kcal/mol (**18**; TS$_{CH_3}$); for X = NH_2, 6.6 kcal/mol (**24**; TS$_{ortho}$) and −1.3 kcal/mol (**25** TS$_{CH_3}$); for X = F, 6.6 kcal/mol (**31**; TS$_{ortho}$) and 3.4 kcal/mol (**32**; TS$_{CH_3}$).

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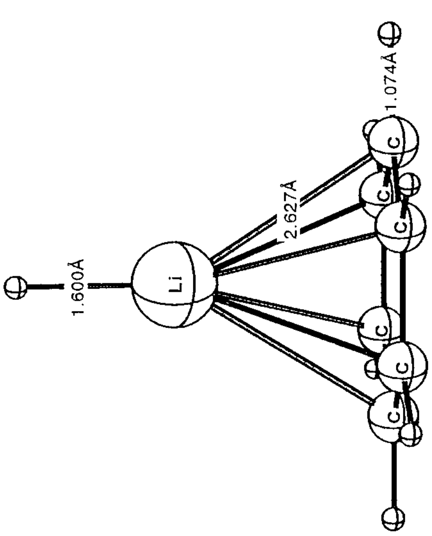
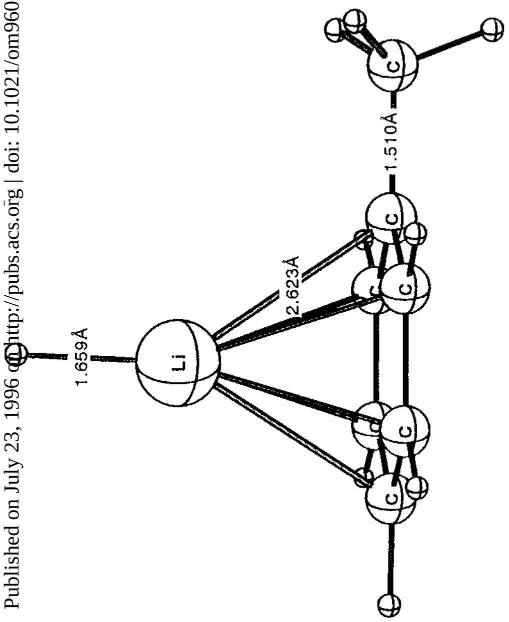
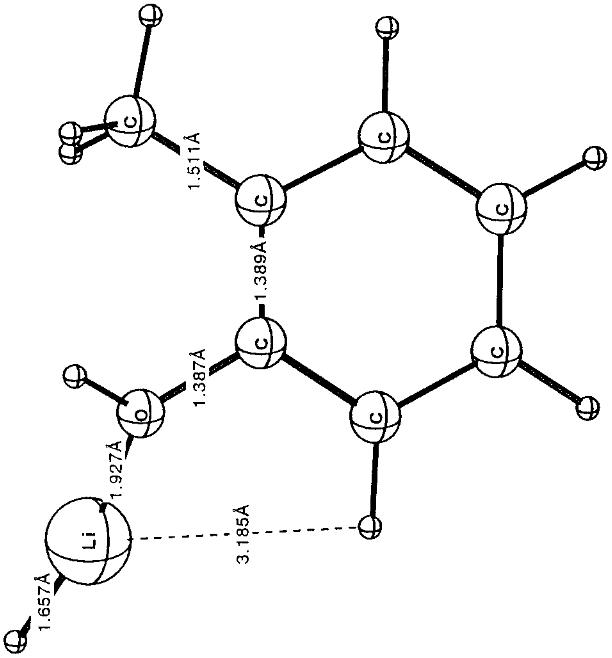


