the available FFs is their "intrinsic preference" for some conformational state (e.g., α-helix), irrespective of number of residues, nature of substituents at the C^{α}, and environmental effects. Several experimental studies have, however, unequivocally shown that the above parameters have a profound effect on the secondary structure of peptides and proteins.

All these discrepancies have been settled in our FF using a number of adjustable parameters lower than in other FFs. The keys to this success appear to be the physically based choice of potential energy functions, the use of softer nonbond interactions, and the re-examination of vicinal interactions. The above results and the reasonable trends obtained for the onset of different helical structures in representative polypeptides show that we have succeeded in obtain a well-balanced set of parameters. Furthermore, the flexibility of the parametrization leaves room for further improvements, especially concerning vibrational frequencies.

Acknowledgment. The authors acknowledge the Italian Research Council (Comitato Informatica) for financial support and Professor P. A. Kollman for a copy of Version 3.0 of the AMBER package.

Registry No. F-Gly-NH_2, 4238-57-7; Ac-Gly-$NHCH_3$, 7606-79-3; Ac-Ala-$NHCH_3$, 19701-83-8; Ac-Aib-$NHCH_3$, 42037-26-3; Ac-$(Ala)_{13}$-$NHCH_3$, 143142-48-7; Ac-$(Aib)_{13}$-$NHCH_3$, 143123-57-3.

Origin of the Regioselective Lithiation of 1,3-Disubstituted Heteroatom Aromatics. MNDO Evidence for Bidentate Complexation

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Abstract: The regioselective lithiation of several prototype 1,3-disubstituted heteroatom aromatics, such as 1,3-dimethoxybenzene (DMB), 1,3-difluorobenzene (DFB), and 3-fluoroanisole (FA), has been studied by means of the semiempirical MNDO method. Calculations show clear-cut evidence for the intermediate formation of chelated species **6**, which formally derives from the bidentate coordination of the coordinatively unsaturated lithium base by the educt working as a "pair of tweezers". A very strong agostic interaction on C_2–H exists at this stage of the reaction coordinate, even though lithium atoms are formally pentacoordinated. In all cases studied the energy barriers corresponding to lithiation at C_2 by the bidentate coordination mode of approach are lower than those of the monodentate coordination mode leading either to lithiation at C_2 or C_6. Both the experimentally observed rate enhancement and regioselectivity are thus fully supported by the bidentate coordination mode of approach. These results can be satisfactorily explained by examining the "neighbor" and "non-neighbor" interactions being developed in reaching the alternative transition states. Thus, by partitioning the MNDO-calculated transition state total energy it can be recognized that five large, overall attractive, neighbor interactions (two O–Li, one C–H, and two C_2–Li) are being established in reaching the transition structure ($TS_{6\text{-}C2}$) by the bidentate coordination mode, but only three major interactions (one O–Li, one C–H, and one C_2–Li) develop throughout the monodentate coordination mode.

The so-called heteroatom-directed lithiation,[1] also termed ortho lithiation,[2] is a class of directed ortho metalations (DoM)[3] which allows for the regioselective introduction of lithium (hydrogen–lithium exchange) onto heteroatom-substituted aromatics. The lithiation of 1,3-disubstituted heteroatom aromatics, in particular, merits special mention because of its exceptional features. Not only does this reaction take place rapidly but, more importantly, it does so in a highly regioselective (C_2) manner. In other words, due to some poorly understood "cooperative effect",[3] lithiation at the C–H flanked by both heteroatom-based functional groups is kinetically and/or thermodynamically[4] favored over competitive lithiations at C_6 or C_4.

This large enhancing effect on rate shown by meta (relative to ortho or para) substituents such as fluoro, methoxyl, and dimethylamino was ascribed to the "coordinative involvement of the two moieties", from early work by Huisgen et al.[5] on the kinetics of the lithiation of substituted bromobenzenes. Unfortunately, no further kinetic data has been reported since then for other closely related compounds.[6] On other other hand, synthetic chemists have taken advantage of the high regioselective nature of the lithiation of this kind of substrates for the preparation of the difficult-to-synthesize 1,2,3-trisubstituted aromatics.[7]

The very recent work of Bauer and Schleyer[8] brought to light a comprehensive[9] mechanistic explanation for the formation of aromatic organolithium compounds by hydrogen–lithium exchange. On the basis of one-dimensional (^{1}H, ^{13}C, and ^{6}Li) and two-dimensional (HOESY ^{6}Li–^{1}H) NMR studies[10] as well as MNDO calculations, these authors proposed a generalized

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(1) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1.

(2) Excellent monographs and reviews on the subject are available. See, for example: (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (c) Wardell, J. L. In *Comprehensive Organic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 1, p 57. (d) Narsimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957. (e) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (f) Narasisimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63. See also refs 1 and 3.

(3) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879 and references therein.

(4) See: Ziegler, F. E.; Fruler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.

(5) Huisgen, R.; Mack, W.; Herbig, K.; Ott, N.; Anneser, E. *Chem. Ber.* **1960**, *93*, 412.

(6) Only scattered, qualitative kinetic data is available for other 1,3-disubstituted aromatics. See, for example: Thornton, T. J.; Jarman, M. *Synthesis* **1990**, 295.

(7) For an extensive list of examples, see refs 1 and 3. For recent, interesting applications for the preparation of fluorosubstituted aromatics, see: Ladd, D. L.; Weinstock, J. *J. Org. Chem.* **1981**, *46*, 203. Adejare, A.; Miller, D. D. *Tetrahedron Lett.* **1984**, *25*, 5597.

(8) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

(9) For previous studies, see: Ellison, R. A.; Kotsonis, F. N. *Tetrahedron* **1973**, *29*, 805; *J. Org. Chem.* **1973**, *38*, 4192. Graybill, B. M.; Shirley, D. A. *J. Org. Chem.* **1966**, *31*, 1221.

(10) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371. Bauer, W.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 970. Bauer, W.; Müller, G.; Pi, R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1103. See also ref 17.

0002-7863/92/1514-9093$03.00/0

mechanism for the ortho lithiation of heteroatom-substituted aromatics by the action of *n*-BuLi. In the key step, one lithium atom in a highly reactive butyllithium dimer[11] (presumably in very low stationary equilibrium concentration) coordinates with the aromatic (ArX) both through the heteroatom lone pair(s) and by agostic Li···H_{ortho} interaction.[12] Hydrogen removal then occurs from the activated ortho C–H bond in the mixed complex $(BuLi)_2L_2$–ArX (L stands for a monodentate ligand). Apparently, fluorobenzene is an exception to this generalized mechanism since complex formation could not be observed by NMR, and agostic interaction could not be "detected" in MNDO calculations. The authors concluded that fluorine's inductive effect might be the dominant factor in controlling the regioselectivity of fluorobenzene lithiation.

Some mechanistically important questions, however, still remain to be answered. In particular, the above mechanistic proposal fails to provide a satisfactory explanation for the enhanced kinetic reactivity and highly regioselective hydrogen–lithium exchange that occurs with 1,3-disubstituted heteroatom aromatics such as 1,3-dimethoxybenzene[13] and related compounds.

