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Mechanisms of Aromatic Lithiation

Influence of Aggregation and Directing Groups

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Abstract : High level *ab initio* calculations (MP2(fc)/6-31+G*//MP2(fc)/6-31G*+ΔZPE//6-31G* show that the reaction of aromatic compounds with methyllithium is not an electrophilic substitution, but a hydrogen transfer along an almost linear path, with the (coordinatively highly unsaturated) "active" lithium cation bridging the methyl carbanion and the carbon atom being lithiated. Aggregation (modelled with lithium hydride) does not change the mechanism. However, intra-aggregate bonding stabilizes the "active" lithium (*i.e.*, the one directly undergoing transfer). The mixed dimer of methyllithium and lithium hydride is predicted to be more reactive than methyllithium monomer in the lithiation of benzene, due to interaction of the "passive" lithium with the aromatic π-system and the carbon atom being lithiated. The accelerating and *ortho*-directing effect of Lewis base substituents is due to stabilization of the "active" lithium in the transition state by intramolecular coordination and favorable electrostatic interactions. These stabilizing effects are strongest for reaction of a monomer, but are also significant in the reaction of anisole with the mixed dimer of methyllithium and lithium hydride.

Introduction

Metalation, the reaction of "acidic" hydrocarbons with organometallic compounds, provides a convenient method for introducing new functionalities into a molecule [1]. Reaction of the carbon acid, *e.g.* with butyllithium at low temperature, results in substitution of the acidic hydrogen by lithium. This, in turn, can easily be replaced by other functionalities. In the late 1930's, Wittig [2] and Gilman [3] independently discovered that metalation of anisole takes place preferably at the ortho position. This discovery initiated the development of a new aromatic substitution chemistry ("neue Aromatenchemie" [4]), based on *ortho*-directed metalation, which beautifully complements the traditional methods based on electrophilic substitution. In recent years, these new methods were exploited successfully in numerous total syntheses of natural products [5].

Not only do heteroatom-containing substituents direct the regiochemistry of the reaction, they also have a strong accelerating influence. Under conditions where benzene is unreactive towards the lithiating agent, *ortho*-lithioanisole is formed readily [6]. Even substituents like fluorine [7] or trifluoromethyl [8] accelerate and *ortho*-direct the reaction, although these form weak complexes at best. A rationalization for the observed regioselectivity and increased reactivity was first proposed by Roberts and Curtin [8]. They assumed an initial coordination of the metal to a lone pair of the substituent, which, apart from increasing the inductive effect of the substituent, would bring the metalating reagent in the vicinity of the *ortho* hydrogen atom and thus facilitate its removal by the carbanion. This explanation has become generally accepted [5, 6]. Many other examples of reactions, in which complexation between reactive species is likely to control reactivity and regio- and stereoselectivity, have been recognized [9] and the designation "complex induced proximity effects" [10] has been coined to describe this phenomenon.

Roberts and Curtin already noted [8] that this explanation is not completely satisfactory: in a number of cases, the regiochemistry deviated from what was expected on the basis of complexation to the heteroatom [11]. Rationalizations which focus on initial complexation seem contradictory. If the initial complex is weakly bound, the fraction of reactive species that takes part in the complexation will be small and regioselectivity consequently will be low. If complexation is strong, a high regioselectivity might be expected, but the complexation energy has to be overcome in order to reach the transition state. Thus, high regioselectivity would be accompagnied by lower reactivity, which is opposite to the experimental findings.

NMR investigations [12] have shown that strong complexation between substrate and organolithium reagent can indeed be counterproductive. The complex of anisole with butyllithium in [$^2H_8$]toluene, detected by means of HOESY NMR spectroscopy, is unreactive even at room temperature. However, reaction occured readily even at low temperature in the presence of TMEDA, but no complexation of anisole was indicated in the HOESY spectrum under these conditions. Fluorine is another good *ortho*-directing group [7], but fluorobenzene and butyllithium are not complexed in [$^2H_8$]toluene [12]. Of course, this does not imply that precursor complexes are not involved at all in the reaction.

Stabilization due to coordination might increase on going from the initial complex to the transition state. Indeed, several authors have recognized the importance of transition state effects [e.g. 1a, 13, 14] and discussed these qualitatively. Possible transition structures, generally similar to the geometries of the initial complexes, have been proposed [1a, 13], in which "complexation of the lithium by the heteroatom brings the carbanion into an enthalpically and entropically favorable position for the reaction" [see 13c, footnote 5]. However, the geometries of complexes and transition structures need not be related at all. Calculations of transition structures, at the semiempirical MNDO level, have been reported by Saá et al. for the metalation of phenols and naphthols [15].

In a preliminary communication [16], we have emphasized the influence of the directing substituents in the transition states rather than in the initial complexes. The directing and accelerating effect of substituents is not due to the stabilization of the initial complex, but to the stronger stabilization in the transition structures. The metal will be involved in partial bonds and coordination by the heteroatom will become stronger in the transition structure than in the initial complex. Furthermore, the charge distribution in the transition structure shows an electrostatically favorable alternation of positive and negative charges. The geometries of precursor complex and transition structure can be radically different. As the term "complex induced proximity effects" can be misleading, we proposed "kinetically enhanced metalation" as a more suitable alternative [16].