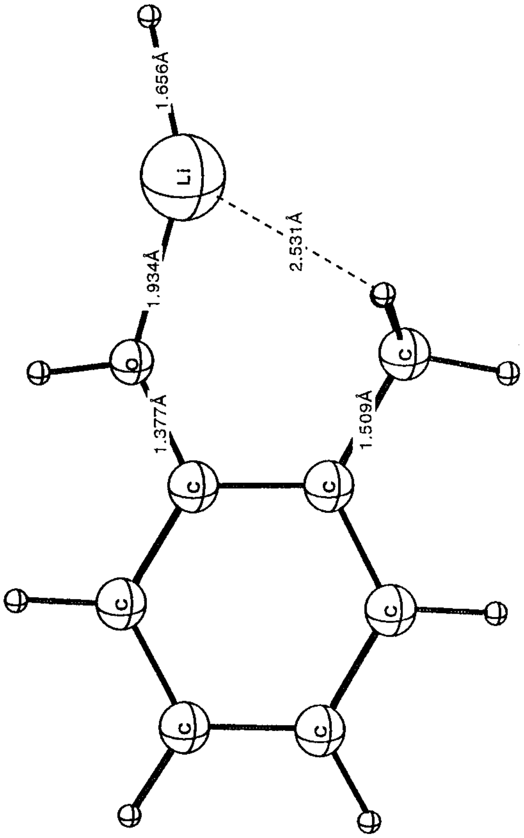
4, C_{6v}



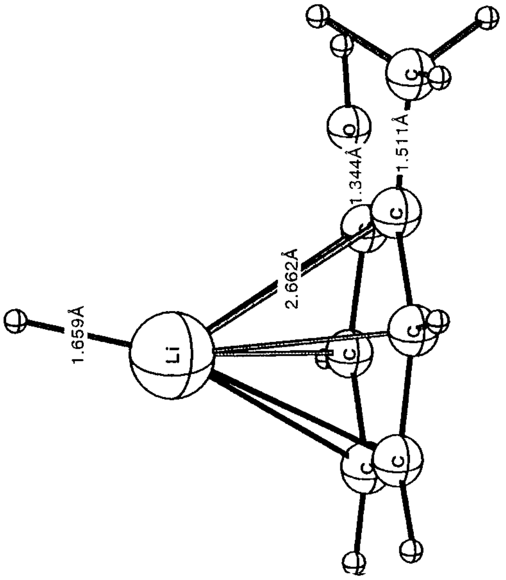
8, C_s



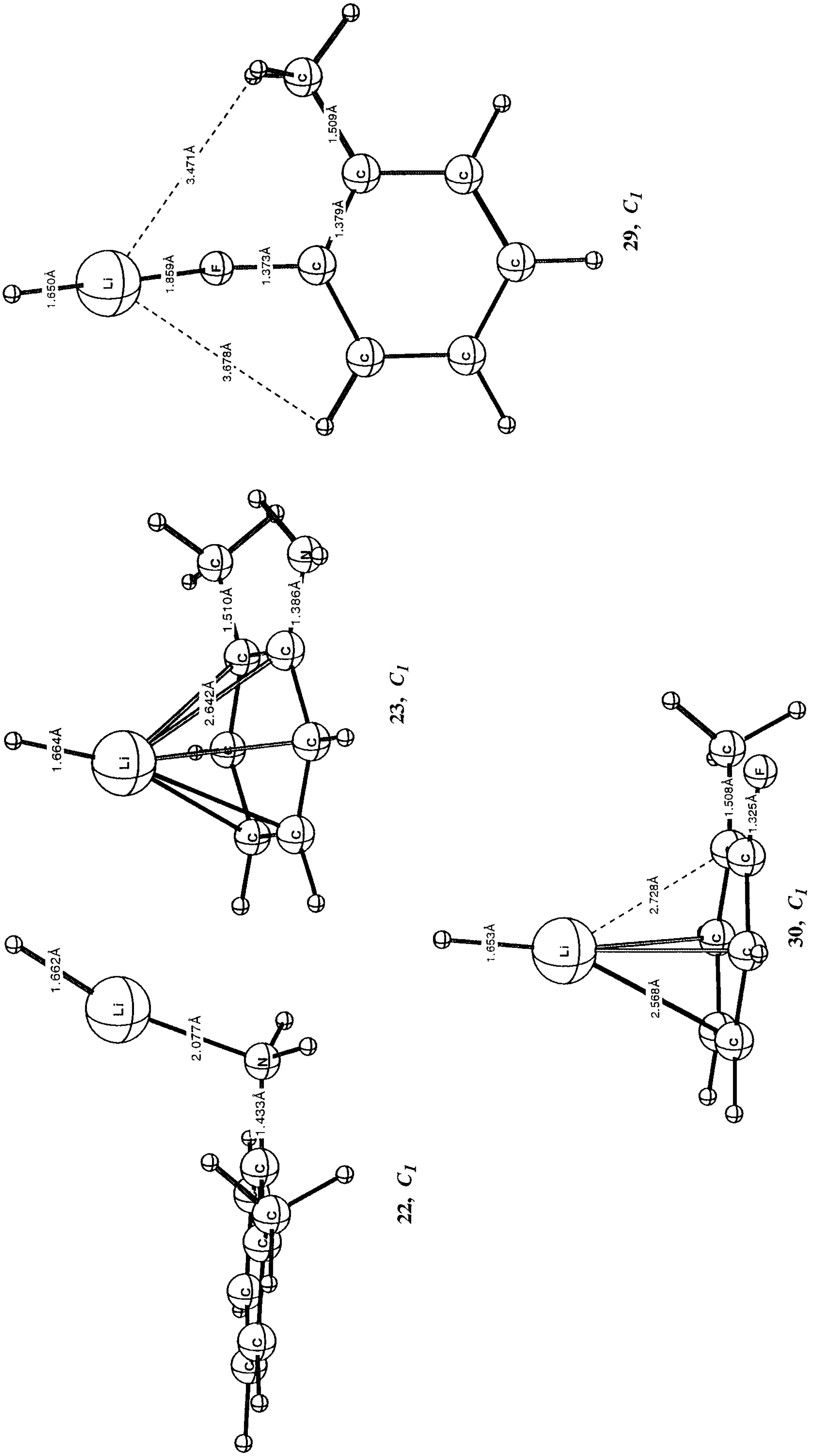
14, C_1



15, C_1



16, C_1



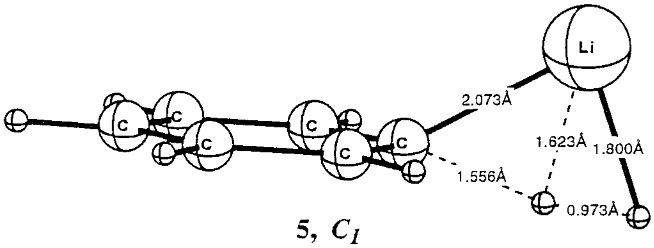
22, C_1

23, C_1

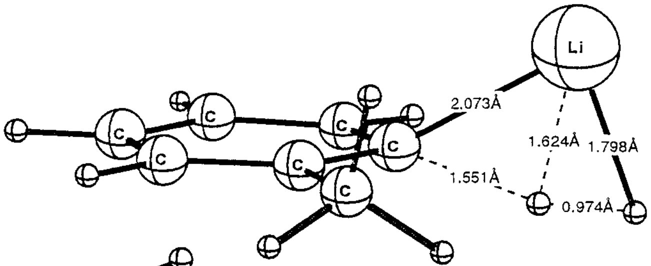
29, C_1

30, C_1

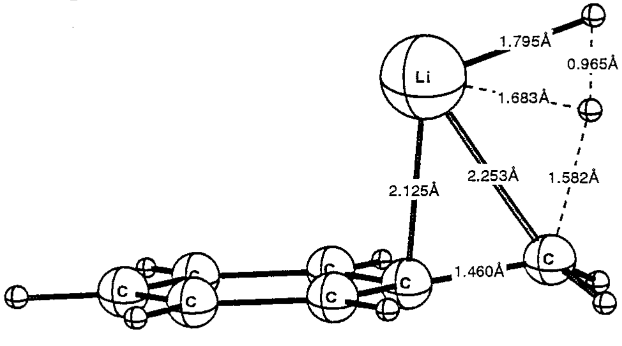
Figure 1. RHF 6-31G* optimized structures of the initial complexes of **3**, **7**, **13**, **21**, and **28** with LiH.