Herewith we report a theoretical study, based on semiempirical (MNDO) calculations,[14] of the lithiation of prototype compounds: 1,3-dimethoxybenzene (DMB), 3-fluoroanisole (FA), and 1,3-difluorobenzene (DFB) which favors the intervention of a chelated complex in equilibrium with monocoordinated complexes. To outline, our findings[15] demonstrate that the transition structure (leading to lithiation at C_2–H) of lowest energy is that derived from a chelated complex involving, on one side, the aromatic educt acting as "a pair of tweezers" and, on the other, the lithium base dimer. Furthermore, the origin of Snieckus's "cooperative effect" or Huisgens's "enhanced coordinative involvement of the two moieties" can be ascribed to a subtle interplay of electrostatic and covalent interactions between neighbor and non-neighbor atoms which develops in moving from reactants to the final lithiated products. Though different in nature, these interactions are of the type recently described by Jorgensen[16] and Rebek[17] for the molecular recognition between neutral hydrogen donors and acceptors.

Computational Methods

Calculations[18] were performed using dimeric CH_3Li solvated with two H_2O molecules (per lithium) as a working model,[19] unless otherwise noted. This simplified model is standard in computational chemistry,[20] and more importantly, it has been proven to be highly useful for qualitatively describing important mechanistic features regarding lithium coordination in organolithium compounds.

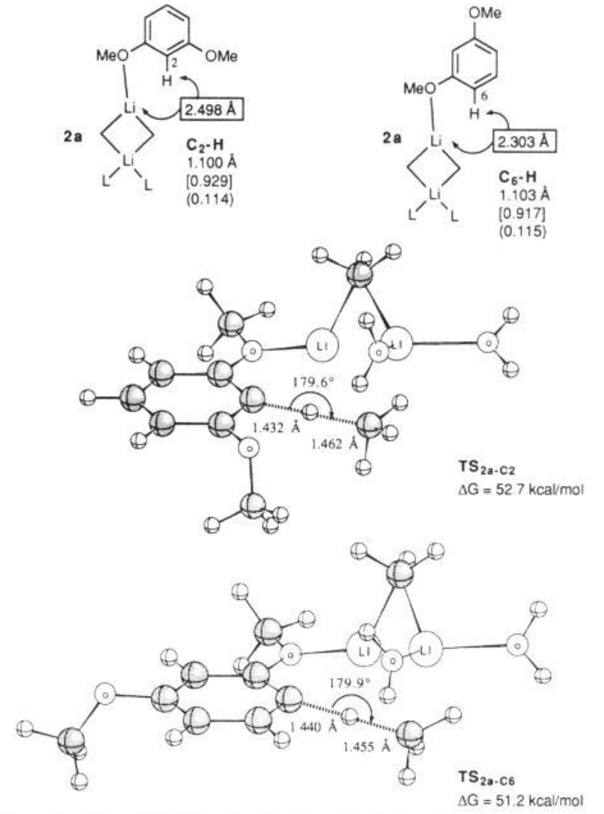

Figure 1. Top: MNDO-calculated agostic interaction parameters on C_2–H or C_6–H for the monocoordinated dimethoxybenzene complex **2a** (distances in angstroms; bond orders in brackets; net positive atomic charges on hydrogens H_2 or H_6 in parentheses). Middle and bottom: ball and stick transition state structures $TS_{2a\text{-}C2}$ and $TS_{2a\text{-}C6}$ (bonds between the CH_3 undergoing reaction and lithium atoms are not shown for clarity).

Theoretical calculations were carried out at the restricted Hartree–Fock (RHF) level using the MNDO[21] semiempirical SCF-MO method, as implemented in a modified version[22] of the MOPAC[23] program. Despite its well-known limitations (overestimation of C–Li[24] and H–Li[25] interactions) MNDO is generally considered the method of choice for studying the structure of large organolithium species such as lithiated aromatics, otherwise impossible to tackle by ab initio calculations.

All structures were optimized and further refined by using the keyword PRECISE. No symmetry constraints were imposed. All stationary points on the potential energy surfaces were characterized by calculating and diagonalizing the Hessian matrix and by checking the number of negative eigenvalues.[26]

Results and Discussion

In their study of lithiation of 1,3-dimethoxybenzene (DMB, **1a**) by the action of *n*-BuLi in toluene-d_8, Bauer and Schleyer rationalized their NMR observations by assuming that complexation occurred, as for the case of anisole, in a monodentate

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(11) Dimers have been shown to react faster than tetramers and hexamers. See: McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810.

(12) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395. Koga, N.; Obara, S.; Morokuma, K. *J. Am. Chem. Soc.* **1984**, *106*, 4625. Erker, G.; Frömberg, W.; Angermund, K.; Schlund, R.; Krüger, C. *Chem. Commun.* **1986**, 372. Bauer, W.; Feigel, M.; Müller, G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 6033. Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597. See also refs 8 and 27.

(13) Gilman, H.; Morton, J. W. *Org. React.* (*N.Y.*) **1954**, *8*, 258. Shirley, D. A.; Johnson, J. R.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209, 217.

(14) MNDO calculations have been extremely valuable in predicting the general structural features of organolithium compounds. See: Kos, A. I.; Clark, T.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 620. Bauer, W.; Müller, G.; Pi, R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1103. Neugebauer, W.; Geiger, G. A. P.; Kos, A. J.; Stezowski, J. J.; Schleyer, P. v. R. *Chem. Ber.* **1985**, *118*, 1504. Hacker, R.; Schleyer, P. v. R.; Reber, G. A. P.; Müller, G.; Brandsma, L. *J. Organomet. Chem.* **1986**, 316, C.4. Hacker, R.; Kaufmann, E.; Schleyer, P. v. R.; Mahdi, W.; Dietrich, H. *Chem. Ber.* **1987**, *120*, 1533. Gregory, K.; Bremer, M.; Bauer, W.; Schleyer, P. v. R.; Lorenzen, N. P.; Kopf, J.; Weiss, E. *Organometallics* **1990**, *9*, 1485. Wind, B.; Sygula, A.; Govindarajan, U.; Edlund, U.; Sethson, I.; Rabideau, P. *J. Org. Chem.* **1991**, *56*, 618.

(15) Presented, in part, at the 3rd European Symposium on Organic Reactivity (ESOR III), Göteborg, 1991, ESOR III Abstracts, p 139.

(16) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008. Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 209.

(17) Jeong, K. S.; Tjivikua, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3215. Jeong, K. S.; Tjivikua, T.; Muehldorf, G.; Deslongschamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201.

(18) Carried out on VAX 8820 and VAX 9000 computers of the Centre de Càlcul de la UIB (Palma de Mallorca, Spain).

(19) Bauer, W.; Feigel, M.; Müller, G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 6033.

