A PM3 and MNDO Study on the Mechanism and the Regioselectivity of the Lithiation of Lithium Methyl-1- and Methyl-2-naphthylcarbamate and Lithium 1,2,3,4-Tetrahydroisoquinolinecarbamate with Toluene†

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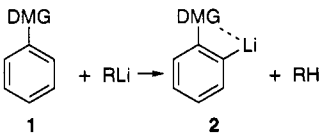
To assess the reliability of the MNDO and PM3 semiempirical methods in predicting the regioselectivity and mechanism of lithiation reactions, we calculated the reaction course of several lithium carbamates (**4a**, **4b**, **8**) with MeLi, the phenol/LiH complex, and the toluene (**10**)/LiMe system. For those carbamates in which H-atoms at *two identically hybridized carbon centers* compete for the incoming lithium cation (sp^2-C in the case of lithium methyl-1-naphthylcarbamate (**4a**) and **4b**, its 2-isomer; sp^3-C in the case of lithium 1,2,3,4-tetrahydroisoquinolinecarbamate (**8**)), both methods describe the experimentally observed regioselectivity of the metalation steps correctly. Nevertheless, almost invariably *erroneous results* will be obtained by semiempirical methods for comparable reactions in which *two differently hybridized carbon centers* of the substrate might be involved. These findings follow from ab initio and semiempirical calculations for the toluene (**10**)–LiMe reaction. Here and in related cases of competing sp^2- and sp^3-centers, both semiempirical methods will predict the wrong regioselectivity. In the past, the feasibility of a H/Li exchange has been attributed to the "agostic activation", which results in an elongated C–H bond. In this paper we report that such an activation is an artifact of the semiempirical methods.

Introduction

Directed *ortho* metalation (DOM) (Scheme 1)[1] and other regioselective lithiation reactions have a wide applicability in organic synthesis.[2] In spite of the enormous wealth of knowledge acquired over the past years on the structure of organolithium compounds in the solid state,[3] in solution by colligative property measurements,[4] and by NMR techniques such as $^6Li-^{13}C$ coupling[5] or $^6Li,^1H$-HOESY investigations,[6] a controversy exists regarding the reaction mechanisms and transition states of lithiation reactions. Usually for transition states of lithiation reactions, a four-membered arrangement of the atoms is found.[7] The X-ray structure of [Li-(*t*-BuOH)$_2$(thf)$_2$][cb] indicates that the metalation of carbazole with *t*-BuOLi proceeds via a six-center deprotonation–lithiation mechanism.[8] Little theoretical work has been done concerning the regioselectivity of lithiation reactions.[9]

Scheme 1. Reaction of Phenylic Compounds Containing a DMG (Directing Metalation Group) (1) with Organolithium Reagents



Semiempirical calculations can be a useful and rapid method for the investigation of the mechanisms and regioselectivities of lithiation reactions of large molecules. In this paper we discuss the application of PM3 and MNDO to selected problems. The metalation of lithium methyl-1-naphthylcarbamate·2H$_2$O, lithium methyl-2-naphthylcarbamate·2H$_2$O, lithium 1,2,3,4-tetrahydroisoquinolinecarbamate·2H$_2$O with CH$_3$Li·3H$_2$O, and toluene with CH$_3$Li were chosen as model reactions as well as the complexation of phenol with LiH.

CO$_2$-protected lithiation of substituted amines and alcohols is a useful synthetic method for functionalizing a wide range of amines, OH derivatives, and heterocyclic compounds.[10] This method is a very useful one-pot synthetic sequence in which the protecting group can be easily introduced and removed. *Ortho*-substituted aromatic amines are important starting materials for heterocyclic compounds and pharmaceuticals.[11] The meta-

† This article is dedicated to Prof. Dr. P. v. R. Schleyer on the occasion of his 65th birthday.

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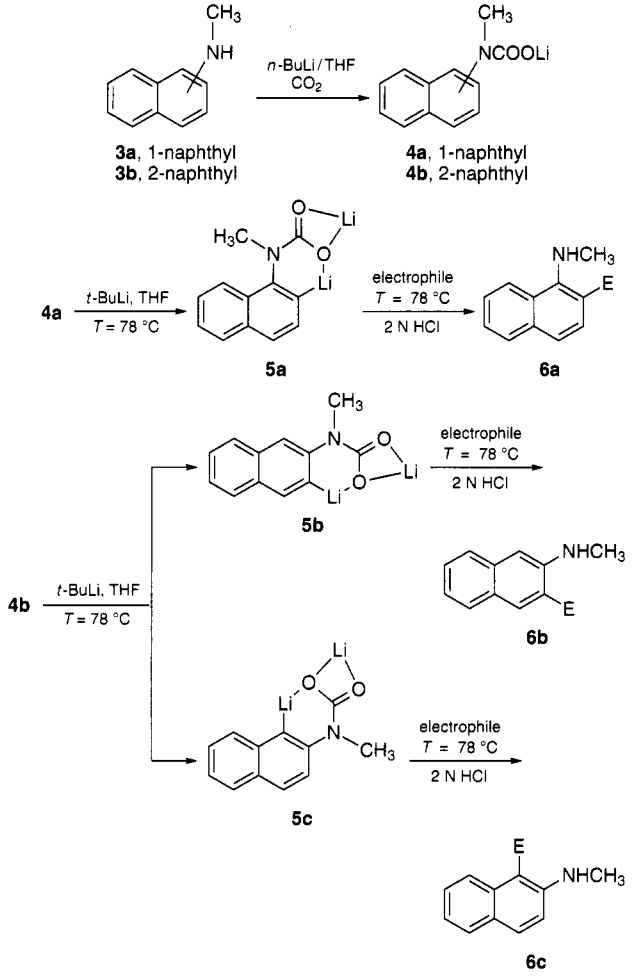
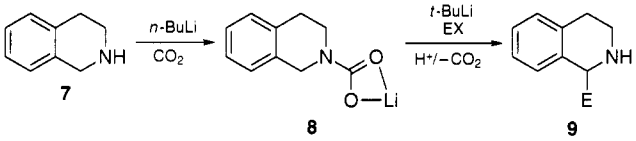
Scheme 2. CO_2 Protection and Regioselectivity of the Lithiation of Methylnaphthylamines 3a and 3b.