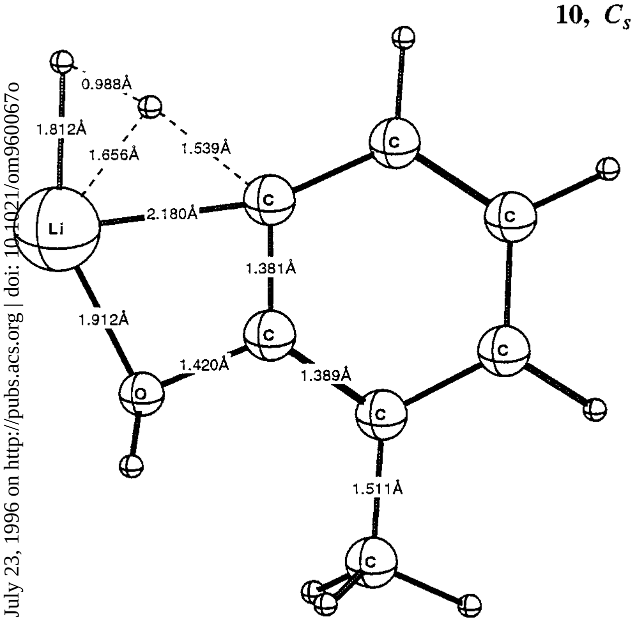
5, C_1



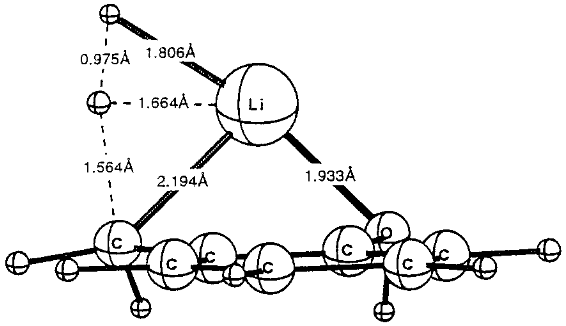
9, C_1



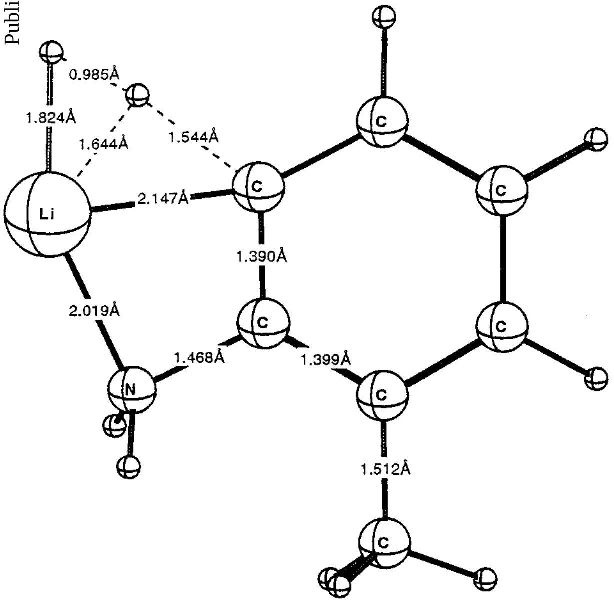
10, C_s



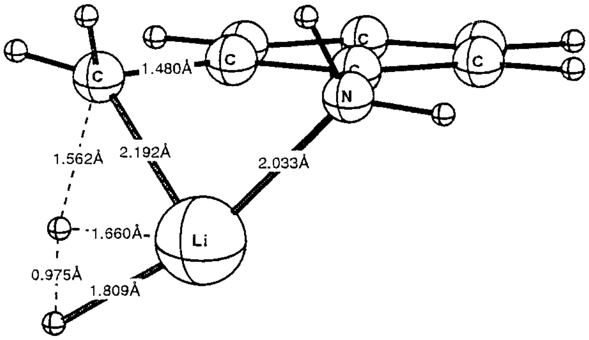
17, C_1



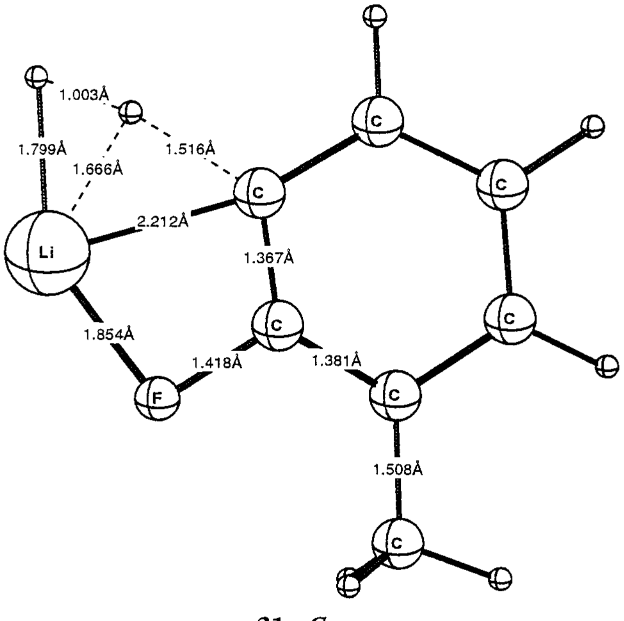
18, C_1



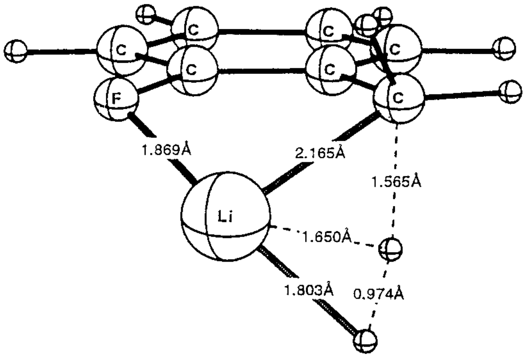
24, C_1



25, C_1



31, *C*₁



32, *C*₁

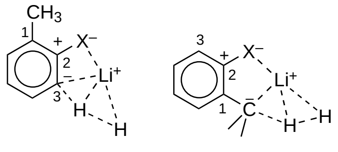
Figure 2. RHF 6-31G* optimized transition structures for the lithiation of **3**, **7**, **13**, **21**, and **28** with LiH.

The overall reaction energies (given in Table 2) show a similar trend. Ortho lithiation of benzene and toluene are endothermic by 6.4 (**6**) and 6.8 kcal/mol (**11**), respectively; benzylic metalation of toluene to give benzyllithium (**12**) is exothermic by −2.0 kcal/mol. When the ortho substituents are present, both ortho and side-chain metalations are exothermic. The energies are, for X = OH, −5.9 kcal/mol (**19**; ortho) and −6.7 (**20**; CH_3); *i.e.*, the relative energies of both reactions are similar. For X = NH_2 the benzylic lithiation (**27**) is exothermic by −8.9 kcal/mol, whereas the ortho-lithiated isomer (**26**) is less favorable by only −3.8 kcal/mol. With X = F ortho metalation (**33**) is the most exothermic by −7.5 kcal/mol; the alternative benzylic reaction (**34**) at −4.1 kcal/mol is also favorable.

The transition structures for the ortho metalation are strongly influenced by the substituent. In the transition structures for ortho lithiation of benzene and toluene (**5** and **9**), the C−Li−H−H groupings lie in the symmetry plane perpendicular to the benzene ring. In the TS structures for ortho lithiation of *o*-amino- (**24**), *o*-fluoro- (**31**), and *o*-hydroxytoluene (**17**), however, the C−Li−H−H groupings lie in the plane of the aromatic ring, since lithium interacts with X. The Li−X distances in these transition states are shorter than both in the complexes and in the products (compare Figures1−3). The shorter Li−X distance compensates for the effective lowering of the metal coordination due to the partial character of Li bonding in the transition state.

In the toluene (**10**) side-chain-metalation transition state, the C−Li−H−H group lies in the symmetry plane perpendicular to the benzene ring. The short $Li-C_{ipso}$ distance 2.125 Å (which actually is shorter than in benzyllithium (**12**), //RHF 6-31G*: 2.171 Å) partially compensates energetically for the lower metal coordination in the transition state. As in the ortho-directed metalations, the electronegative substituent X provokes significant structural changes in the transition state geometry. The strong $Li-C_{ipso}$ interaction is absent, as is shown by the greater 2.523 Å (**25**; X = NH_2), 2.531 Å (**18**; X = OH), and 2.964 Å (**32**; X = F) distances. The Li−X interactions are most important. The various substituents X in side-chain metalations, however, do not show unique behavior. The $Li-NH_2$ distance in the transition state (**25**) is shorter than in both the complexes (**22**) and in the products (**27**); the Li−O distances are almost unchanged throughout the reaction, and the Li−F distance in the TS (**32**) is 0.01 Å longer than in the complex (**29**) but is 0.02 Å shorter than in the product (**34**).

The NBO charges (see Tables 3 and 4) on lithium, the metalated carbon atom, the migrating hydrogen, and the hydride are very similar for each X in the same reaction type. The charges on all the migrating hydrogens are very low; hence, both directed metalations should be considered as hydrogen atom transfers (or as multicenter processes) rather than as proton transfer reactions. In the transition states for ortho directed metalations (**TS_{ortho}**), a electrostatically favorable arrangement of charges is provided by the (positive) lithium, the (negative) ipso carbon, the (positive) ortho carbon, and the (electronegative) substituent X. The electrostatic arrangements for the benzylic metalations (**TS_{CH_3}**) are not as good; C_1 is nearly uncharged, and the charges on Li, X, and the reacting hydrogens are slightly smaller than in the ortho-metalation transition structures. The difference in the charges on the carbon atoms being metalated is more pronounced. Whereas for the benzylic metalations, C_{CH_3} bears nearly a unit charge, the charges in the reacting carbons in the ortho metalation (C_2) are only about −0.5.