(20) Monomeric unsolvated LiH has also been used as model for alkyl lithiums and their aggregates in ab initio calculations. See: (a) Kaufmann, E.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 121. (b) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y. D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (c) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821.

(21) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(22) (a) Olivella, S. QCPE Program No. 486. (b) Olivella, S.; Vilarrasa, J. *J. Heterocyclic Chem.* **1981**, *18*, 1189.

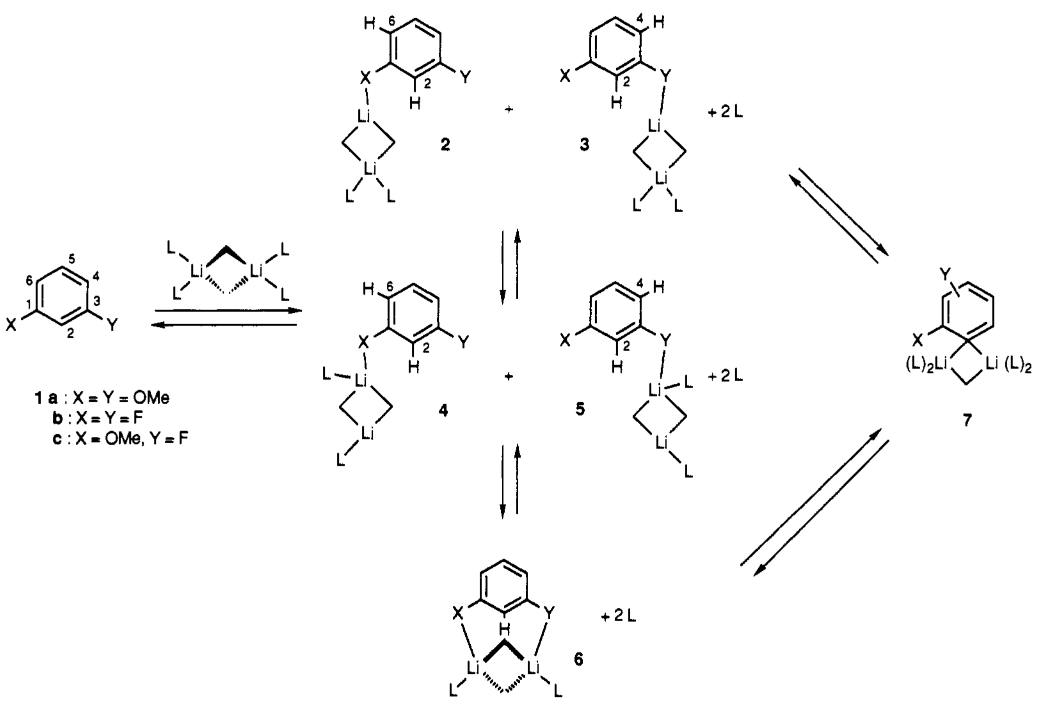
(23) VAX Version: Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101. Lithium parametrization: W. Thiel and T. Clark, unpublished (W. Thiel, personal communication to S. Olivella, January 1982).

(24) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355.

(25) Li–H Interactions are overestimated by MNDO. See: Kauffmann, E.; Raghavachari, K.; Reed, A.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597.

(26) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

Scheme I



coordination manner and that two complexes (each one involving the oxygen atom of an OMe group) ought to be in rapid equilibrium with each other on the NMR time scale. The conclusion drawn (no supporting MNDO calculations were provided in this case) was that lithiation of DMB could occur in an analogous manner to that shown for anisole. In other words, lithiation of DMB was suggested to involve the intermediate formation of a reactive complex (not observable in NMR due to its low equilibrium concentration) in which the substrate interacts with a butyllithium species, having a lithium atom with two vacant sites for coordination, through both an oxygen lone pair and by agostic Li···H_{ortho} interaction.[8]

Our extensive studies on the lithiation of phenols and alkoxyaromatics[27] had led us to establish an empirical rule according to which *the stronger the agostic interaction on a particular C–H bond the easier the hydrogen–lithium exchange*. To our surprise, preliminary MNDO calculations applied to the DMB case,[28] acting as a monodentate ligand, predicted that abstraction should preferably occur at C_6–H rather than at C_2–H, as indicated by the agostic interaction indicators shown (Figure 1). These predictions were confirmed by calculation of the corresponding reaction coordinate starting from the monocoordinated complex **2a**. Thus, the transition structure ($TS_{2a\text{-}C6}$) corresponding to C_6–H abstraction was found to lie at a slightly lower energy (ΔG = 51.2 kcal/mol) than that ($TS_{2a\text{-}C2}$) for the abstraction of C_2–H (ΔG = 52.7 kcal/mol),[29] using the monodentate coordination mode. In other words, according to MNDO, *lithiation of DMB by the monocoordination mode of approach should occur not at C_2 but, rather, at C_6*, in striking contrast with experiment.[13]

It occurred to us that DMB (and, presumably, other related compounds as well) could function as "a pair of tweezers" thereby providing a bidentate complex, presumably in equilibrium with monodentate complexes (Scheme I). In other words, we speculated the idea that atoms were preorganized[30] in DMB (and, presumably, other compounds as well) so that DMB could act as a chelating agent toward a dimeric, coordinatively unsaturated lithium base (MNDO calculated O–O distance in DMB = 4.741 Å; Li–Li distance in tetracoordinated dimeric methyllithium = 2.229 Å). The resulting aesthetically appealing chelated complex was envisaged as ideally suited (presumably) for undergoing H-2 abstraction.

Our initial attempts to find bidentate complex **6a** in a direct manner by imposing symmetry constraints to our calculations failed. A search for the bidentate complex **6a** was then launched by using a modified mixed coordinate[31] and starting at the geometry of the monocoordinated complex **4a** (X = Y = OMe; ΔG = +5.6 kcal/mol).[32] Careful analysis of this reaction coordinate

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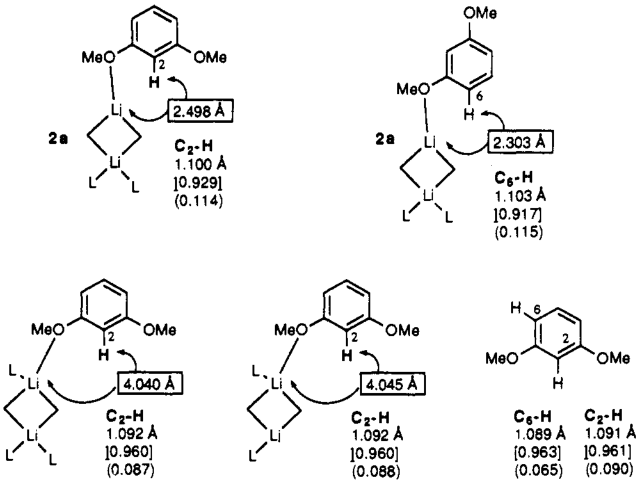
(27) Morey, J.; Costa, A.; Deyá, P. M.; Suñer, G. A.; Saá, J. M. *J. Org. Chem.* **1990**, *55*, 3902. Suñer, G. A.; Deyá, P. M.; Saá, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 1467.