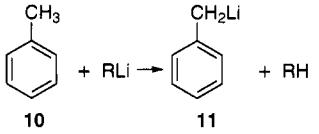
Scheme 3. CO_2 Protection and Regioselectivity of the Lithiation of 1,2,3,4-Tetrahydroisoquinoline (7)



lation of lithium methylnaphthylcarbamates **4a** and **4b** occurs in a regioselective manner (Scheme 2). Lithium methyl-1-naphthylcarbamate (**4a**) reacts at the 2-position, while lithium methyl-2-naphthylcarbamate (**4b**) reacts predominantly at the 3-position to give **6b** with the formation of only a small amount of the isomeric product **6c**. Lithium 1,2,3,4-tetrahydroisoquinolinecarbamate (**8**, Scheme 3) reacts with *t*-BuLi to afford 1-substituted compounds.

Mechanistic discussions of the lithiation of CO_2-protected compounds have been quite controversial: for lithium *N*-methylanilinecarbamate and lithium 1,2,3,4-tetrahydroisoquinolinecarbamate the formation of the dilithiated compound is demonstrated by the reaction with D_2O.[10b,c] Surprisingly, an NMR study of the metalation of lithium phenothiazinecarbamate failed to detect formation of the C(1)-lithiated species. The reaction is only observed when the metalation reagent (*t*-BuLi) and the electrophile (TMSCl) are added together.[12]

Scheme 4. Reaction of Toluene (10) with Organolithium compounds



Toluene (**10**) reacts with organolithium reagents to give benzyllithium (**11**) (Scheme 4).[13] It has been shown for 1-mesityllithium, which was synthesized by bromine/lithium exchange, that at temperatures $T > -10$ °C transmetalation occurs which yields the benzylic species.[14] These experiments show that side-chain lithiation of toluene and related compounds is favored both kinetically and thermodynamically. Ab initio calculations confirm these results.[15]

Computational Methods

Calculations were performed at the restricted Hartree–Fock (RHF) level with the PM3[16] and MNDO[17] method in the MOPAC 6/PC[18] program by using the lithium parameters for MNDO[19] and PM3.[20] Geometries were optimized without symmetry constraints. All stationary points on the potential energy surface were characterized as minima or transition states by calculating and diagonalizing the Hessian matrix.[21]

Results and Discussion

Agostic Activation. In the literature several authors suggest on the basis of MNDO investigations that the regioselectivity of lithiation reactions can be explained by agostic activation.[22] Here we discuss systems of the type R(H)DMGLiR (DMG: directing metalation group), with DMGs containing an oxygen atom. MNDO calcula-

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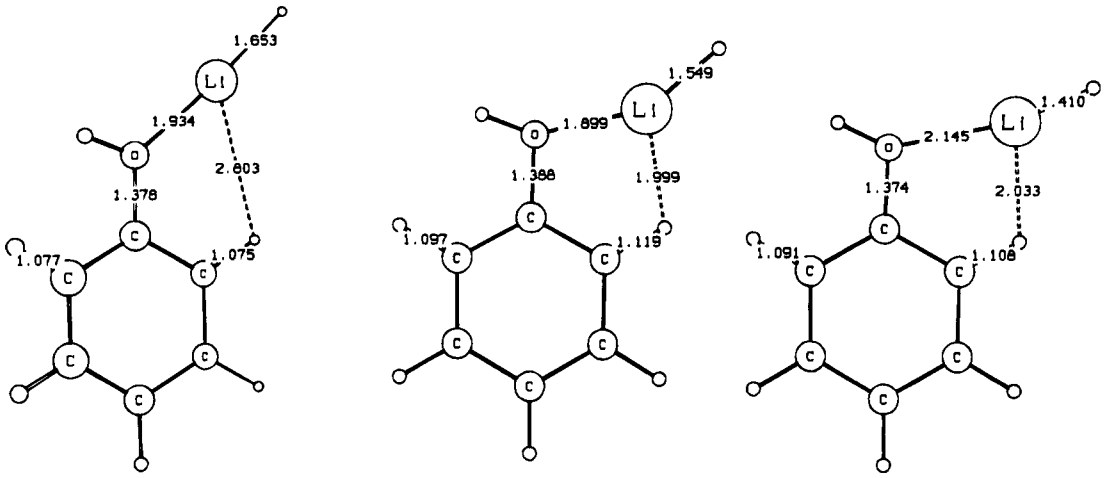

Figure 1. Characteristic data of the adduct complexes of phenol and LiH. From left: ab initio (MP2/6-31+G*//6-31G*), PM3, and MNDO results.