TS_{ortho} TS_{CH_3}

Role of the Metal. The X-ray structures of several ortho-lithiated phenyl ethers and phenylamines are known.[39] Short Li−N and Li−O distances indicate the

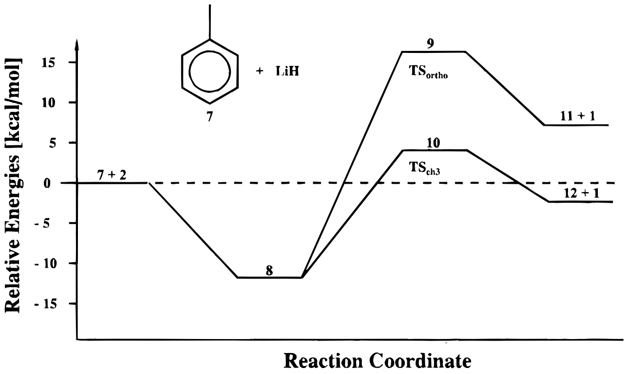


Figure 3. Reaction energies for the lithiation of toluene (**7**) with LiH (Becke3LYP 6-311++G**//RHF 6-31G* + ΔZPE).

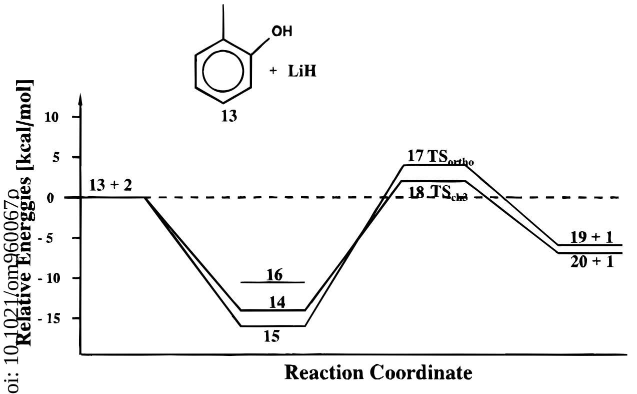


Figure 4. Reaction energies for the lithiation of *o*-hydroxytoluene (**13**) with LiH (Becke3LYP 6-311++G**//RHF 6-31G* + ΔZPE).

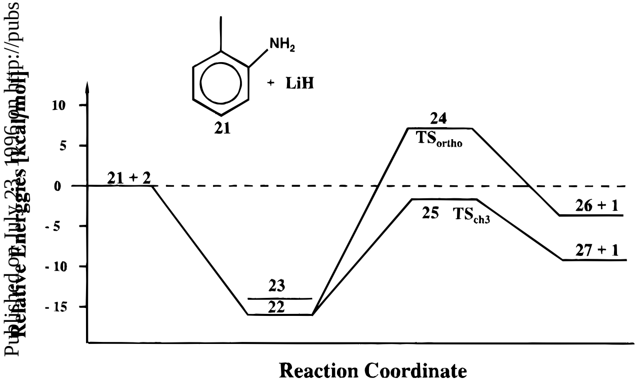


Figure 5. Reaction energies for the lithiation of *o*-aminotoluene (**21**) with LiH (Becke3LYP 6-311++G**//RHF 6-31G* + ΔZPE).

importance of intramolecular as well as intermolecular complexation. The reduced heats of protonation of ortho-lithiated benzenes (as compared to their para isomers) also show the stabilizing effect of an ortho donor substituent.[1b] Unfortunately, neither X-ray nor thermochemical studies on ortho-substituted benzyl–alkali-metal derivatives have been reported so far.

The nature of the metal may be decisive in directing the regiochemistry of a metalation reaction.[16] On the basis of the X-ray structures of alkali metals with delocalized π-electron systems as counterions (e.g. the fluorenyl anion), it can be assumed generally that alkali metals of different size may favor different positions above a delocalized carbanion.[26m,n,39,40] The larger cation prefers interaction with many centers; the smaller cation interacts with centers, where the charge is more localized. The importance of intramolecular complexation in ortho-substituted benzyl–alkali-metal derivatives has not yet been studied experimentally. Hence, we used *ab initio* calculations to evaluate (a) the preferred coordination site of different alkali metals (eq 5), (b) the stabilization of phenyl–alkali-metal compounds and of benzyl–alkali-metal compounds by ortho donor substituents (NH$_2$, OH, F) (eqs 6 and 7), and (c) the preferred metalation products if both the metal and the substituent are considered (eq 8). Selected NBO charges of the molecules calculated (depicted in Figure 7) are given in Table 5.

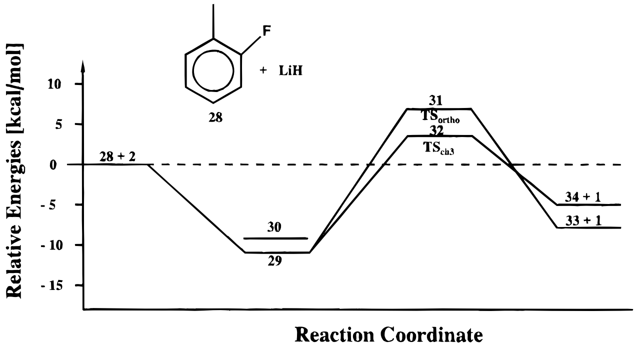
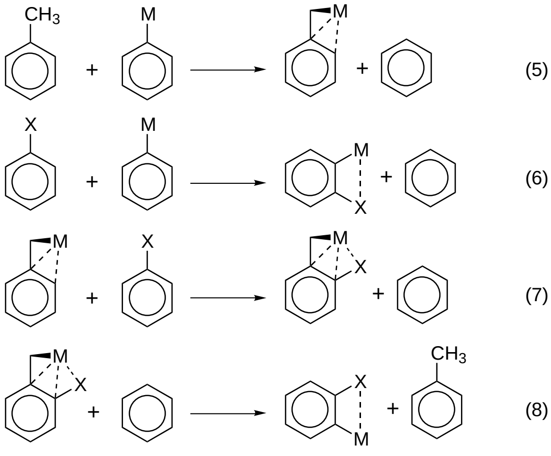


Figure 6. Reaction energies for the lithiation of *o*-fluorotoluene (**28**) with LiH (Becke3LYP 6-311++G**//RHF 6-31G* + ΔZPE).