The present contribution extends our earlier computational study significantly. Methyllithium is now employed in place of lithium hydride [17] as the model lithiating reagent, and anisole is examined (rather than phenol as its model). We present more refined, higher level calculations on the reaction of methyllithium with benzene, fluorobenzene, anisole and dimethylaniline. As organolithium reagents seldomly react as monomers, we investigate the effect of aggregation on the mechanism of the metalation of benzene and anisole. Mixed aggregates of methyllithium and lithium hydride are used in these calculations for reasons of computational effeciency.

Computational Methods

All calculations were performed using the Gaussian 92 program package [18a]. Geometries were first optimized at RHF/6-31G* [18b] level using standard gradient optimization techniques and were characterized as minima or transition structures by calculation of the vibrational frequencies. Structures were subsequently refined at MP2(fc)/6-31G* [18c] level, i.e. with the electrons in the core excluded from the correlation treatment. Final energies were calculated at the MP2(fc)/6-31+G* [18d] level using the MP2(fc)/6-31G* optimized geometries. Corrections for differences in zero point vibrational energy, calculated at RHF/6-31G*, were scaled by 0.91 [18e]. Atomic charges and bond orders were calculated using the Natural Population analysis and Natural Bond Orbital analysis methods developed by Reed and Weinhold [18f, g].

In a few cases, a small imaginary frequency (in the order of 10i cm^{-1}) was present, which corresponded to rotation of the methyl group of methyllithium. Since the energetic effect of such small imaginary frequencies is neglegible, we have not reoptimized the structures. In the case of **12**, the imaginary vibration corresponded to a deformation to a structure with C_1 symmetry, but since refinement at MP2 level changed the structure significantly, we again refrained from reoptimizing the structure at RHF level.

It should be kept in mind that the calculations presented in this contribution refer to isolated molecules in the gas phase at a temperature of 0 K, while organolithium reactions usually take place in solution at higher temperatures. Therefore, a direct comparison *e.g.* with experimental reactivity data may not be possible.

Results and Discussion

Absolute and zero point vibrational energies are given in Table 1. Relative energies are given in Table 2. Selected geometrical data is included in the pictures. In the discussion, all energies are at MP2(fc)/6-31+G* //MP2(fc)/6-31G* + ΔZ.P.E.//6-31G* level, unless indicated otherwise.

Initial Complexes

Both monomeric methyllithium and the model dimer of methyllithium and lithium hydride form a η^6 complex with benzene, with binding energies of -16.7 and -13.3 kcal/mol, respectively. A recent X-ray structure [19] provides an example of η^6 coordination of a lithium compound to an aromatic system [20]. The tetrameric model aggregate, consisting of methyllithium and three lithium hydride molecules, binds η^3 to benzene, with a complexation energy of -12.2 kcal/mol. The lower symmetry of the complex may be due to the symmetry of the $CH_3Li{\cdot}(LiH)_3$ model aggregate, since the complex of benzene and tetrameric lithium hydride has a η^6 structure.

Bonding in these complexes is mainly electrostatic in character. In complex **4**, the π-system of benzene is polarized by the dipole of methyllithium. The NBO analysis provides no indication for a significant covalent contribution to the bonding, despite the small lithium ring distance of 2.09Å. The NLMO bond order [18g] (which can be taken as a measure for the degree of covalency) between lithium and an aromatic carbon is 0.01. The complexes **8** and **12** are more weakly bound. The main contribution to the complexation energy is the interaction between the aromatic ring and the nearby lithium cation. In these cases, too, covalent bonding plays no significant role.

Table 1 Absolute energies (-a.u.) and zero point vibrational energies (kcal/mol).