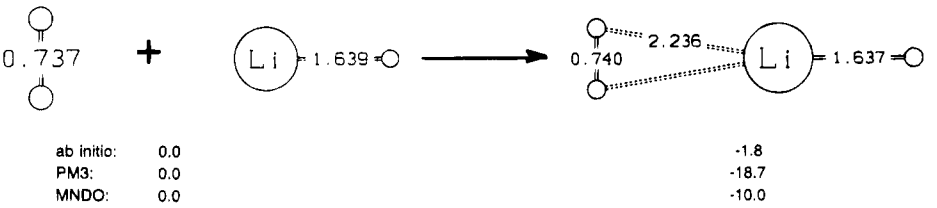

Figure 2. Energies [kcal/mol] for the reaction of lithium hydride with hydrogen (ab initio: MP4SDTQ/6-31+G*//MP2/6-31+G*).

Table 1. Heats of Formation ΔH_f and Energies E_{rel} [kcal/mol] Relative to the Separated Reactants with Different Methods for the Metalation of Lithium Methyl-1-naphthylcarbamate·2H₂O (12) and Lithium Methyl-2-naphthylcarbamate·2H₂O (19) with CH₃Li·3H₂O

	PM3		MNDO			PM3		MNDO	
compound	ΔH_f	E_{rel}	ΔH_f	E_{rel}	compound	ΔH_f	E_{rel}	ΔH_f	E_{rel}
12 + $CH_3Li·3H_2O$	−364	0.0	−427.5	0.0	**19** + $CH_3Li·3H_2O$	−366.2	0.0	−429.8	0.0
13 + H_2O	−375.5	−11.3	−451.1	−23.6	**20** + H_2O	−377.6	−11.4	−453.5	−23.7
14 + $2H_2O$	−368.8	−4.6	−447.4	−19.9	**21** + $2H_2O$	−371.2	−5.0	−449.9	−20.1
15a (2) + $2H_2O$	−365.5	−1.3	−445.6	−18.1	**22a** (1) + $2H_2O$	−367.9	−1.7	−446.8	−17.0
15b (8) + $2H_2O$	−362.0	2.2	−445.3	−17.8	**22b** (3) + $2H_2O$	−368.3	−2.1	−448.6	−18.8
16a (2) + $2H_2O$	−361.8	2.4	−429.5	−2.0	**23a** (1) + $2H_2O$	−363.0	3.2	−430.5	−0.7
16b (8) + $2H_2O$	−360.3	−3.9	−428.2	−0.7	**23b** (3) + $2H_2O$	−364.4	1.8	−430.5	−0.7
17a (TS 2) + $2H_2O$	−344.3	19.9	−396.8	30.7	**24a** (TS 1) + $2H_2O$	−349.0	17.2	−397.7	32.1
17b (TS 8) + $2H_2O$	−340.1	24.1	−392.4	35.1	**24b** (TS 3) + $2H_2O$	−349.9	16.3	−399.8	30.0
18a (Pr 2) + CH_4 + H_2O	−369.3	−5.1	−438.3	−10.8	**25a** (Pr 1) + CH_4 + H_2O	−371.7	−5.5	−440.4	−10.6
18b (Pr 8) + CH_4 + H_2O	−367.3	−3.1	−443.3	−15.8	**25b** (Pr 3) + CH_4 + H_2O	−373.1	−6.9	−441.8	−12.0

tions of the complexes of 1- and 2-naphthyl-O·(Li_2-CH_3·$3H_2O$) and PhOMe·[$(BuLi)_2$·TMEDA] reveal an agostic activation of the *ortho* hydrogen. For the MNDO- and PM3-calculated complexes PhOH·LiH (Figure 1), agostic activation of the *ortho* hydrogens is observed, resulting in elongated CH bond lengths (PM3, 1.119 Å; MNDO, 1.108 Å) compared to the nonactivated *ortho* hydrogens (PM3, 1.097 Å; MNDO, 1.091 Å). This trend can also be found with minimal ab initio basis sets, e.g. STO-3G ("activated" *ortho* 1.085 Å, compared with 1.083 Å for the nonactivated *ortho'* C−H bond). In contrast to these results, the MP2/6-31+G*//6-31G*-calculated complex PhOH·LiH shows no agostic activation.[7] To explain this contrary result, the complexation reaction was calculated: H_2 + LiH → H_2·LiH (Figure 2). Compared with ab initio results, both semiempirical methods severely overestimate the stability of these adducts (ab initio −1.8 kcal/mol; PM3 −18.7 kcal/mol; MNDO −10.0 kcal/mol). Together with several analogous findings for similar complexes,[9a,b,22d] we therefore conclude that the agostic activation in systems such as R(H)DMGLiH, which is generally observed in calculations with semiempirical methods (MNDO *and* PM3), is an artifact of the methods caused by the overestimation of the RLi···HR' interaction. It seems very likely that agostic activation occurs in general by application of minimal basis sets and can be described as a basis set superposition error.[23]