(28) As suggested by a referee, significant parameters (C–H distances in angstroms; bond orders in brackets; net atomic charges on hydrogens H_2 or H_6 in parenthes(s) for several "nonagostic systems" related to **2a** are given, for comparison purposes.



For closely related examples, see also ref 27.

(29) For the sake of comparison, all free energy values are referred to starting compounds (1,3-disubstituted aromatic + dimeric, solvated methyllithium) and were calculated at –60 °C (213 K).

(30) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009.

(31) The reaction coordinate (r_1) was taken to be

$$r_1 = a_1 - a_2 + 2.5$$

instead of Dewar's:

$$r_1 = a_1 - a_2 + 1$$

See: Bodor, N.; Dewar, M. J. S.; Wasson, J. S. *J. Am. Chem. Soc.* **1972**, *94*, 9095.

eventually led us to find a very soft potential energy surface with complex **6a** (Figure 2) as a local minimum ($\Delta G = 14.6$ kcal/mol). Notable among its features, **6a** showed an unusually strong agostic interaction on the C_2–H bond, in spite of the fact that both lithium atoms were already tetracoordinated. In other words, agostic interaction is not a property of coordinatively unsaturated metal systems only, but it can also work on formally saturated, weak complexes such as **6a**, thereby activating spatially close C–H bonds for abstraction. Precedents in the recent literature for similar interactions in organolithium compounds are known.[33]

The large, selective agostic interaction on the C_2–H bond of **6a** was supported (Figure 2) by the following four standard parameters: (1) the close proximity between both lithium atoms and the hydrogen atom to be removed (2.644 and 2.729 Å); (2) the lengthening of the C_2–H bond (1.102 Å); (3) the corresponding decrease of its bond order (0.920); (4) the net positive charge formed on hydrogen (0.127). The short distance (2.858 Å) between H_2 and the closest CH_3 group (of methyllithium) is an additional clear-cut indicator of the proximity and nature of the nearby transition state. Upper and side views of the bidentate coordination complex **6a** are shown in Figure 2.

Starting from chelated complex intermediate **6a** the corresponding transition state structure for lithiation $TS_{6a\text{-}C2}$ (Figure 3) was easily found by using the standard reaction coordinate method. Noteworthy features present in $TS_{6a\text{-}C2}$ are as follows: (1) the almost ideal linearity of the hydrogen–lithium exchange (angle C_2–H–CH_3 = 176.2°)[34] and (2) the extent to which hydrogen atom H_2 is "half" transferred, as revealed by the close proximity of C_2–H (1.400 Å) and H–CH_3 (1.470 Å) distances.

Comparison of **6a** and **2a** or, rather, transition state structures $TS_{6a\text{-}C2}$ and $TS_{2a\text{-}C2}$ immediately reminded us of the recent studies by Jorgensen's[16] and Rebek's[17] groups on the subtle effects governing the binding (recognition) of neutral, complementary hydrogen donors and acceptors. In our study of the alternative reaction routes for lithiation, attention will be paid to both bond-forming and bond-breaking interactions. For the sake of clarity, bond-forming interactions are clasified as "neighbor" and "non-neighbor". Neighbor interactions (boldface lines in Figure 4) are meant to describe bonding interactions between pairs of atoms (A,B), in the substrate and the reagent, which become actually bonded (neighbor) in the final product. Those established between any other pairs of atoms not to become bonded in the products are called non-neighbor (lightface lines in Figure 4).[35]

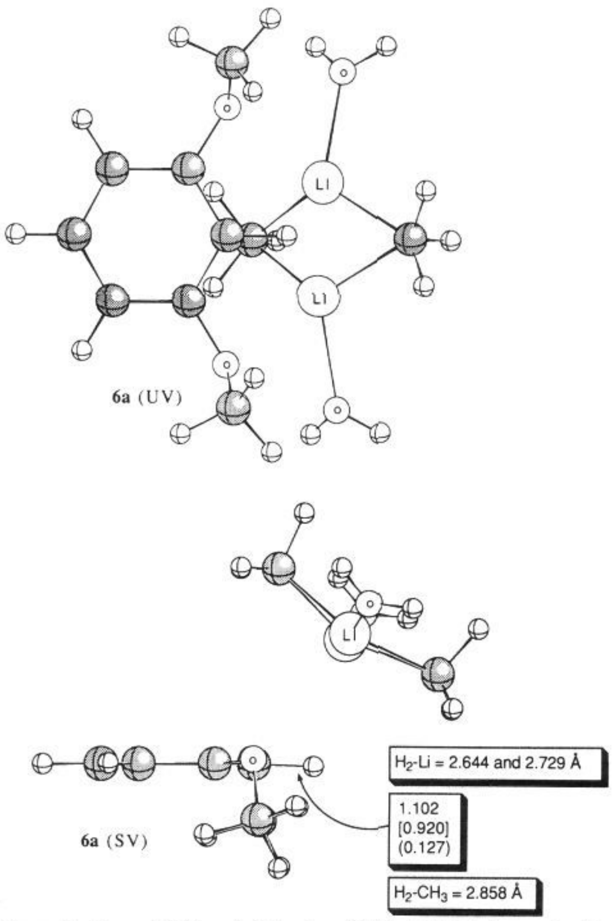


Figure 2. Upper (UV) and side views (SV) of chelated complex **6a** (bonds between oxygen atoms and lithium atoms are not shown for clarity). MNDO agostic interaction parameters on C_2–H are shown inside the boxes (distances in angstroms; bond orders in brackets; net positive atomic charges on hydrogen H_2 in parentheses).

A qualitative examination of saddle point structures $TS_{6a\text{-}C2}$ ($\Delta G = 49.6$ kcal/mol, $\Delta H = 51.2$ kcal/mol, $\Delta S = 8$ eu) and $TS_{2a\text{-}C2}$ ($\Delta G = 52.7$ kcal/mol, $\Delta H = 53.5$ kcal/mol, $\Delta S = 4$ eu) corresponding to lithiation at C_2 clearly shows (Figure 4) that five large interactions (two Li–O bonds,[36] one C–H bond, and two C_2–Li bonds) actually develop in going toward $TS_{6a\text{-}C2}$, but only three[35] (one O–Li, one C–H, and one C_2–Li bond) large interactions are involved in moving from **2a** toward the alternative saddle point structure $TS_{2a\text{-}C2}$. A more detailed, quantitative analysis of the energy contribution made by each interacting pair of atoms was carried out by partitioning the transition state total energies calculated by MNDO.[22b] This operation revealed several interesting observations worth being discussed (Table I). First, the difference in total energy can be assigned to the very large difference in "two-center" energies corresponding to neighbor interactions (−14.96 eV for $TS_{6a\text{-}C2}$ and −13.20 eV for $TS_{2a\text{-}C2}$) somewhat balanced by the leveling effect of non-neighbor inter-

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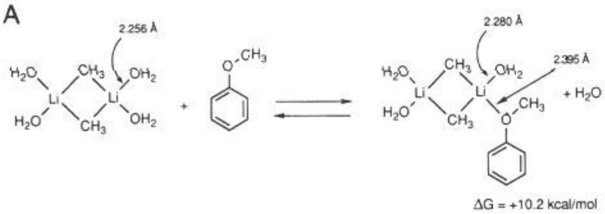
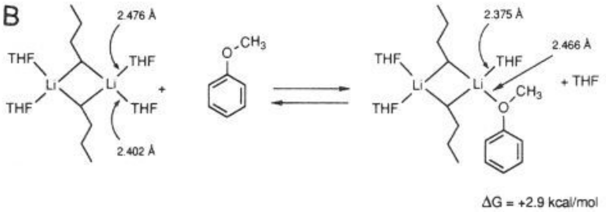
(32) The calculated ΔG values of the monodentate complexation of our model lithium base with anisole was found to be positive (+10.2 kcal/mol).