Species	Point group	6-31G* //6-31G*	ZPE [a] //6-31G*	MP2(fc)/6-31G* //MP2(fc)/6-31G*	MP2(fc)/6-31+G* //MP2(fc)/6-31G*
1 CH_4	T_d	40.19517	29.99 (0)	40.33255	40.33408
2 C_6H_6	D_{6h}	230.70314	67.58 (0)	231.45773	231.47199
3 CH_3Li	C_{3v}	47.01554	22.28 (0)	47.16211	47.16681
4 C_6H_6-$LiCH_3$	C_{3v}	277.74212	90.78 (1) [b]	278.65221	278.66672
5 T.S. C_7H_9Li	C_s	227.66766	87.99 (1)	278.59211	278.61037
6 C_6H_5Li	C_{2v}	237.53112	59.97 (0)	238.29950	238.31654
7 $CH_3Li \cdot LiH$	C_s	55.06714	26.57 (0)	55.23153	55.23496
8 C_6H_6-$CH_3Li \cdot LiH$	C_s	285.78488	94.82 (0)	286.71535	286.72914
9 T.S. $C_7H_{10}Li_2$	C_s	285.72326	92.47 (1)	286.67220	286.68495
10 $C_6H_5Li \cdot LiH$	C_{2v}	245.58834	64.61 (0)	246.37517	246.39025
11 $CH_3Li \cdot (LiH)_3$	C_{3v}	71.17266	37.65 (0)	71.37932	71.38199
12 C_6H_6-$CH_3Li \cdot (LiH)_3$	C_s	301.88650	105.68 (1) [b]	302.85914	302.87413
13 T.S. $C_7H_{12}Li_4$	C_s	301.80907	102.48 (1)	302.79867	302.81337
14 $C_6H_5Li \cdot (LiH)_3$	C_s	261.68922	75.05 (0)	262.52148	262.53712
15 C_6H_5F	C_{2v}	329.55467	62.24 (0)	330.47700	330.50099
16 C_6H_5F-$LiCH_3$	C_s	376.59224	85.17 (0)	377.66605	377.68896
17 C_6H_5F-$LiCH_3$ π-cpx.	C_s	376.58917	85.33 (0)	377.66714	377.69091
18 T.S. C_7H_8LiF	C_s	376.53813	82.34 (1)	377.63340	377.65769
19 *ortho*-FC_6H_4Li	C_s	336.40607	54.74 (0)	337.34694	337.36996
20 $C_6H_5OCH_3$	C_s	344.58326	89.81 (0)	345.64566	345.66717
21 $C_6H_5OCH_3$-$LiCH_3$	C_s	391.62793	112.67 (1) [b]	392.83989	392.86342
22 T.S. $C_8H_{11}LiO$	C_1	391.56761	110.24 (1)	392.80264	392.82707
23 *ortho*-$CH_3OC_6H_4Li$	C_s	351.43258	82.46 (0)	352.51252	352.53497
24 $C_6H_5OCH_3$-$CH_3Li \cdot LiH$	C_s	399.67421	117.21 (0)	400.90626	400.92878
25 T.S. $C_8H_{12}Li_2O$	C_1	399.60484	114.63 (1)	400.86660	400.88607
26 *ortho*-$CH_3OC_6H_4Li \cdot LiH$	C_s	359.48735	87.11 (0)	360.58559	360.60794
27 $C_6H_5N(CH_3)_2$	C_s	363.78024	117.04 (0)	364.96588	364.98878
28 $C_6H_5N(CH_3)_2$-$LiCH_3$	C_s	410.82617	140.10 (1) [b]	412.16406	412.18899
29 T.S. $C_9H_{14}LiN$	C_1	410.76811	137.68 (1)	412.12743	412.15293
30 *ortho*-$(CH_3)_2NC_6H_4Li$	C_s	370.63333	109.84 (0)	371.83684	371.85935

[a] Number of imaginary frequencies in parentheses. [b] See text.

Table 2 Energies, relative to the separated reactants (kcal/mol).

Species	6-31G* //6-31G*	MP2(fc)/6-31G* //MP2(fc)/6-31G*	MP2(fc)/6-31+G* //MP2(fc)/6-31G*	MP2(fc)/6-31+G* incl.ΔZPE//6-31G*
4 $C_6H_6\text{-}LiCH_3$	-14.71	-20.31	-17.52	-16.68
5 T.S. C_7H_9Li	32.02	17.40	17.84	16.14
6 $C_6H_5Li\text{+}CH_4$	-4.77	-7.66	-7.42	-7.33
8 $C_6H_6\text{-}CH_3Li\cdot LiH$	-9.16	-16.37	-13.92	-13.31
9 T.S. $C_7H_{10}Li_2$	29.51	10.71	13.81	12.28
10 $C_6H_5Li\cdot LiH\text{+}CH_4$	-8.30	-11.58	-10.90	-10.49
12 $C_6H_6\text{-}CH_3Li\cdot(LiH)_3$	-6.71	-13.86	-12.64	-12.21
13 T.S. $C_7H_{12}Li_4$	41.87	24.08	25.49	23.01
14 $C_6H_5Li\cdot(LiH)_3\text{+}CH_4$	-5.39	-10.66	-10.80	-10.95
16 $C_6H_5F\text{-}LiCH_3$	-13.82	-16.91	-13.22	-12.63
17 $C_6H_5F\text{-}LiCH_3$ π-cpx.	-11.90	-17.58	-14.26	-13.52
18 T.S. C_7H_8LiF	20.13	3.58	6.40	4.41
19 *ortho*-$FC_6H_4Li\text{+}CH_4$	-19.47	-25.34	-22.68	-22.49
21 $C_6H_5OCH_3\text{-}LiCH_3$	-18.28	-20.16	-18.47	-17.94
22 T.S. $C_8H_{11}LiO$	19.57	3.22	4.34	2.66
23 *ortho*-$CH_3OC_6H_4Li\text{+}CH_4$	-18.17	-23.41	-22.01	-21.68
24 $C_6H_5OCH_3\text{-}CH_3Li\cdot LiH$	-14.94	-18.25	-16.72	-15.96
25 T.S. $C_8H_{12}Li_2O$	28.59	6.65	10.08	8.49
26 *ortho*-$CH_3OC_6H_4Li\cdot LiH\text{+}CH_4$	-20.16	-25.70	-25.03	-24.37
28 $C_6H_5N(CH_3)_2\text{-}LiCH_3$	-19.07	-21.19	-18.64	-17.58
29 T.S. $C_9H_{14}LiN$	17.36	0.35	3.32	0.91
30 *ortho*-$(CH_3)_2NC_6H_4Li\text{+}CH_4$	-20.53	-25.98	-23.75	-23.29

In the anisole complexes **21**, with methyllithium, and **24**, with the mixed dimer of methyllithium and lithium hydride, and in the dimethylaniline methyllithium complex **28**, the lithium cation is coordinated to the electronegative substituents. The complexes **21** and **24** are not planar like the complex of phenol and LiH [16]; the methoxy carbon and the coordinated lithium are in the plane of symmetry, which bisects the aromatic ring (The preferred conformation of the methoxy group in anisole is in the plane of the ring [21]). However, this preference is not due to interaction of the lithium cation with the π-system: the Li-O-C angles in **21** and **24** are 121.2° and 122.8°, respectively. The complexation energy for **21** is -17.9 kcal/mol, while a value of -16.0 kcal/mol is computed for **24**. The lithium oxygen distances are 1.94Å in **21** and 1.93Å in **24**.