Lithium Methyl-1-naphthylcarbamate·2H₂O and Lithium Methyl-2-naphthylcarbamate·2H₂O. To simulate the reaction of the lithium methylnaphthylcarbamates **4a,b** with monomeric *t*-BuLi,[14] we used as model compounds lithium methylnaphthylcarbamate solvated with two water molecules (**12** and **19**) and $CH_3Li·3H_2O$ (Table 1, Scheme 5). Lithium methyl-1-naphthylcarbamate·$2H_2O$ (**12**) reacts with $CH_3Li·3H_2O$ in the first step to give a six-membered ring system (**13**). Loss of one

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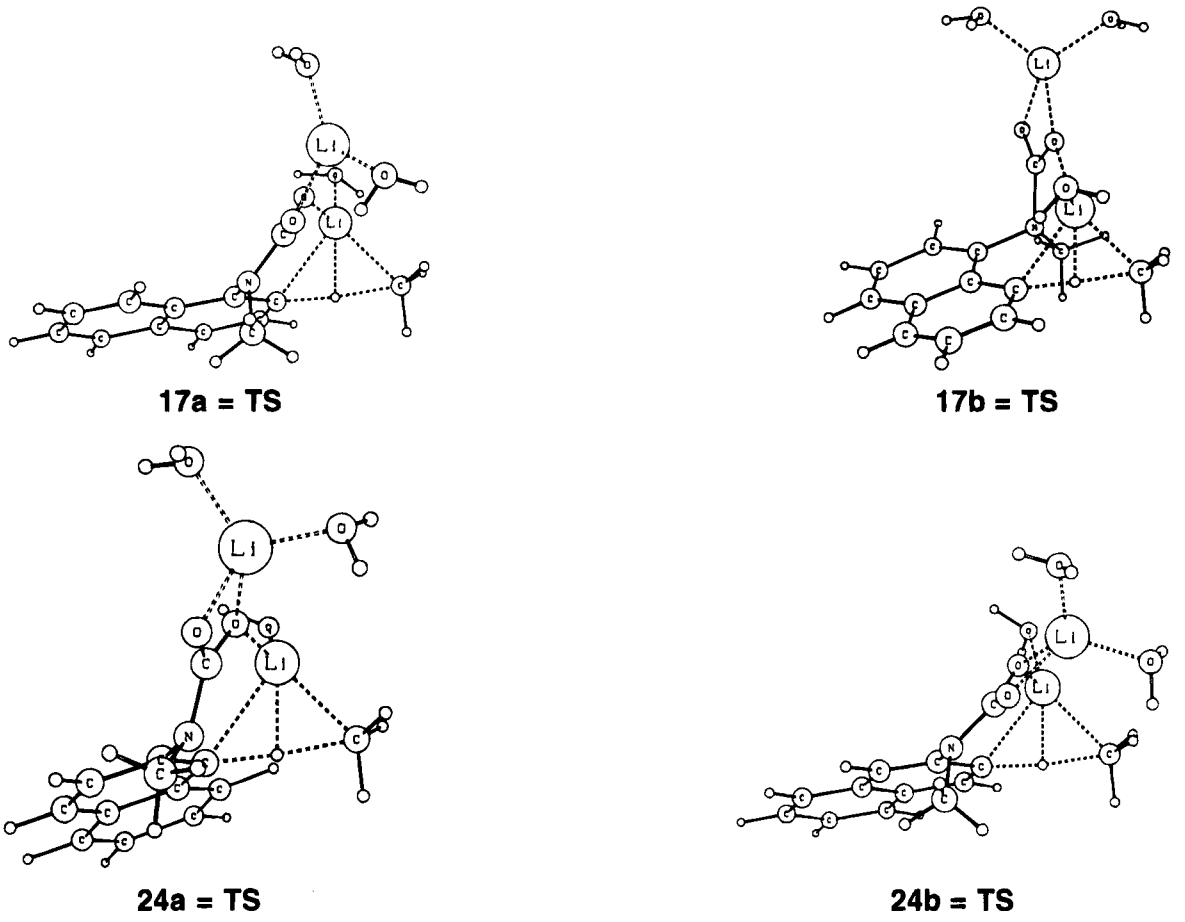


Figure 3. PM3-calculated transition states **17a, 17b, 24a**, and **24b** of the lithiation of **12** and **19** with $CH_3Li{\cdot}3H_2O$.

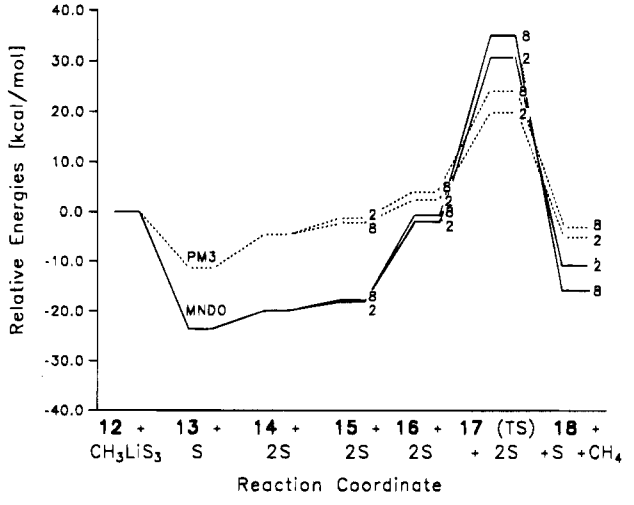


Figure 4. Reaction coordinate of the metalation of lithium methyl-1-naphthylcarbamate·$2H_2O$ (**12**) with $CH_3Li{\cdot}3H_2O$. PM3 and MNDO results.