This discrepancy is due to a combination of the following two factors: (1) the tendency of MNDO to overestimate steric interactions, which should be particularly intense for **2a**, **4a**, and related complexes such as **2c** and **4c**. (2) the choice of a small molecule such as H_2O as ligand for our model lithium base; a ligand-exchange reaction of H_2O by a larger ligand such as anisole not only involves an unfavorable entropy change but, more importantly, unfavorable enthalpy changes also. Note that the process shown (reaction A) actually involves cleavage of a Li–O bond (2.256 Å) and the formation of a weaker one (2.395 Å). In agreeement with this reasoning we have examined the thermodynamics of following ligand exchange reaction:



As expected, the resulting complex (Li–O = 2.466 and 2.375 Å) is now very similar to that of the model base (dimeric butyllithium solvated with four THF ligands) which has very close Li–O values (2.476 and 2.402 Å). Accordingly, ΔG was found to be +2.9 kcal/mol, only, as shown in reaction B.

(33) See: Bauer, W.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 970 and references therein.

(34) Liotta, D.; Saindane, M.; Waykole, L.; Stephens, J.; Grossman, J. *J. Am. Chem. Soc.* **1988**, *110*, 2667 and ref 11.

(35) Non-neighbor interactions, due to the large distance between the atoms involved, are "minor" forces (<0.4 eV) relative to neighbor interactions (>1 eV). Thus, among others, C_2–Li_2, Y–Li_2 (in the monodentate coordination mode) or Me_2–Y, Me_2–C_3 (in the bidentate coordination mode) are considered non-neighbor. Accordingly they are collected as $\sum E_{AB(NN)}$ in Table I.

(36) Sannigrahi, A. b.; Kar, A. T.; Niyogi, B. G.; Hobza, T.; Schleyer, P. v. R. *Chem. Rev.* **1990**, *90*, 1061.

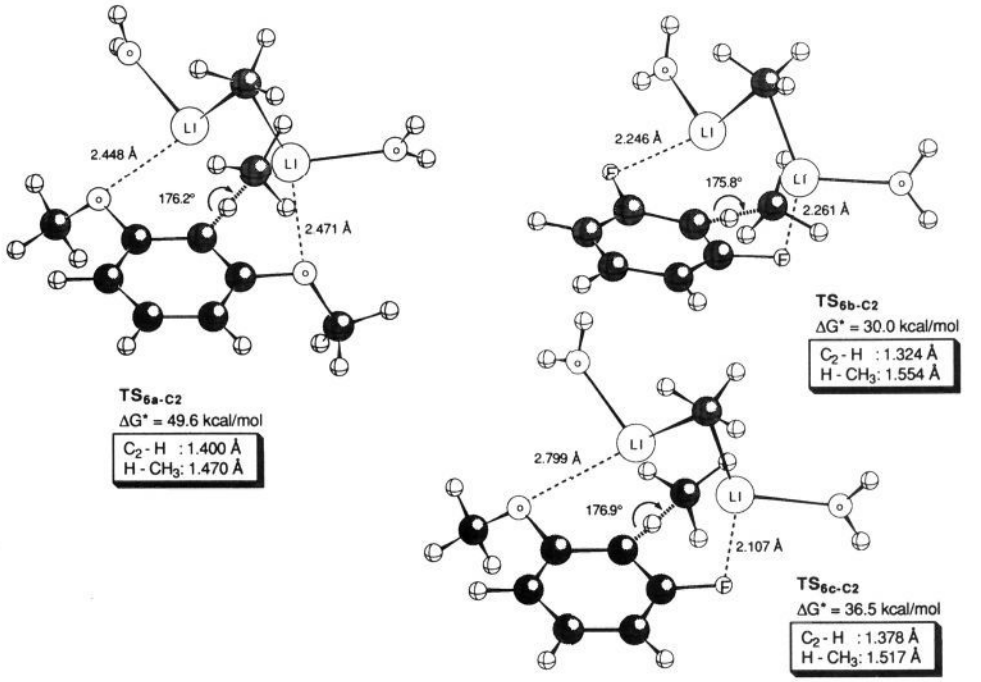


Figure 3. MNDO-calculated transition state structures for C_2 lithiation of dimethoxybenzene ($TS_{6a\text{-}C2}$), difluorobenzene ($TS_{6b\text{-}C2}$), and fluoroanisole ($TS_{6c\text{-}C2}$) by the bidentate coordination mode of approach (bonds between the CH_3 group undergoing reaction and lithium atoms are not shown for clarity).

Table I. Two-Center Energies[a] Corresponding to the Neighbor (Left), Non-Neighbor (Center), and Bond-Breaking (Right) Interactions[b]

transition state	$E_{Li1\text{-}X}$	$E_{C2\text{-}Li1}$	$E_{Me1\text{-}H}$	$E_{C2\text{-}Li2}$	$E_{Li2\text{-}Y}$	$\sum E_{AB(NN)}$	$E_{C2\text{-}H}$	$E_{Li1\text{-}Me1}$	$E_{Li2\text{-}Me1}$
Bidentate Coordination									
$TS_{6a\text{-}C2}$ X = Y = OMe	−2.53	−2.49	−4.92	−2.38	−2.64	−0.04	−6.10	−3.73	−3.75
$TS_{6b\text{-}C2}$ X = Y = F	−4.17	−2.14	−4.21	−2.12	−4.27	−0.31	−7.03	−4.03	−3.93
$TS_{6c\text{-}C2}$ X = OMe, Y = F	−1.38	−3.24	−4.65	−1.40	−5.35	−0.21	−6.44	−3.89	−3.82
Monodentate Coordination									
$TS_{2a\text{-}C2}$ X = Y = OMe, Z = H	−3.61	−4.17	−5.42	−0.30[c]	−0.23[c]	−0.08	−5.78	−4.16	−3.32
$TS_{2a\text{-}C6}$ X = Z = OMe, Y = H	−3.39	−4.58	−5.38	−0.41[c]	0.02[c]	−0.46	−5.63	−3.99	−3.28
$TS_{2b\text{-}C2}$ X = Y = F, Z = H	−5.61	−3.59	−5.32	−0.29[c]	−0.12[c]	−0.25	−6.07	−4.15	−3.55
$TS_{2b\text{-}C6}$ X = Z = F, Y = H	−5.47	−3.89	−5.38	−0.27[c]	0.04[c]	−0.29	−5.96	−4.01	−3.56
$TS_{3c\text{-}C2}$ X = F, Y = OMe, Z = H	−5.68	−3.62	−5.55	−0.29[c]	−0.21[c]	−0.07	−5.80	−4.03	−3.44
$TS_{3c\text{-}C4}$ X = F, Y = H, Z = OMe	−5.49	−3.99	−5.42	−0.27[c]	0.03[c]	−0.28	−5.88	−3.94	−3.59
$TS_{2c\text{-}C2}$ X = OMe, Y = F, Z = H	−3.55	−4.12	−5.24	−0.32[c]	−0.15[c]	−0.30	−6.02	−4.25	−3.44
$TS_{2c\text{-}C6}$ X = OMe, Y = H, Z = F	−3.35	−4.49	−5.33	−0.45[c]	0.03[c]	−0.51	−5.68	−4.03	−3.36