In contrast, the methyllithium moiety in complex **28** with dimethylaniline is in the plane of the aromatic ring. Interaction between the nitrogen lone pair and the aromatic ring, which would be possible in a bisected structure analogous to **21**, is prohibited by coordination to lithium. The complexation energy for **28** is -17.6 kcal/mol. The lithium nitrogen distance in **28** is 2.09Å.

Two different structures are calculated for the complex of methyllithium and fluorobenzene: a planar structure **16**, with lithium coordinated to fluorine, and the π-complex **17**, in which lithium is η^6 coordinated to the aromatic ring. The lithium fluorine distance in **16** is 1.90Å, while the distance between lithium and the aromatic ring in **17** is 2.12Å. Complexation energies are much lower [16] than for the complexes discussed above, –12.6 kcal/mol for **16**, because of the lower coordinating ability of fluorine, and –13.5 kcal/mol for the ring-coordinated complex **17**, due to the inductive effect of fluorine. Therefore, no complex between fluorobenzene and organolithium compounds will be observable in aromatic solvents. Indeed, HOESY NMR spectroscopy indicates no complexation between butyllithium and fluorobenzene in $[^2H_8]$toluene [12]

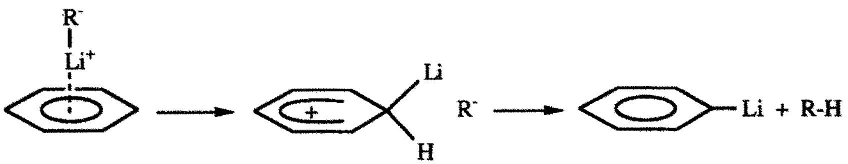
In all cases, complexation of the organolithium by Lewis base solvents, like ethers or amines, is stronger than the interaction with the substrate. Typical values for solvent complexation energies are -19.7 kcal/mol for methyllithium with dimethylether and -21.5 kcal/mol with trimethylamine [22]. This implies that in the presence of coordinating solvents or ligands, the precoordination equilibrium, exchange of a lithium bound solvent molecule with the substrate, will be predominantly on the side of the uncomplexed substrate [12].

Transition Structures for the Metalation of Benzene

In the initial complexes **4**, **8**, and **12**, the lithium cations interacts with the aromatic π-system. This kind of interaction is absent in **5**, the transition structure for metalation by monomeric methyllithium. The lithium cation occupies a bridging position above the methyl carbon, the migrating hydrogen and the aromatic carbon being lithiated and is not coordinated otherwise. The activation barrier is 16.1 kcal/mol (32.8 kcal/mol relative to **4**).

A different situation is encountered in transition structure **9**, for metalation by the model dimer of methyllithium and lithium hydride. Analogous to **5**, one lithium cation occupies a bridging position above the migrating hydrogen, while the other lithium interacts η^6 with the aromatic ring. The hydride, model for the second carbanion in the dimer, interacts with both lithium cations. The activation barrier is 12.3 kcal/mol (25.6 kcal/mol relative to **8**) significantly lower than for transition structure **5**.

In transition structure **13**, two lithium cations of the tetrameric model aggregate interact with the aromatic π-system. These interactions, however, are weaker than in the case of **9**. An optimal coordination can not be realized without serious distortion of the remaining intra-aggregate bonds, so that only contacts to the *ortho* carbon atoms are possible. Consequently, stabilization within the transition state is lower than in **9**. A higher activation barrier of 23.0 kcal/mol (35.2 kcal/mol relative to **12**) results.



(1)

One might consider aromatic lithiation an electrophilic aromatic substitution reaction, in which the aromatic ring is attacked by the lithium cation, a C-Li bond is formed and a C-H bond are broken in the transition structure and the proton is transferred to the methyl anion (Eq. 1). This view is not supported by our calculations. In an electrophilic substitution, the incoming electrophile, Li$^+$, and the leaving proton are expected to be located on opposite sides of the aromatic ring. However, the migrating hydrogens, and the