Whereas the structures of the phenyl–alkali metal species (M = Li, Na, K) are very similar (C_{2v} isomers are the global minima),[40] the corresponding benzyl–alkali-metal compounds adopt different global minimum geometries: Li (**12**) is η^3, Na (**37**) η^2, and K (**38**) η^4-coordinated. In the MP2-optimized structures, Na (**37**) is η^4 and K (**38**) η^7-coordinated, interacting with all the carbon atoms.[41] As potential energy surfaces of ion pairs involving delocalized carbanions often are quite flat, especially with increasing metal to ring distance, different metal cation locations may be observed in the same compound.[42,43] Hence, the energies

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Table 3. NBO Charges in the Metalation of Toluene

molecule	C_1	C_2	C	$H(C_2)$	Li	H_1 (CH_3)	H_2 (CH_3)	H_3 (CH_3)	H(Li)
7, $C_6H_5CH_3$	−0.037	−0.237	−0.645	0.228		0.227	0.227	0.233	
8, Cpx_{π} $C_6H_5CH_3$-LiH	−0.046	−0.257	−0.652	0.251	0.673	0.239	0.239	0.241	−0.697
9, TS_{ortho} $C_6H_5CH_3$/LiH	−0.039	−0.569	−0.465	0.122	0.926	0.215	0.223	0.226	−0.377
10, TS_{CH_3} $C_6H_5CH_3$/LiH	−0.080	−0.180	−0.876	0.235	0.875	0.101	0.228	0.228	−0.324
11, *o*-$C_6H_4LiCH_3$	−0.088	−0.640	−0.637		0.908	0.218	0.208	0.208	
12, $C_6H_5CH_2Li$	−0.039	−0.418	−1.047	0.224	0.920		0.212	0.215	

Table 4. NBO Charges in the Metalation of Substituted Toluenes

molecule	C_1	C_2	C_3	$C(CH_3)$	X	Li	H_{ortho}	$H_1(CH_3)$	$H_2(CH_3)$	$H_3(CH_3)$	H(Li)	$H_1(X)$	$H_2(X)$
					X = OH								
13, *o*-$C_6H_4CH_3OH$	−0.138	0.374	−0.288	−0.659	−0.759		0.244	0.226	0.226	0.239		0.509	
14, Cpx_{ortho} $C_6H_4CH_3OH$−LiH	−0.103	0.352	−0.300	−0.656	−0.831	0.697	0.233	0.246	0.230	0.230	−0.713	0.532	
15, Cpx_{CH_3} $C_6H_4CH_3OH$−LiH	−0.095	0.317	−0.266	−0.656	−0.847	0.702	0.247	0.242	0.224	0.241	−0.716	0.533	
16, Cpx_{π} $C_6H_4CH_3OH$−LiH	−0.137	0.368	−0.304	−0.665	−0.747	0.673	0.264	0.255	0.256	0.252	−0.699	0.517	
17, TS_{ortho} $C_6H_4CH_3OH$/LiH	−0.105	0.263	−0.495	−0.649	−0.870	0.924	0.133	0.234	0.216	0.232	−0.389	0.522	
18, TS_{CH_3} $C_6H_4CH_3OH$/LiH	−0.047	0.217	−0.231	−0.933	−0.856	0.900	0.241	0.118	0.203	0.235	−0.354	0.526	
19, $C_6H_3LiOHCH_3$	−0.114	0.227	−0.600	−0.647	−0.879	0.909		0.230	0.233	0.212		0.516	
20, $C_6H_4OHCH_2Li$	−0.039	0.289	−0.294	−1.107	−0.848	0.894	0.218		0.205	0.218		0.520	
					X = NH_2								
21, *o*-$C_6H_4CH_3NH_2$	−0.103	0.208	−0.200	−0.648	−0.896		0.224	0.230	0.219	0.235		0.400	0.402
22, Cpx $C_6H_4CH_3NH_2$−LiH	−0.085	0.160	−0.269	−0.653	−0.972	0.685	0.232	0.241	0.224	0.235	−0.709	0.417	0.420
23, Cpx_{π} $C_6H_4CH_3NH_2$−LiH	−0.111	0.208	−0.313	−0.655	−0.886	0.672	0.247	0.238	0.238	0.240	−0.698	0.416	0.412
24, TS_{ortho} $C_6H_4CH_3NH_2$/LiH	−0.066	0.076	−0.465	−0.645	−1.006	0.908	0.131	0.232	0.219	0.222	−0.385	0.409	0.403
25, TS_{CH_3} $C_6H_4CH_3NH_2$/LiH	−0.041	0.082	−0.240	−0.933	−0.987	0.887	0.223	0.118	0.204	0.232	−0.352	0.416	0.409
26, $C_6H_3LiNH_2CH_3$	−0.069	0.030	−0.556	−0.641	−1.016	0.892		0.217	0.229	0.217		0.401	0.401
27, $C_6H_4NH_2CH_2Li$	−0.028	0.054	−0.236	−1.062	−0.982	0.889	0.219		0.194	0.209		0.405	0.414
					X = F								
28, *o*-$C_6H_4CH_3F$	−0.110	0.466	−0.295	−0.644	−0.401		0.247	0.225	0.239				
29, Cpx $C_6H_4CH_3F$−LiH	−0.094	0.432	−0.279	−0.650	−0.464	0.717	0.255	0.237	0.243	0.243	−0.724		
30, Cpx_{π} $C_6H_4CH_3F$−LiH	−0.111	0.460	−0.307	−0.651	−0.384	0.673	0.268	0.235	0.247	0.254	−0.698		
31, TS_{ortho} $C_6H_4CH_3F$/LiH	−0.102	0.361	−0.495	−0.641	−0.491	0.933	0.139	0.227	0.235	0.235	−0.403		
32, TS_{CH_3} $C_6H_4CH_3F$/LiH	−0.059	0.379	−0.267	−0.956	−0.467	0.913	0.248	0.118	0.236	0.211	−0.359		
33, $C_6H_3LiFCH_3$	−0.109	0.325	−0.613	0.638	−0.505	0.921		0.224	0.232	0.232			
34, $C_6H_4FCH_2Li$	−0.052	0.378	−0.274	−1.116	−0.472	0.902	0.244		0.205	0.208			

for eq 5 (see Table 6) are very different (Li < K) and are smaller than the free anion value. Ring metalation is favored by all alkali metals and is strongly favored by the heavier alkali metals due to multicenter bonding.[39b]

The various substituents X have different ortho phenyl alkali-metal stabilizing potentials (eq 6 and Table 7). With both OH and F the organometallic is stabilized by a favorable coulomb−dipole interaction for Li, Na, and K. The energies follow the Allred−Rochow electronegativities[44] Li > Na < K,[26l−n] and F > OH > NH_2 (the highest energy is calculated for *o*-FC_6H_4K). With X = NH_2, the interactions are different for the three alkali metals. While a strong stabilization of −10.3 kcal/mol is calculated for Li, Na and K are only stabilized modestly. In the lithium compound (**39**) the lone pair on nitrogen is clearly oriented toward the metal, and the Li−N interaction can be described as intramolecular complexation. With potassium, however (**41**), the lone pair no longer is oriented toward the metal but prefers π interaction with the aromatic ring. Only a smaller electrostatic interaction can be expected in such NH_2 species (**39**−**41**). Whereas the charge on X is highest for X = NH_2, the heteroatom X bearing carbon (C_2) is nearly uncharged and the favorable charge alternation is interrupted (see Table 5).

The various benzyl alkali-metal derivatives adopt different structures.[41] Consequently, the X-substituent stabilizing effects also vary for Li, Na, and K. The strongest (−6.4 kcal/mol) stabilization is found for lithium with X = NH_2 (**27**); the nitrogen lone pair is oriented toward lithium, resulting in a favorable N−Li interaction (chelation). The same is true for the sodium derivative **48**. With K as the metal (**49**), however, the situation is different. Whereas in benzylpotassium (**38**) the metal is coordinated to four carbon atoms, substituents such as NH_2 localize this interaction; the lone pair on N compensates for the reduced coordination on the metal only to some extent. The same tendency is calculated for the benzyl alkali-metal derivatives with an ortho OH substituent. As the OH group interacts less than NH_2, the chelation energies for the hydroxy compounds are somewhat smaller (eq 7, Table 7). The resulting stabilization with X = F is due to the coulomb−dipole interaction, which is, however, not as favorable as in the phenyl compounds, with their four-center charge alternation. In the benzylic derivatives the charges on X and M are smaller than in the phenyl species; however, the higher negative charge on the metalated benzylic carbon atom compensates the reduced charge alternation to some extent (see NBO charges in Table 8).