[a] In electronvolts. [b] See Figure 4. [c] Included in $\sum E_{AB(NN)}$ (non-neighbor interactions).

actions. Second, by dividing the two-center energy contributions into their "net electrostatic" and covalent components,[22b] neighbor interactions are identified as largely covalent. Actually, the net electrostatic component is always (slightly) repulsive except for the C–H interaction which was found to be attractive.

On the other hand, the MNDO-predicted preference for C_6 (instead of C_2) lithiation by the monodentate coordination mode appears to be of entropic origin, as the enthalpy term for both $TS_{2a\text{-}C2}$ (see above) and $TS_{2a\text{-}C6}$ ($\Delta G = 51.2$ kcal/mol, $\Delta H = 53.6$ kcal/mol, $\Delta S = 11$ eu) is almost identical.

In summary, the lowest energy barrier ($\Delta G = 49.6$ kcal/mol) of all three approaches examined for the ortho lithiation of DMB is that of the bidentate coordination approach ("pair of tweezers" mechanism). Actually, it was found to be 3.1 kcal/mol lower than that of the lithiation at C_2 by the monodentate coordination approach, but only 1.6 kcal/mol lower than that of the C_6 lithiation by the monodentate coordination mode. This energy difference satisfactorily explains both the experimentally observed kinetic acceleration and the regiospecific removal of C_2–H in the directed lithiation of 1,3-dimethoxybenzene (see below for the clear-cut DBF and FA cases).[37,38] The well-known tendency of MNDO

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[38] For the lithiation of FA, see ref 6. Huisgen, R.; Rist, H. *Ann. Chem.* **1955**, *594*, 137. Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett.* **1991**, 731. For the lithiation of 2- and 4-fluoroanisole, see: Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. Furlano, D. C.; Calderon, S. N.; Chen, G.; Kirk, K. L. *J. Org. Chem.* **1988**, *53*, 3145.

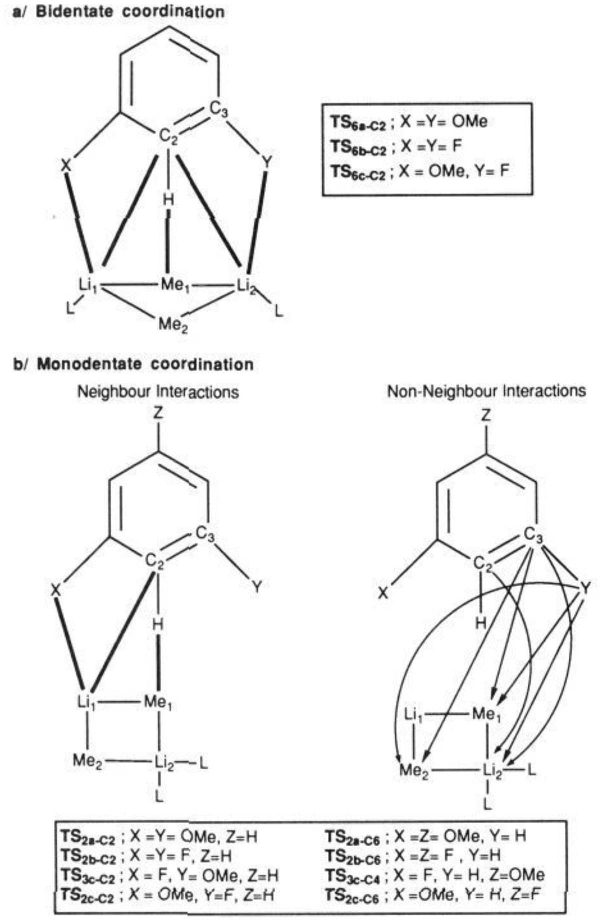

Figure 4. Neighbor interactions (boldface lines) in transition structures corresponding to the (a) bidentate ($TS_{6a,b,c\text{-}C2}$) and (b) monodentate coordination modes of approach ($TS_{2a,b\text{-}C2}$, $TS_{3c\text{-}C2}$, $TS_{2a,b\text{-}C6}$, and $TS_{3c\text{-}C4}$). For clarity, non-neighbor interactions (lightface lines) are shown only for the monodentate coordination mode of approach.

to overestimate repulsive steric interactions which seemingly will still enlarge this difference should be kept in mind.

A further noteworthy feature of the above study is that the calculated 2-lithio derivative of DMB, **7a**, closely resembles the crystal structure described by Schleyer et al.,[39] thus supporting the use of MNDO for studying large lithium structures. Actually, MNDO correctly predicts the most remarkable feature of **7a**, namely, that C_2 is (almost) planar. Geometrical parameters for **7a** are provided as supplementary material.

This result convinced us of the need to check whether or not chelated complexes such as **6a** would also intervene as intermediates in related examples having different heteroatoms in a meta relationship (Scheme I). Two fluoro-substituted aromatics, namely, 1,3-difluorobenzene (DFB)[37] and 3-fluoroanisole (FA) were chosen for study.[38] As shown below, our expectations were fully corroborated by calculations.