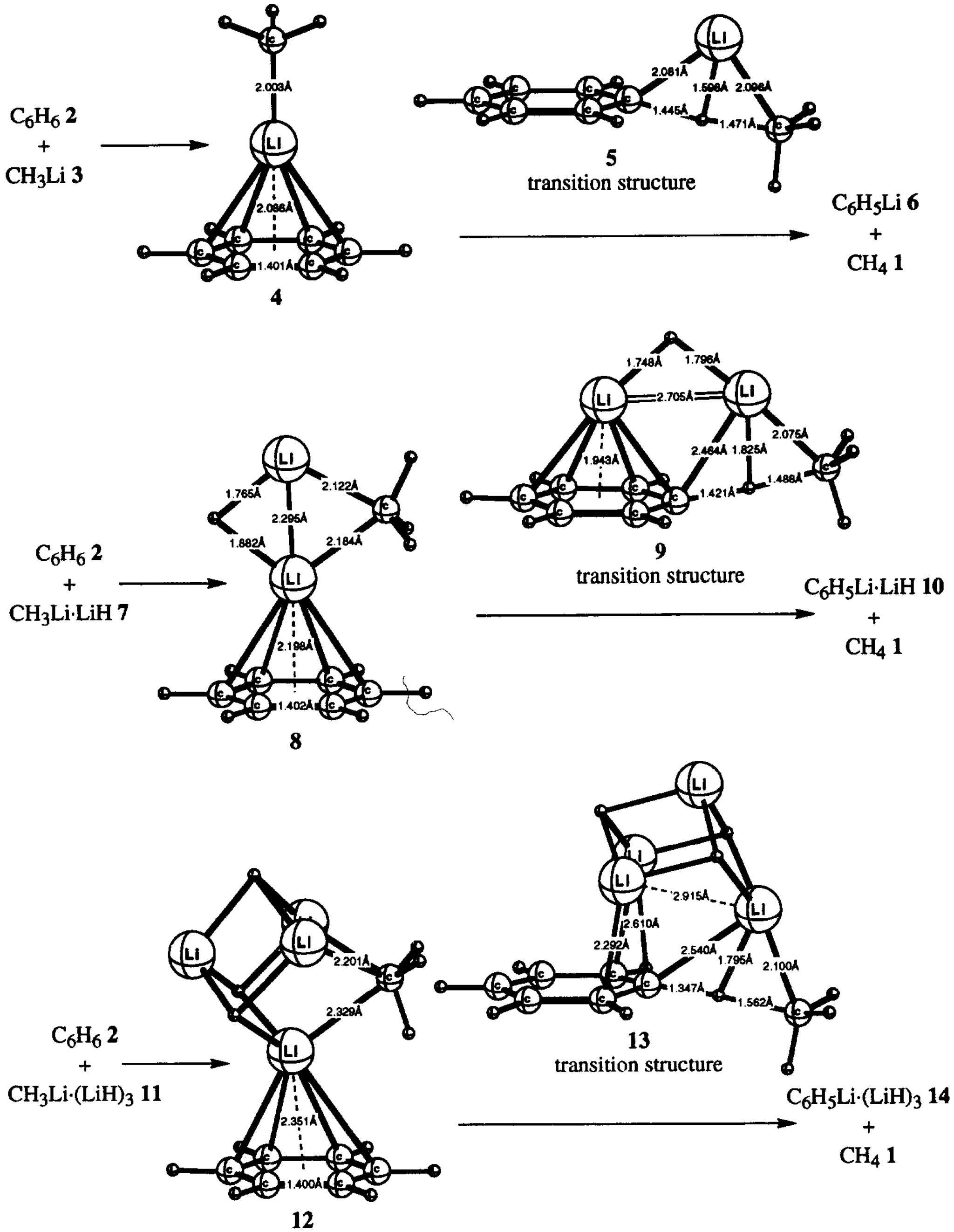


Figure 1. Reaction of benzene with monomeric methyllithium, with the mixed dimer of methyllithium and lithium hydride and with the mixed tetramer of methyllithium and three lithium hydride.

methyl carbanions, in **5**, **9**, and **13** are located close to the plane of the aromatic ring. In **9**, hydrogen and lithium are even located on the same side of the ring. The C-H-C angle varies from 172.2° in **5** to 175.9° in **13** indicating linear hydrogen transfer [23].

Furthermore, natural population analysis indicates that a hydrogen transfer rather than a proton transfer, as would be expected in an epectrophilic substitution, takes place in aromatic lithiation [24]. Compared to the hydrogen atoms bound to the aromatic ring or to the methyl carbon, the NPA charges on the migrating hydrogens in the transition structures **5**, **9**, and **13** are only slightly more positive. Lithium has a positive charge of almost unity, the negative charge is shared by the phenyl and methyl moieties.

In all three transition structures **5**, **9**, and **13**, the *ipso* carbon, the methyl carbon, the migrating hydrogen, and the lithium cation are located in the plane of symmetry, which bisects the aromatic ring. The distances between C_{ipso} and C_{methyl} are almost identical, 2.908±0.002Å, but the distances between C_{ipso} and the migrating hydrogen differ significantly. The distance of 1.35Å in **13** indicates that hydrogen transfer in this transition structure is less advanced than in **9** (C_{ipso}-H = 1.42Å) and in **5** (C_{ipso}-H = 1.45Å). The C_{ipso}-H NLMO bond orders show a similar trend: the values for **5**, **9**, and **13** are 0.367, 0.356 and 0.407, respectively, the corresponding C_{methyl} - H bond orders are 0.277, 0.267 and 0.224.

A significant difference between the transition structure **5** and the structures **9** and **13** lies in the environment of the lithium cations. While only one lithium is present in **5**, one can differentiate in **9** and **13** between the "active" lithium, bridging the *ipso* and methyl carbon atoms and the migrating hydrogen, and the other, "passive" lithium cations. The "active" lithium in **5** is coordinatively highly unsaturated. It is bound only to the partially negatively charged carbon atoms. The activation barrier relative to **4** is high, due to the loss of coordination of lithium to the π-system. In **9** and **13**, the "active" lithium is incorporated in an, albeit distorted, aggregate. Bonding to the "passive" anions in the aggregate (modelled by hydride in the present study) supplements the coordination sphere of the "active" lithium.