What can be expected if the two different metalation sites as well as the different substituents are considered together? We used isodesmic eq 8 (see Table 8) to evaluate the relative energies of the different metalation products. The result depends both on the substituent and on the metal: with NH_2, benzylic metalation is clearly favored over ring metalation with all metals. For

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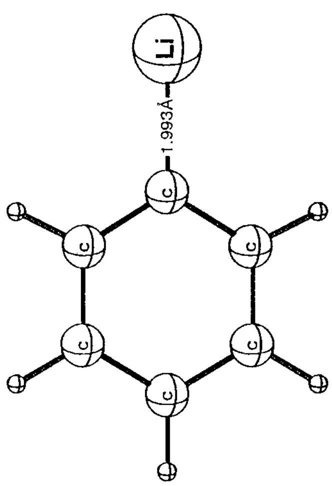
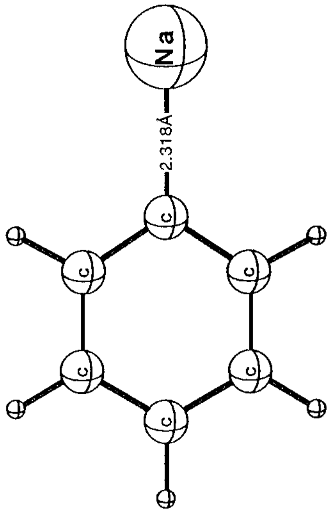
(42) (a) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355. (b) Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151.

(43) (a) Streitwieser, A. *Acc. Chem. Res.* **1984**, *17*, 353. (b) Boche, G.; Etzrod, H.; Massa, W.; Baum, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 863.

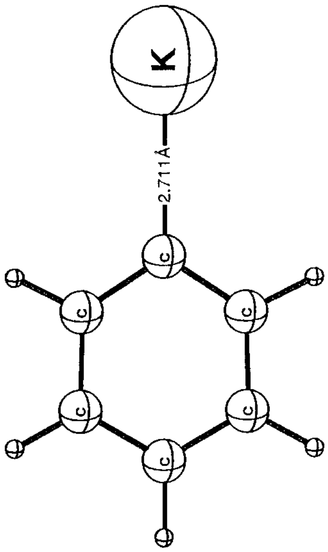
(44) Allred, A. L.; Rochow, E. G. *J. Inorg. Nucl. Chem.* **1958**, *5*, 264.