Thus, according to calculations, lithiation of DFB at C_2 by the monodentate coordination approach, that is, involving complex **2b** ($\Delta G = -16.0$ kcal/mol), is predicted to be slightly more energetically costly ($TS_{2b\text{-}C2}$; $\Delta G = 36.6$ kcal/mol) than would lithiation at C_6 ($TS_{2b\text{-}C6}$; $\Delta G = 36.1$ kcal/mol). Apparently, the influence exerted by the second fluorine atom on its ortho position (C_2) is almost identical (in fact, lower!) to that on the para (C_6) position. This result obviously calls for reconsideration of the role

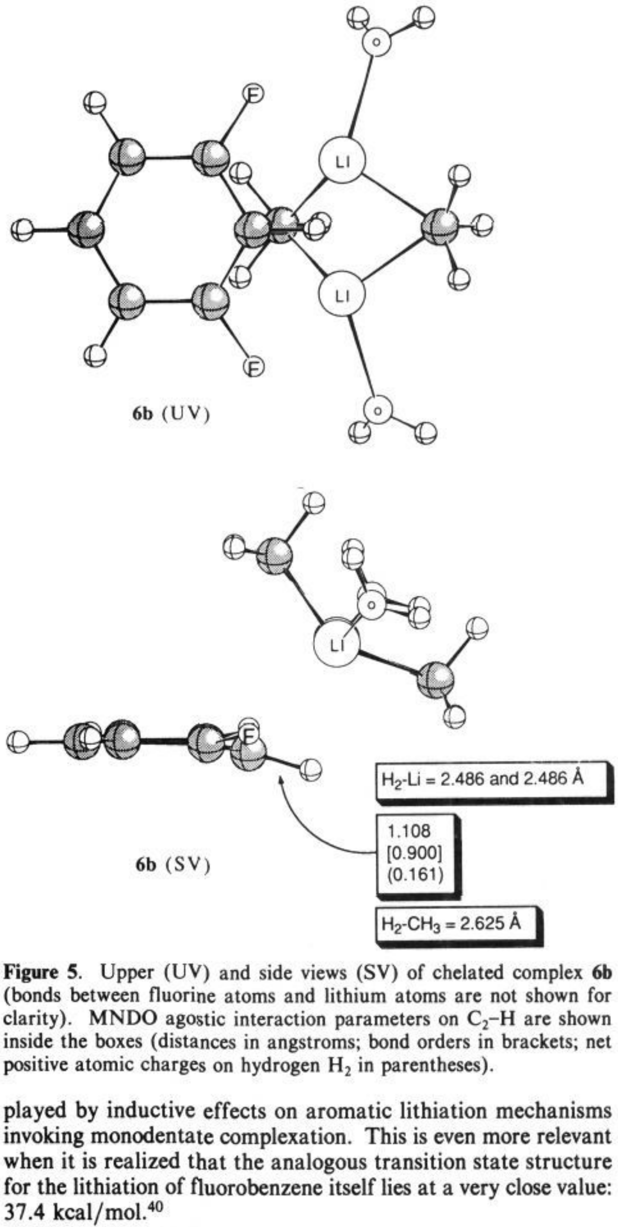

Figure 5. Upper (UV) and side views (SV) of chelated complex **6b** (bonds between fluorine atoms and lithium atoms are not shown for clarity). MNDO agostic interaction parameters on C_2–H are shown inside the boxes (distances in angstroms; bond orders in brackets; net positive atomic charges on hydrogen H_2 in parentheses).

played by inductive effects on aromatic lithiation mechanisms invoking monodentate complexation. This is even more relevant when it is realized that the analogous transition state structure for the lithiation of fluorobenzene itself lies at a very close value: 37.4 kcal/mol.[40]

For the case of DFB, our MNDO calculations demonstrate that chelated complex **6b** (easily available from **4b**) is a local minimum which, due to its high energy ($\Delta G = +9.2$ kcal/mol), should not be observable by NMR. Complex **6b**, as is the case for **6a**, showed strong agostic interaction on C_2–H as indicated by the standard parameters: short Li–H distances (2.486 and 2.486 Å); enlarged C_2–H bond (1.108 Å); decreased C_2–H bond order (0.900); large net atomic charge on hydrogen (0.161). Interestingly one of the CH_3 groups is located at only 2.625 Å from the nearby H_2, i.e., it is "ready" to abstract H_2 (Figure 5).

The transition state structure $TS_{6b\text{-}C2}$ corresponding to the bidentate coordination mode of approach was easily obtained for **6b** by the standard coordinate method and found to lie at $\Delta G = 30.0$ kcal/mol,[29] i.e., 6.6 kcal/mol lower than that corresponding to the monodentate coordination mode. Among its most significant structural features the almost ideal C_2–H–C angle (175.8°) stands as the most noticeable (Figure 3). Summarizing, as for the case of DMB, only when the bidentate coordination mode of approach is invoked, can the experimentally observed rate acceleration and regioselectivity for the lithiation of DFB be satisfactorily explained.

Here, too, we see that $TS_{6b\text{-}C2}$ ($\Delta G = 30.0$ kcal/mol, $\Delta H = 32.0$ kcal/mol, $\Delta S = 10$ eu) is strongly favored over the alternative

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$TS_{2b\text{-}C2}$ (ΔG = 36.6 kcal/mol, ΔH = 38.3 kcal/mol, ΔS = 8 eu) because, in the latter, only three large (instead of five large, in the former) overall attractive neighbor interactions develop in moving from complexes **6b** or **2b** to the corresponding saddle point structures and, eventually, to the final products. On the other hand, the calculated preference for C_6 lithiation ($TS_{2b\text{-}C6}$, ΔG = 36.1 kcal/mol, ΔH = 38.1 kcal/mol, ΔS = 10 eu) instead of lithiation at C_2, by the monodentate coordination mode, can be traced down largely to the entropy term since the enthalpy term is very close for both saddle point structures.

MNDO correctly predicts that DFB is lithiated faster than DMB. The extremely large difference between both transition state energies (30.0 vs. 49.6 kcal/mol, respectively) appears to be a consequence of the fact that fluorine atoms interact with lithium atoms at much lower interatomic distances, thus bringing the adjacent C_2–H bond much closer to the attacking CH_3. Agostic interaction parameters also bear on this point. Actually, chelated complex **6a** is 14.6 kcal/mol above starting reactants, and the corresponding transition state $TS_{6a\text{-}C2}$ stays at 49.6 kcal/mol. In contrast, **6b** is 9.2 kcal/mol above starting materials, but the corresponding transition state $TS_{6b\text{-}C2}$ sits at only 30.0 kcal/mol. Major energy changes are thus taking place after the intermediate complexes are formed as suggested by the spatio–temporal hypothesis.[41]

We also studied the different alternative pathways for lithiation of fluoroanisole (FA) (**1c**) starting from monodentate complexes **2c** or **3c**, the former involving complexation through oxygen and the latter through fluorine (Scheme I). As shown above for the DBF case, MNDO calculations predict that organolithium bases should form strong lithium bonds[24] with the fluorine atom of fluoroaromatics such as FA (**1c**). Coordination of alkaline metal ions by C–F bonds appears to be a general phenomena as illustrated recently by both experimental observations[42] and theoretical calculations.[43] Actually, complexes featuring either mono- or bidentate[42a,b,f-h] coordination by C–F bonds have been described in the recent literature.