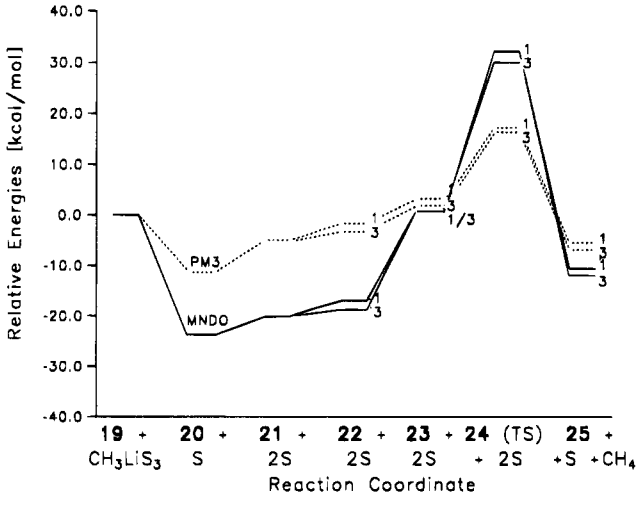
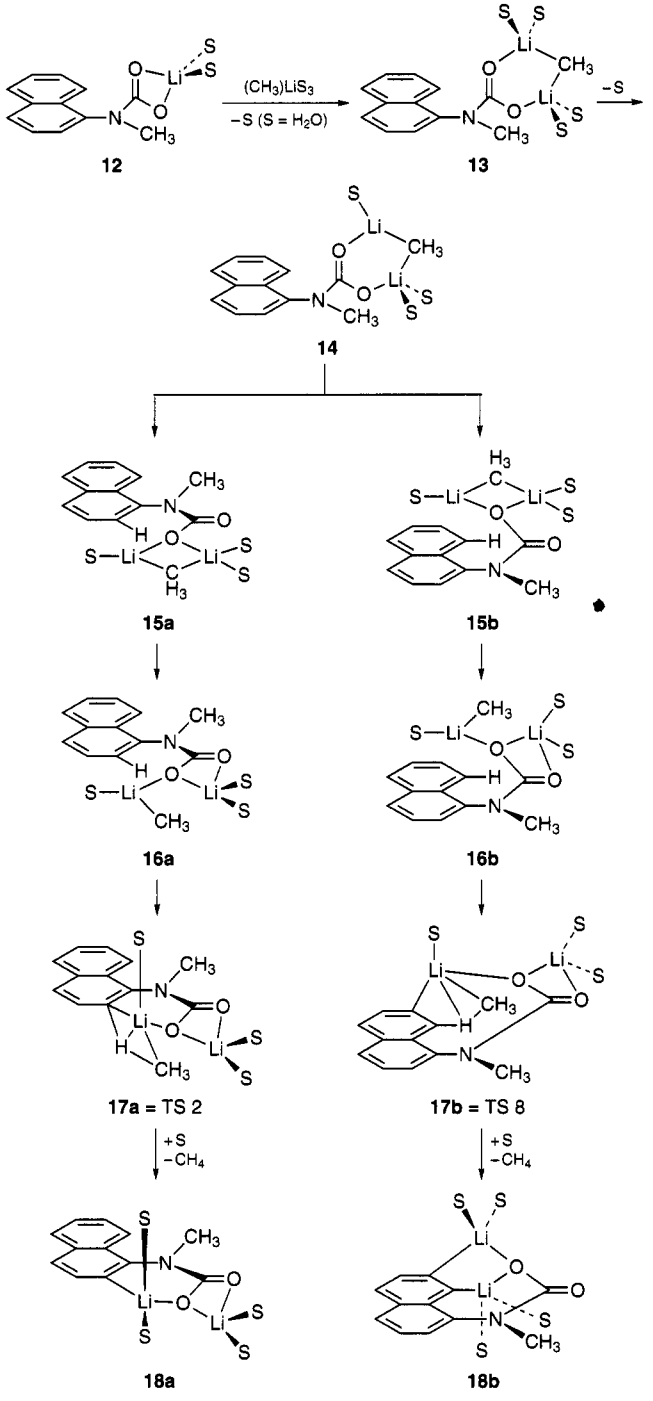


Figure 5. Reaction coordinate of the metalation of lithium methyl-2-naphthylcarbamate·$2H_2O$ (**19**) with $CH_3Li{\cdot}3H_2O$. PM3 and MNDO results.

solvent molecule yields a mixed aggregate (**14**) from which two four-center mixed aggregates **15a,b** are formed, which rearrange to the scissorlike intermediates **16a,b**. Again, it is assumed that the observed agostic activation is an artifact of the semiempirical methods (vide supra). The energy for **TS 2** (**17a**) is calculated by PM3 (MNDO) to be 4.2 (4.4) kcal/mol lower than that for **TS 8** (**17b**) (Table 1). In both four-center C–H–CH_3–Li transition states, the lithium cation is complexed by one solvent molecule and one oxygen atom (Figure 3). PM3 calculates the 2-lithiated product **18a** to be more stable. MNDO favors the 8-lithiated product **18b**. Thus, with PM3 a kinetic *and* thermodynamic preference of **18a** is observed, while MNDO shows only a kinetic preference of **18a** (Figure 4). The calculated regioselectivity agrees quite well with the experimental result. MNDO calculates the double bridged product **18b** to be more stable than the alternative product, in which the one lithium is complexed by the CO_2 group and the other by the CO_2 unit and the carbon C(8). The latter is calculated to be more stable with PM3 (not included in the figures).