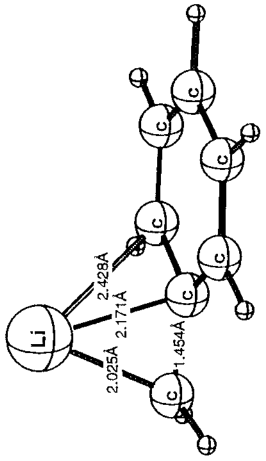
6, C_{2v}



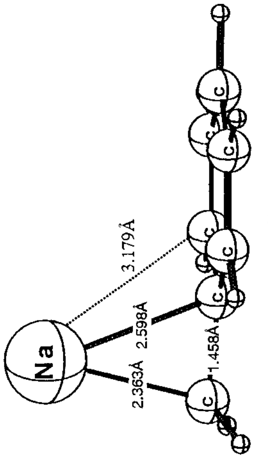
35, C_{2v}



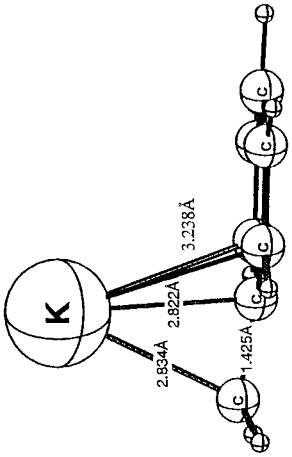
36, C_{2v}



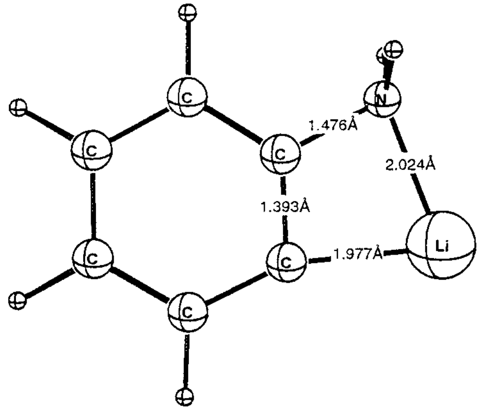
12, C_1



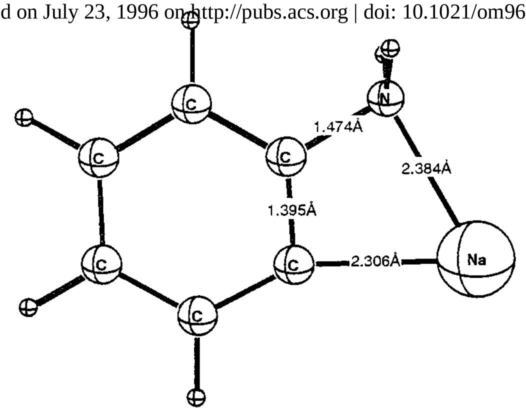
37, C_s



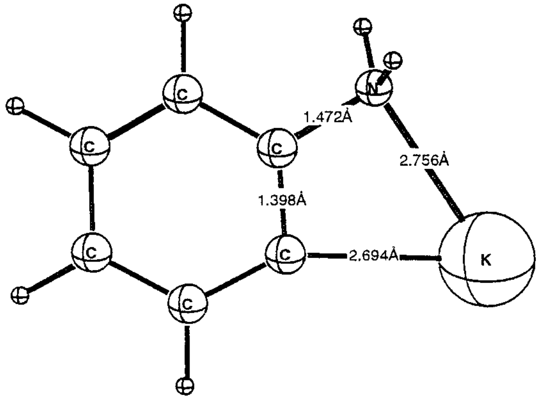
38, C_s



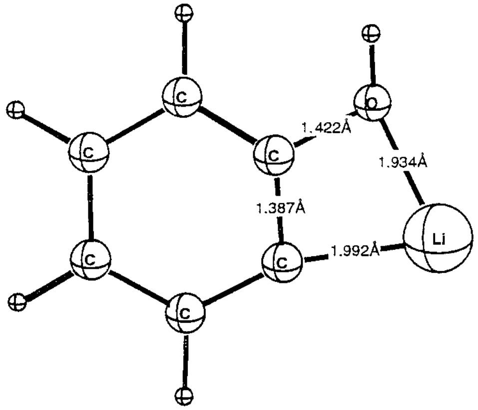
39, C_s



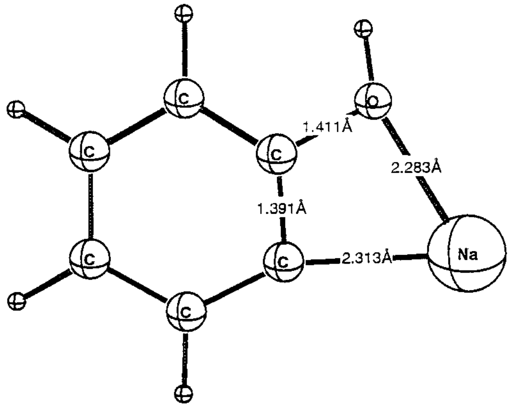
40, C_s



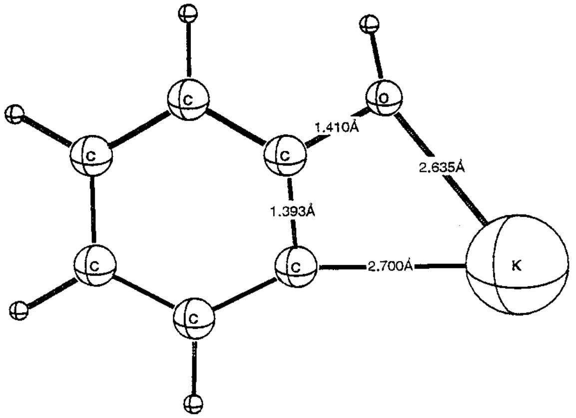
41, C_1



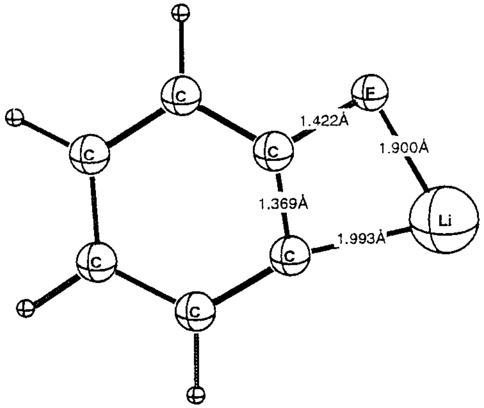
42, C_s



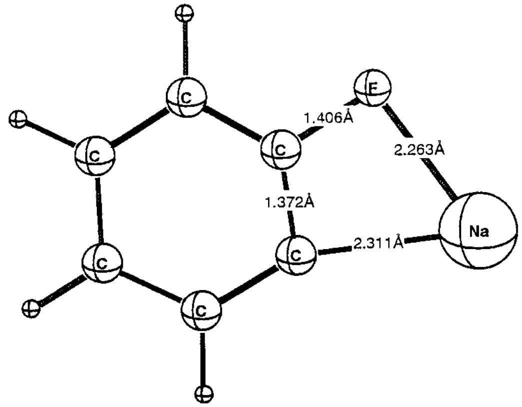
43, C_s



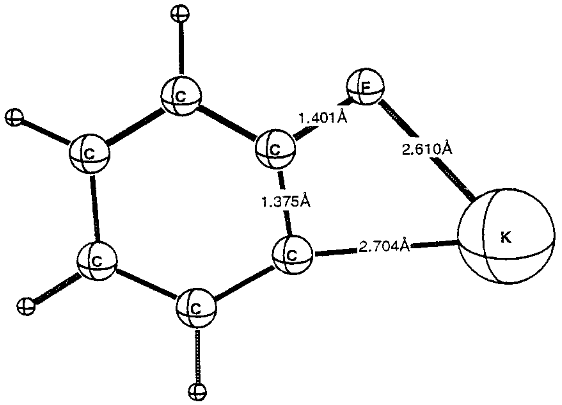
44, C_s



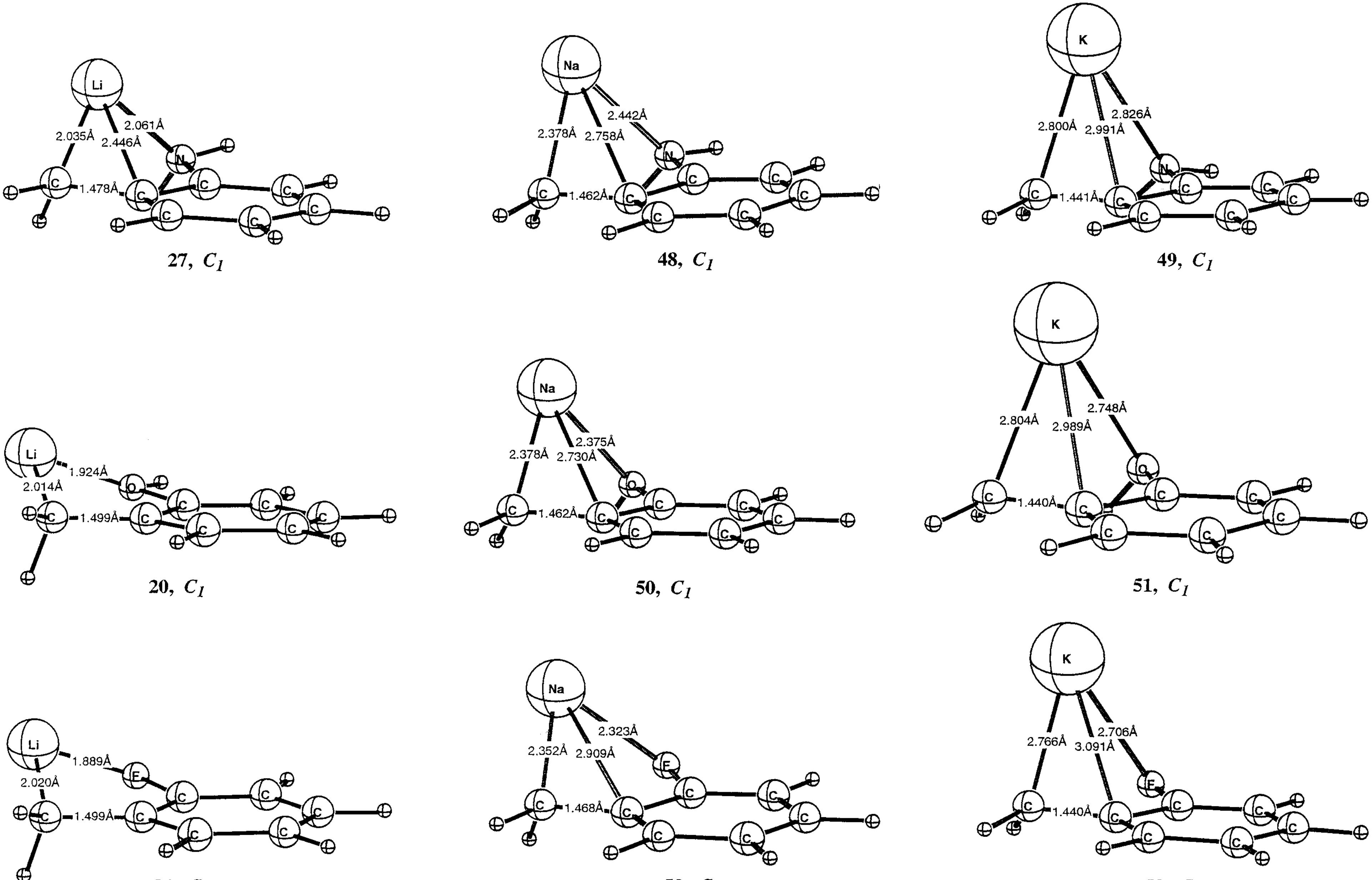
45, C_s



46, C_s



47, C_s



27, C_1 **48**, C_1 **49**, C_1

20, C_1 **50**, C_1 **51**, C_1

34, C_1 **52**, C_1 **53**, C_1

Figure 7. RHF 6-31G* optimized structures of ortho X-substituted phenyl and benzyl alkali-metal derivatives (M = Li, Na, K; X = H, NH_2, OH, F).