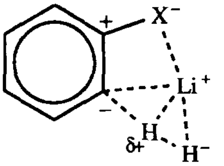
More important is the interaction of the one "passive" lithium in **9** and two of the "passive" lithiums in **13** to the aromatic ring. The carbanionic center being formed at the *ipso* carbon is stabilized electrostatically by the presence of the additional lithium cations. In **9**, optimal coordination of the passive lithium to the aromatic ring is possible, while in **13**, only contacts to the *ortho* carbons are realized. The effect of these interactions on the activation barriers is impressive and opposite to common wisdom. Reactivity is usually expected to increase upon going to smaller aggregates. Indeed, the highest barrier, 23.0 kcal/mol, is computed for the reaction of the tetramer, via transition structure **13**, 6.9 kcal/mol above that for reaction of the monomer, 16.1 kcal/mol, via **5**. However, the barrier for reaction of the dimer, via transition structure **9**, is only 12.3 kcal/mol, 3.8 kcal/mol lower than for reaction of the monomer. Interaction of the "passive" lithium with the aromatic ring in **9** leads to this drastic reduction of the activation barrier and to the dimer becoming more reactive than the monomer.

These large differences in activation energy are not reflected in the reaction energies, which are similar in all three cases. The reason is obvious: the aggregation does not change in the reaction. Lithiation of benzene by methyllithium monomer **3** gives phenyllithium monomer **6**, reaction of the mixed dimer **7** gives the mixed dimer **10** of phenyllithium and lithium hydride and reaction of the mixed tetramer **11** yields the mixed tetramer **14** of phenyllithium and three lithium hydride molecules. The small difference in relative energy between **6**, –7.3 kcal/mol, and **10** and **14**, –10.5 and –11.0 kcal/mol respectively, is due to the absence in **6** of (weak) interactions between the lithiums and the aromatic π-system.

We do not expect the results discussed above to depend on the use of the model aggregates consisting of methyllithium and lithium hydride. The lithium-lithium distances vary little between methyllithium oligomers and the mixed aggregates. Furthermore, the distances of the hydrides (the "passive" anions in the dimeric and tetrameric model aggregates) to the aromatic ring in **9** and **13** are so large that replacing them by methyl anions would not have a significant steric influence.

Transition Structures for the Metalation of Substituted Benzenes

In the transition structures **5**, **9**, and **13**, the "active" lithium cation is located in the plane of symmetry, perpendicular to the aromatic ring. Interaction with an electronegative substituent strongly influences the structure due to intramolecular coordination. With the smallest substituent, fluorine, a planar transition structure **18**, in which the lithium cation, the methyl carbon and the migrating hydrogen are all in the plane of the aromatic ring, results. Transition structure **22** for lithiation of anisole is very similar, but not completely planar: the dihedral angle O-C-C-Li is 4.8°, while the angle between the aromatic ring and the plane through C_{ipso}, C_{methyl} and Li is 30.6°. The transition structure for lithiation of phenol reported previously [16] is planar. The distances to the lithium cation are very similar in **18** and **22**, with the exception of the Li-F and Li-O distances of 1.88Å and 1.92Å, respectively, which is 0.02Å shorter than in the complexes **16** and **21**. The lithium nitrogen distance in **29** is longer, 2.05Å, but 0.04Å shorter than in complex **28**. The Li-N distance in **29** can only be realized with strong deviation from planarity. The N-C-C-Li dihedral angle is 19.1°, the angle between the aromatic ring and the plane through C_{ipso}, C_{methyl} and Li is 38.2°.



(2)

The positive charge on lithium in the transition structures is almost unity. The negative charge is divided over the anionic methyl moiety and the *ipso* carbon. The distances between lithium and these centers of negative charge are larger than the lithium methyl distance in the precursor complexes. The interaction with the partially positively charged migrating hydrogen is repulsive. Hence, the effective coordination of the lithium cation, in the absence of interaction with a substituent, is lower in the transition state than in the ground states. Intramolecular complexation compensates for this lower coordination of lithium. The shorter distances between lithium and the substituents in the transition structures than in the complexes indicate that complexation of the lithium cations is stronger in the T.S. In addition, the charge distribution in the transition structures, *i.e.* the alternation of positive and negative charges is favorable electrostatically [16].

The effect on the activation energies is profound. The barriers, relative to the separated reactants, are 4.4 kcal/mol for **18**, 2.7 kcal/mol for **22**, and 0.9 kcal/mol for **29**, significantly lower than the barrier of 16.1 kcal/mol computed for the lithiation of benzene, via transition structure **5**. Activation barriers relative to the precursor complexes are 17.9 kcal/mol for **18**, 20.6 kcal/mol for **22** and 18.5 kcal/mol for **29**. The higher value for the reaction of anisole seems to suggest that fluorine would be a better *ortho*-directing substituent than methoxy. Experiment clearly shows the opposite. For example, Schlosser *et al.* found that *ortho-* and *para-*fluoroanisole are lithiated next to the methoxy group by butyllithium in THF solution [25]. Comparing the barriers relative to the complexes is misleading here, since the influence of the solvent has to be considered. As