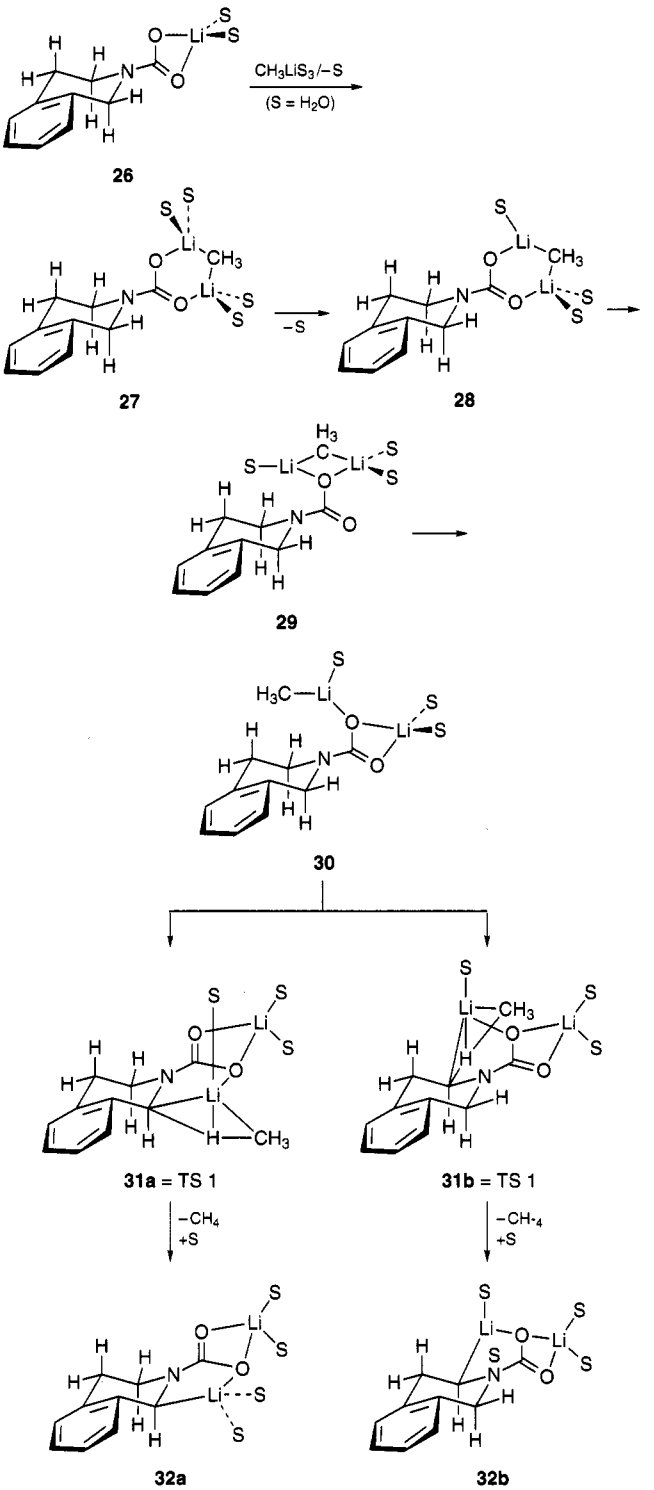
Scheme 5. MNDO-Calculated Reaction Pathway of the Metalation of Lithium Methyl-1-naphthylcarbamate·2H₂O (12) with CH₃Li·3H₂O



The reaction pathway (Table 1, Figure 5) of the metalation of lithium methyl-2-naphthylcarbamate·2H₂O (**19**) is similar to that of **12**.[24] **TS 3** (**24b**) is calculated by PM3 (MNDO) to be only 0.9 (2.1) kcal/mol more favorable than that of **TS 1** (**24a**). The low-energy difference between **24a** and **24b** is in agreement with the experimental observation that a mixture of both products is formed. Again, in both four-center transition states (Figure 3) the incoming lithium cation is complexed with one solvent molecule and one carbamate oxygen. The

(24) In order to avoid an excessive number of figures, structures **19**–**25**, which are similar to **12**–**18**, are not included in an additional figure.

Scheme 6. Reaction Pathway of the Metalation of Lithium 1,2,3,4-Tetrahydroisoquinolinecarbamate·2H₂O (30) with CH₃Li·3H₂O



3-lithiated product **25b** is favored by PM3 (MNDO) by 1.4 (1.4) kcal/mol versus the 1-lithiated product **25a**. The lithium coordination in **25a** and **25b** is similar to that of **18a**.