Table 5. NBO Charges of Phenyl and Benzyl Alkali Metal Derivatives

species	C_1	C_2	C_3	X	M
6, C_6H_5Li	−0.647	−0.285			0.912
35, C_6H_5Na	−0.570	−0.303			0.891
36, C_6H_5K	−0.579	−0.309			0.953
12, $C_6H_5CH_2Li$	−0.037	−0.425	−1.047		0.920
37, $C_6H_5CH_2Na$	−0.020	−0.400	−1.000		0.930
38, $C_6H_5CH_2K$	−0.015	−0.381	−0.956		0.969
39, *o*-$LiC_6H_4NH_2$	−0.570	0.030		−1.019	0.893
40, *o*-$NaC_6H_4NH_2$	−0.532	0.030		−1.002	0.900
41, *o*-$KC_6H_4NH_2$	−0.545	0.042		−0.995	0.949
42, *o*-LiC_6H_4OH	−0.622	0.251		−0.875	0.912
43, *o*-NaC_6H_4OH	−0.586	0.254		−0.865	0.914
44, *o*-KC_6H_4OH	−0.591	0.261		−0.856	0.956
45, *o*-LiC_6H_4F	−0.627	0.327		−0.499	0.922
46, *o*-NaC_6H_4F	−0.595	0.333		−0.489	0.923
47, *o*-KC_6H_4F	−0.599	0.340		−0.493	0.961
27, *o*-$NH_2C_6H_4CH_2Li$	−0.028	0.054	−1.062	−0.982	0.889
48, *o*-$NH_2C_6H_4CH_2Na$	−0.037	0.056	−1.002	−0.962	0.890
49, *o*-$NH_2C_6H_4CH_2K$	−0.041	0.039	−0.981	−0.956	0.951
20, *o*-$OHC_6H_4CH_2Li$	−0.039	0.289	−1.107	−0.848	0.894
50, *o*-$OHC_6H_4CH_2Na$	−0.050	0.192	−1.010	−0.836	0.909
51, *o*-$OHC_6H_4CH_2K$	−0.054	0.178	−0.983	−0.832	0.961
34, *o*-$FC_6H_4CH_2Li$	−0.052	0.378	−1.116	−0.472	0.902
52, *o*-$FC_6H_4CH_2Na$	−0.053	0.351	−1.029	−0.458	0.898
53, *o*-$FC_6H_4CH_2K$	−0.056	0.316	−0.988	−0.455	0.959

Table 6. Phenyl vs Benzyl: The Preferred Coordination Site of Alkali Metals (Eq 5)

M	//RHF 6-31G*	Becke3LYP 6-311++G**// 6-31G*	Becke3LYP 6-311++G**// 6-31G* + ΔZPE
Li	−3.5	−8.2	−8.4
Na	−3.3	−6.3	−6.4
K	−6.5	−12.3	−12.7
(−)[a]	−11.8	−19.0	−19.6

[a] Using the RHF/6-31+G* geometries.

X = OH our calculations show no preference for the metalation site with either Li or Na: indeed, lithiation of *o*-methylanisole (**B**) with *n*BuLi yielded equal amounts of ortho and benzylic products after trapping with CO_2.[17] With potassium compounds, benzylic products are clearly favored (this is also found experimentally).[16c] With X = F, a preference of −3.4 kcal/mol for ring metalation is calculated for lithium, but this diminishes for Na and vanishes for K. Ortho ring metalation is best achieved with X = F and M = Li. Benzylic metalation with X = NH_2 should be satisfactory for all the metals. With X = OH, specific side-chain metalation is to be expected only when M = K.

Table 7. Stabilization Energies of Phenyl (Eq 6) and of Benzyl (Eq 7) Alkali-Metal Derivatives (kcal/mol)

M	X	//RHF 6-31G*	Becke3LYP 6-311++G** //6-31G*	Becke3LYP 6-311++G** //6-31G* + ΔZPE
			Equation 6	
Li	NH_2	−14.3	−11.3	−10.3
	OH	−13.3	−13.1	−13.0
	F	−14.7	−14.5	−14.4
Na	NH_2	−10.1	−5.9	−5.3
	OH	−12.3	−10.6	−10.6
	F	−15.0	−12.8	−12.8
K	NH_2	−8.2	−5.6	−5.1
	OH	−12.1	−11.7	−11.5
	F	−15.3	−15.1	−14.9
			Equation 7	
Li	NH_2	−10.4	−7.4	−6.4
	OH	−7.0	−4.5	−4.4
	F	−6.0	−2.6	−2.6
Na	NH_2	−7.7	−6.7	−6.0
	OH	−5.9	−4.5	−4.4
	F	−5.1	−4.3	−4.5
K	NH_2	−4.9	−3.8	−2.8
	OH	−4.2	−3.1	−2.7
	F	−2.5	−2.4	−2.2

Table 8. Competitive Ring or Side-Chain Metalation (Eq 8)

M	X	//RHF 6-31G*	Becke3LYP 6-311++G** //6-31G*	Becke3LYP 6-311++G** //6-31G* + ΔZPE
Li	NH_2	−0.4	4.3	4.5
	OH	−2.7	−0.3	−0.3
	F	−5.2	−3.7	−3.4
Na	NH_2	1.0	7.1	7.0
	OH	−3.1	0.2	0.1
	F	−6.6	−2.2	−1.9
K	NH_2	3.3	10.5	10.4
	OH	−1.4	3.7	4.0
	F	−6.2	−0.4	−0.1

Conclusions

The chemistry of polar organometallics provides many examples of inter- and intramolecular complexation of alkali metals by various organic substrates. Whereas complexation of the initial state helps to determine the stability of an organometallic compound, the stabilizing interactions in the transition state govern the reactivity. Our model computations of the metalations in ortho-substituted toluenes (X = NH_2, OH, F) agree well with experimental results (with X = NMe_2, OMe, F). The observed regiochemistry of the metalation reaction (ortho to the X group or benzylic at the side chain) does not correspond to the acidity of the hydrogen exchanged in the starting compounds, nor can it be explained by "complex-induced proximity effects" in the initial complexes. *The stabilizing interactions in the transiton state determine the metalation product.* "Kinetically enhanced metalation" is an apt description. On the basis of our calculations electronegative substituents X (X = NH_2, OH, and F) reduce the barrier of activation for competitive ring or side chain lithiation with respect to unsubstituted toluene. Hence, toluene may be used as a solvent in the metalation reactions of ortho-substituted toluene derivatives.

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Supporting Information Available: Tables giving total and zero point vibrational energies of the ab initio optimized molecules (3 pages). Ordering information is given on any current masthead page.

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