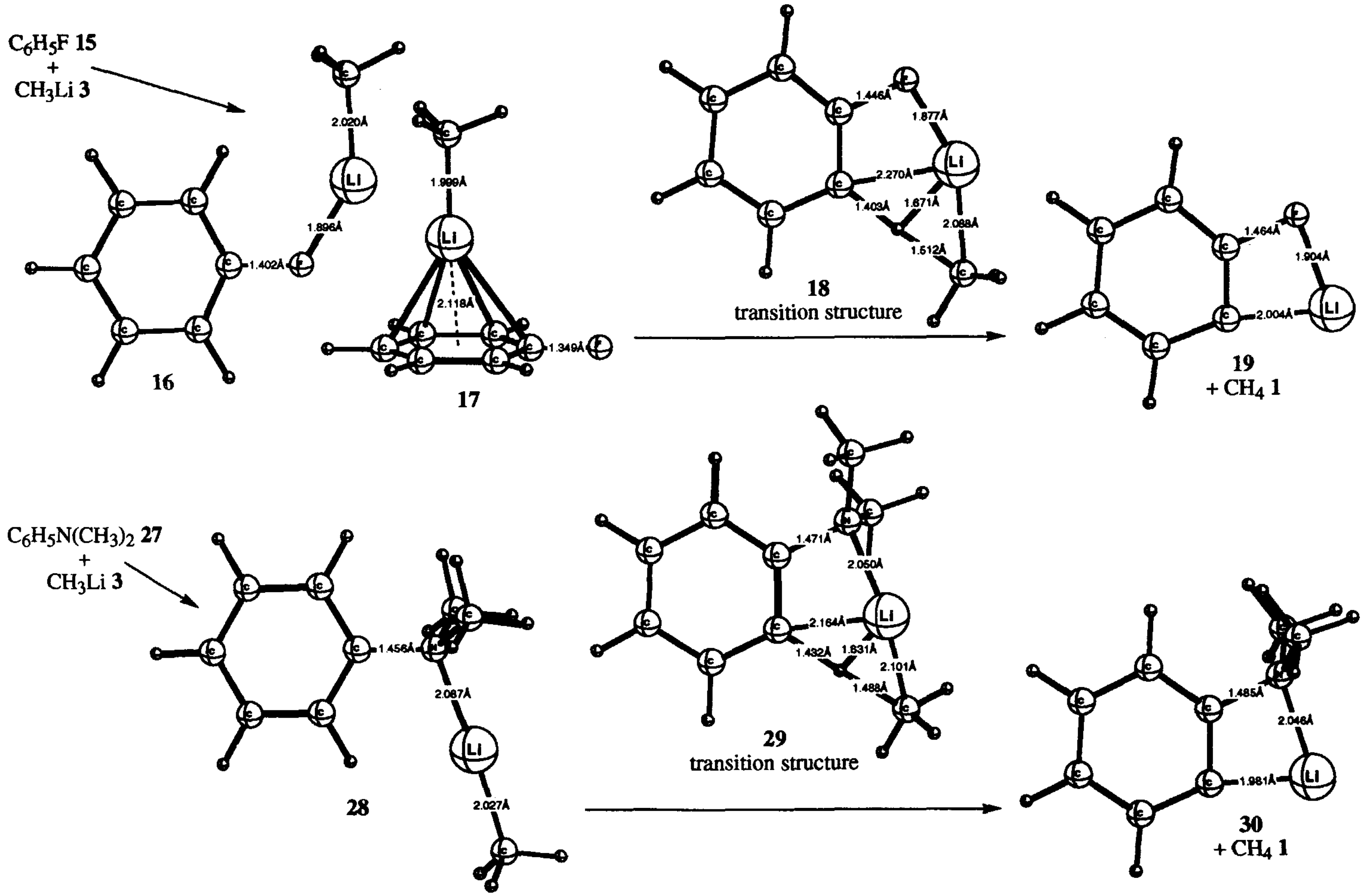


Figure 2. Reaction of fluorobenzene and dimethylamine with monomeric methyllithium.