Lithium 1,2,3,4-Tetrahydroisoquinolinecarbamate·2H₂O. This species reacts with CH₃Li·3H₂O to give a six-membered mixed aggregate (**27**, Scheme 6). Loss of one solvent molecule gives first a six-membered ring system (**28**) and then several rearrangements occur which yield a scissorlike lithium compound (**30**). The activation barrier, corresponding with **TS 1** (**31a**), is

Table 2. Heats of Formation ΔH_f and Energies E_{rel} Relative to the Separated Reactants of the Metalation Reaction of Lithium 1,2,3,4-Tetrahydroisoquinolinecarbamate·2H₂O (26) with CH₃Li·3H₂O. PM3 and MNDO Results

	PM3		MNDO			PM3		MNDO	
compound	ΔH_f	E_{rel}	ΔH_f	E_{rel}	compound	ΔH_f	E_{rel}	ΔH_f	E_{rel}
26 + $CH_3Li·2H_2O$	−392.7	0.0	−453.4	0.0	**31a** (TS 1) + $2H_2O$	−372.7	20.0	−420.5	32.9
27 + H_2O	−401.9	−9.2	−477.2	−23.8	**31b** (TS 3) + $2H_2O$	−372.0	20.7	−418.1	35.3
28 + $2H_2O$	−395.5	−2.8	−470.7	−17.3	**32a** (Pr 1) + CH_4 + H_2O	−400.7	−8.0	−467.2	−13.8
29 + $2H_2O$	−392.8	−0.1	−469.6	−16.2	**32b** (Pr 3) + CH_4 + H_2O	−394.4	−1.7	−464.5	−11.1
30 + $2H_2O$	−389.9	5.8	−451.3	2.1					

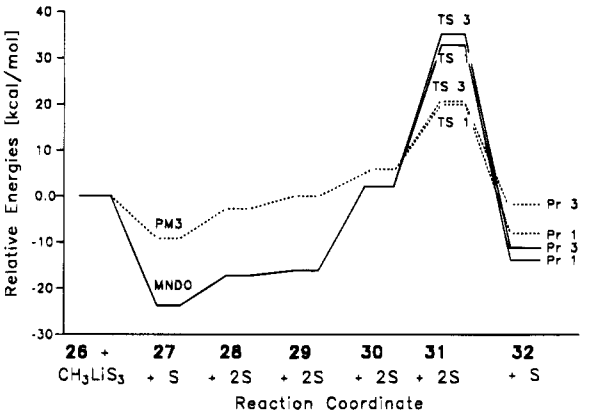


Figure 6. Reaction coordinate of the metalation of lithium 1,2,3,4-tetrahydroisoquinolinecarbamate·2H₂O (**26**) with $CH_3Li·3H_2O$. PM3 and MNDO results.

favored compared with that of **TS 3** (**31b**) by 0.7 (2.4) kcal/mol by PM3 (MNDO) (Table 2, Figures 6 and 7). In both cases the equatorial protons are removed. Further, the 1-lithiated product **32a** is 6.3 (2.7) kcal/mol more stable than the 3-lithiated isomer **32b**.

Lithium *N*-Methyl-*o*-toluidinecarbamate, Lithium Benzyl Carbonte, and Benzyl Alcohol. All the previous examples contain centers with the same type of hybridization (both atoms are either sp^2- or sp^3-carbons). To test the applicability of the proposed model, our investigations were extended to systems containing carbon centers with different hybridization. We therefore examined the reactions of lithium *N*-methyl-*o*-toluidinecarbamate·2H₂O (**33**) and lithium benzyl carbonate·2H₂O (**34**), with $CH_3Li·3H_2O$ as well as benzyl alcohol (**35**) with $(CH_3Li·2NH_3)_2$ (Figure 8).[25] For the latter ammonia was applied as solvent molecule to simulate TMEDA, which was used in the experimental procedure.[26] For **33** and **34**, both PM3 and MNDO prefer the *ortho* lithiation while experimentally exocyclic (α) lithiation is observed. For **33**, PM3 (MNDO) predicts *ortho* lithiation to be preferred by 4.2 (4.7) kcal/mol, for **34**, 10.1 (2.7) kcal/mol. In case of **35** the experimentally observed *ortho* lithiation is reproduced more or less "accidentally" correct by both semiempirical methods. TS-*ortho* is preferred by 2.0 (14.5) kcal/mol.

Table 3. Heats of Formation ΔH_f and Energies E_{rel} [kcal/mol] Relative to the Separated Reactants to the Lithiation of Toluene (10)

	ab initio[a]	PM3		MNDO	
compound	E_{rel}	ΔH_f	E_{rel}	ΔH_f	E_{rel}
10 + $LiCH_3$	0.0	39.6	0.0	12.1	0.0
10·$LiCH_3$	−17.3[b]	20.3[b]	−20.4	−18.8[c]	−30.9
36a (TS-α)	8.6	42.4	2.8	29.7	17.6
36b (TS-o)	16.0	40.2	0.6	28.8	16.7
37a (Pr-α) + CH_4	−12.4[b]	35.5[b]	−4.1	1.1[c]	−11.0
37b (Pr-o) + CH_4	−7.1	33.4	−6.2	−3.7	−15.7

[a] MP2/6-31+G*//6-31G* + ZPE (6-31G*). [b] η^3 coordination. [c] η^6 coordination.

Toluene and Derivatives. To explain the latter findings, we compared ab initio[15] with semiempirical results for the *ortho* and side-chain (α) lithiation of toluene with methyllithium (Table 3). On the basis of MP2/6-31+G*//6-31G* calculations, the adduct complexes are estimated as too stable by both semiempirical methods. MNDO calculates the η^6-adduct more stable than the η^3-compound which is preferred by PM3 and ab initio methods.[25] The activation barriers for the *ortho* and α lithiation are slightly overestimated by MNDO and underestimated by PM3 (Table 3, Figure 9). Both semiempirical methods predict the *ortho* metalation as the kinetically and thermodynamically favored reaction (TS-*ortho* is preferred by 2.2 (0.9) kcal/mol). These results are in clear contrast to the ab initio calculations. Therefore it seems unlikely that the semiempirical methods can be used for the examination of *ortho*

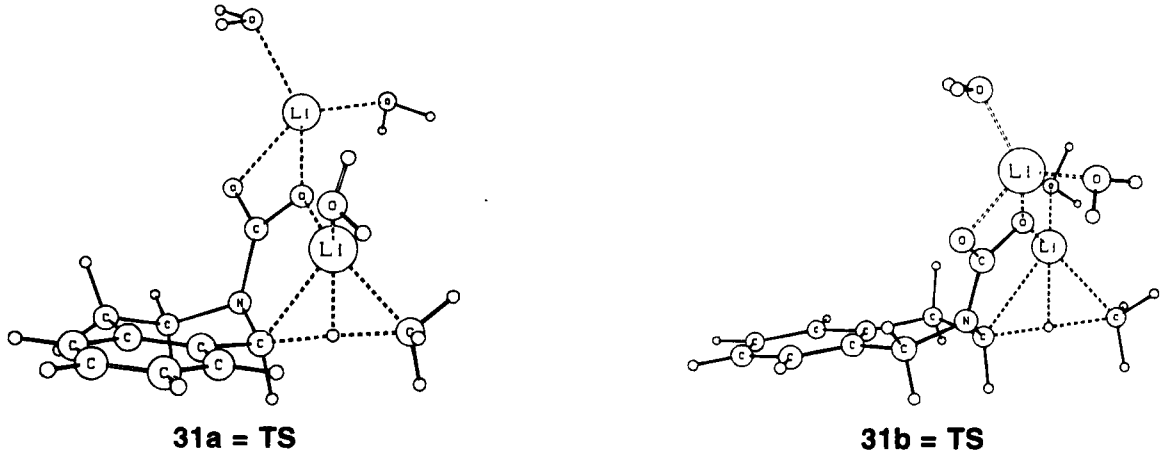
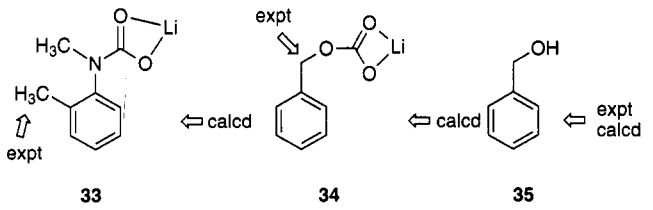


Figure 7. PM3-calculated transitions states **31a** and **31b** for the reaction of lithium 1,2,3,4-tetrahydroisoquinolinecarbamate·2H₂O (**26**) with $CH_3Li·3H_2O$.



33 34 35

Figure 8. Experimental and calculated regioselectivities of some "benzylic" compounds.

lithiation in systems containing competing sp^2- *and* sp^3-centers in the same molecule.

Conclusion

For the model system PhOH·LiH it has been demonstrated that agostic activation of the *ortho* hydrogens is an artifact of the semiempirical methods PM3, MNDO, and ab initio methods, which use a minimal basis set, caused by the overestimation of the RLi···HR′ interaction energies. This effect is certainly relevant for all O-containing directing metalation groups.

The experimentally observed regioselectivities for the metalation reactions of lithium methyl-1-naphthylcarbamate·$2H_2O$ (**12**), lithium methyl-2-naphthylcarbamate·$2H_2O$ (**19**), and lithium 1,2,3,4-tetrahydroisoquinolinecarbamate·$2H_2O$ (**26**) are reproduced quite well by both semiempirical methods. Comparison of ab initio- with PM3- and MNDO-calculated reaction pathways for the *ortho* and α lithiation of toluene (**10**) shows that the activation barriers of the relative to the *ortho* lithiation and the relative stabilities of α- versus the *ortho*-lithiated products are overestimated by the semiempirical meth-ods. Thus, MNDO and PM3 should be used with caution for investigations of the regioselectivity of lithiation reactions of compounds in which, e.g., sp^2- and sp^3-hybridized centers compete for the incoming lithium cation. This general trend was further confirmed for several "benzylic" compounds (benzyl alcohol, lithium benzyl carbonate, lithium *N*-methyl-*o*-toluidinecarbamate). In general, semiempirical calculations are useful methods for investigation of the regioselectivity of lithiation reactions for such molecules in which the carbon centers have the same type of hybridization.

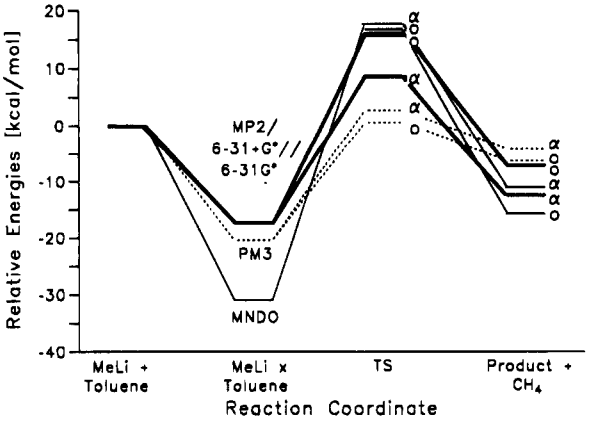


Figure 9. Energy profiles for α and *ortho* lithiation of toluene (**10**) with CH_3Li.

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