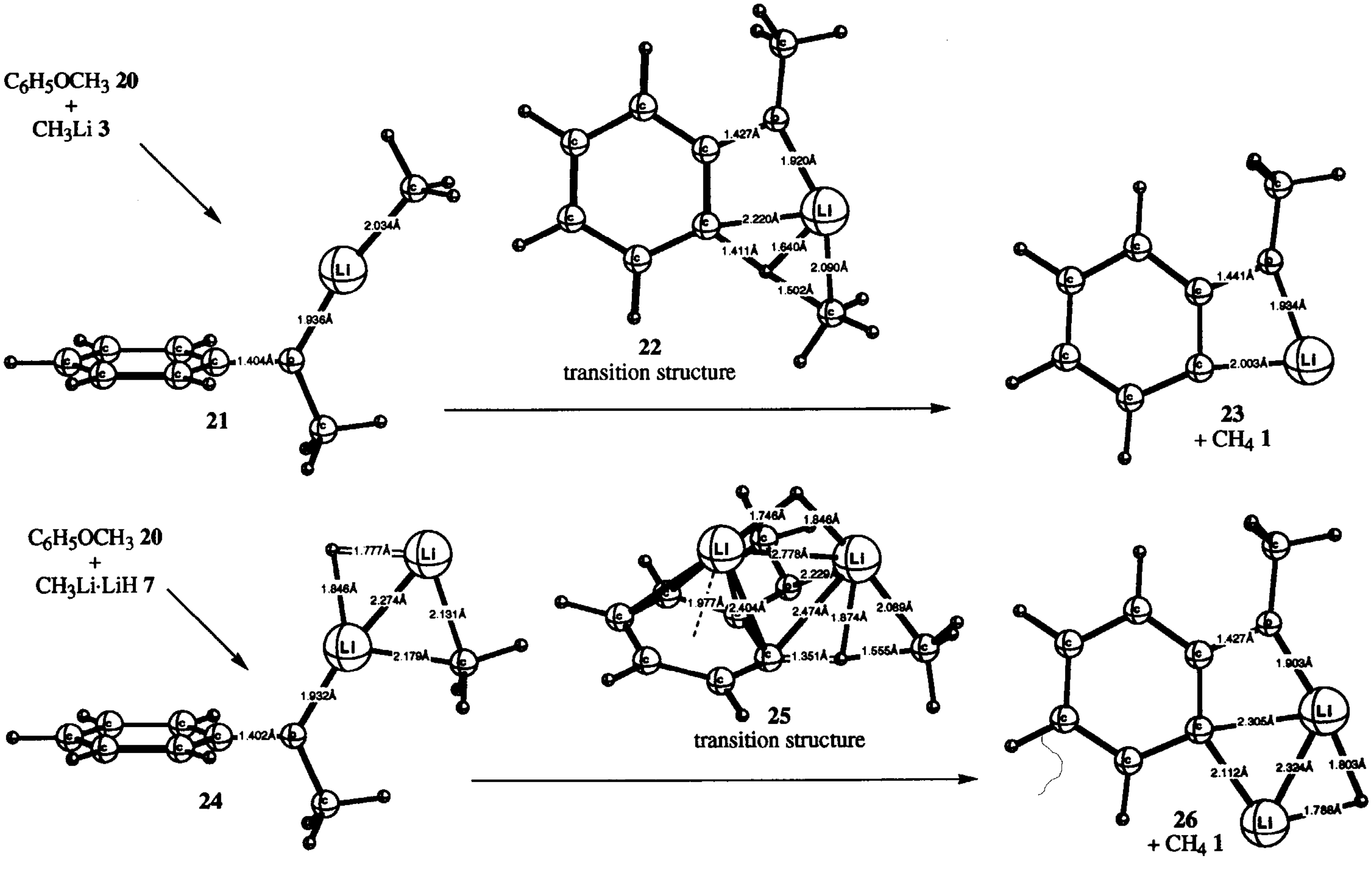


Figure 3. Reaction of anisole with monomeric methyllithium and the mixed dimer of methyllithium and lithium hydride.

discussed above, complexation to a Lewis base solvent is stronger than to the substrate and formation of the precursor complex is much more endothermic for fluorobenzene than for anisole.

One might argue that the choice of the rather high barrier corresponding to transition structure **5** as reference is misleading. The activation energy for metalation by a dimeric organolithium reagent is much lower. Does the influence of a substituent pertain in the reaction with a dimer? Calculations of the reaction between anisole and the mixed dimer of methyllithium and lithium hydride show that this is indeed the case, although the effect is less dramatic than in the lithiation by monomeric methyllithium.

Transition structure **25**, for lithiation of anisole by the model dimer of methyllithium and lithium hydride, combines the structural features of **9** and **22**. The "active" lithium is incorporated in a distorted dimer and coordinated by oxygen, while the "passive" lithium interacts with the aromatic π-system. The lithium ring distance is somewhat larger than in **9**, due to the inductive effect of the methoxy substituent. While the lithium cation in **22** is close to the ring plane, the interaction with the hydride anion above the aromatic ring pulls the "active" lithium out of the plane. The lithium cation in **25** is less strongly coordinatively unsaturated than the lithium cation in **22** and compensation by intramolecular coordination is of less importance. The distance to oxygen in **25** becomes longer, 2.22Å compared to 1.92Å in **22**. The methoxy group does not rotate out of the ring plane to allow optimal interaction with lithium, but remains in the plane of the aromatic ring.

The activation energy corresponding to **25** is 8.5 kcal/mol, 5.8 kcal/mol higher than the activation barrier for **22** and 3.8 kcal/mol lower than the barrier computed for **9**. The effect of the interaction of the "active" lithium with oxygen, although weaker than in **22**, is still considerable. As the lithium oxygen distance is too long for effective coordination, electrostatic interaction between the (negatively charged) oxygen, the (positive) *ipso* carbon, the (negative) *ortho* carbon and the (positive) lithium cation, as indicated in (2), forms the main contribution to the stabilization.

Conclusions and Outlook

Organolithium chemistry is full of examples of stabilizing interactions of lithium cations with various organic substrates. X-Ray structures [20] and NMR studies [12, 26] afford many examples. However, stabilizing interactions in the transition strucures determine organolithium reactivity. High-level ab initio calculations allow transition state effects to be studied in detail. In this contribution, we have presented several examples. Due to interaction of "passive" lithiums (*i.e.* lithium cations in the aggregate not immediately involved in the reaction) with the aromatic π-system, dimeric organolithiums are more reactive than monomers in the lithiation of benzene. Intramolecular complexation of the lithium cation by a Lewis base substituent in the transition structure and especially the favorable electrostatics drastically reduce the activation barrier for *ortho* lithiation. These stabilizing effects, and not initial complexation of the organolithium reagent, are responsible for the accelerating and *ortho*-directing effect of the substituents.

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