Apparently, the above results are in striking contrast with the fact that fluorobenzene does not form an NMR observable complex when treated with hexameric butyllithium (in toluene). These apparent discrepancies would be in accord, however, if it is assumed that the complex rapidly evolves into lithiated products and that the prior deaggregation of hexameric butyllithium into tetrameric and/or dimeric aggregates might be the rate-determining step.[11]

Analogous results to those shown above for DMB and DFB were found for the lithiation of FA by the monodentate coordination (through fluorine) mode, i.e., lithiation at C_2 was found to involve crossing a higher energy barrier ($TS_{3c\text{-}C2}$; ΔG = 39.6 kcal/mol, ΔH = 40.6 kcal/mol, ΔS = 5 eu) than that leading to lithiation at C_4 ($TS_{3c\text{-}C4}$; ΔG = 37.3 kcal/mol, ΔH = 38.9 kcal/mol, ΔS = 7 eu). Contrary to previous cases, the enthalpy term seems to play now a major role. Partitioning the total energy reveals that both neighbor and non-neighbor interactions tend to favor lithiation at C_4, the latter being very important in this regard (Table I). Thus, whereas non-neighbor interactions ($\Sigma E_{AB(NN)}$) are almost nil in $TS_{3c\text{-}C2}$ (–0.07 eV), they amount to an overall –0.28-eV interaction for $TS_{3c\text{-}C4}$. Neighbor interactions, on the other hand, are almost identical for $TS_{3c\text{-}C2}$ and $TS_{3c\text{-}C4}$.

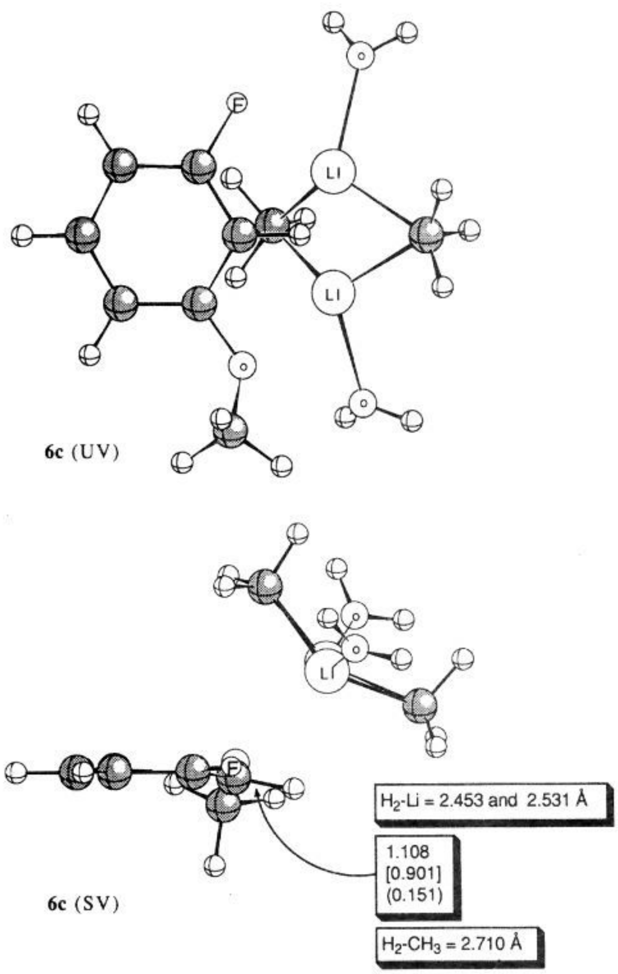

Figure 6. Upper (UV) and side views (SV) of chelated complex **6c** (bonds between oxygen and fluorine atoms and lithium atoms are not shown for clarity). MNDO agostic interaction parameters on C_2–H are shown inside the boxes (distances in angstroms; bond orders in brackets; net positive atomic charges on hydrogen H_2 in parentheses.

Monodentate coordination through the oxygen atom leads to complex **2c** which was used as the starting point for calculating the saddle point $TS_{2c\text{-}C2}$ for lithiation at C_2 (ΔG = 50.1 kcal/mol, ΔH = 51.8 kcal/mol, ΔS = 8 eu). Curiously enough, lithiation at the more "congested" C_2 was now found to be easier than at the alternative C_6 (ΔG = 51.6 kcal/mol, ΔH = 53.7 kcal/mol, ΔS = 10 eu). Partitioning the total energy reveals that unless bond-forming and bond-breaking interactions are taken into consideration, no explanation can be found. Actually, both neighbor (–13.17 vs –12.91 eV) and non-neighbor (–0.51 vs –0.30 eV) interactions favor $TS_{2c\text{-}C6}$ over $TS_{2c\text{-}C2}$. Table I shows that all bond-breaking (C_2–H, Me_1–Li_1, and Me_1–Li_2) interactions are responsible for the calculated result.

Bidentate complex **6c** was successfully calculated by using the standard coordinate method starting at either **4c** or **5c**. As for the previous cases above, a strong agostic interaction on C_2–H was observed at this stage and was characterized by (1) the short (2.453 and 2.531 Å) Li–H_2 distances; (2) the large (1.108 Å) C_2–H bond; bond; (3) the decrease bond order (0.901); (4) the large net atomic charge on H_2 (0.151). The short H_2–CH_3 distance (2.710 Å) further supports the proximity of the transition state (Figure 6).

As expected, lithiation at C_2 from chelated complex **6c** led to transition state $TS_{6c\text{-}C2}$ (36.5 kcal/mol) having significantly (3 kcal/mol) lower energy than any of those derived from the monodentate coordination mode of approach (Figure 3). Again,

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this is in support of the mechanistic proposal according to which 3-fluoroanisole undergoes kinetic lithiation at C_2 because it is capable of acting as "a pair of tweezers" (F–O distance = 4.780 Å) upon a lithium dimer having two coordinatively unsaturated lithium atoms. Again, this preference can be traced down to the strength of the five large neighbor interactions present in $TS_{6c\text{-}C2}$.

In summary, we have presented convincing theoretical (MNDO) evidence for the intermediate formation of weak, bidentate (chelated) complexes in the lithiation of some representative 1,3-disubstituted heteroatom aromatics. This bidentate coordination ("pair of tweezers") mechanism qualitatively explains both the kinetic acceleration (dynamic molecular recognition)[44] and the regioselective hydrogen abstraction at C_2–H experimentally observed. Chelated complexes, which are true local minima on the energy surfaces, show intense C_2–H agostic interactions in spite of the fact that both lithium atoms are formally pentacoordinated. Remarkably, MNDO shows that lithiation by the monocoordination mode at C_6 is favored over that at C_2 for DMB and DFB, because they are entropy-controlled reactions. For enthalpy-controlled reactions, a subtle interplay between neighbor and non-neighbor interactions actually determines the outcome of the lithiation of prototype 1,3-disubstituted aromatics. In particular, by partitioning the MNDO-calculated transition state energy, it can be realized that lithiation at C_2 by the bidentate coordination mode is favored over lithiation by the monodentate coordination mode at either C_2 or C_6 largely because the strength of neighbor interactions is larger through the former route.

We hope these results might help in defining novel ditopic or polytopic chelators for complex bases involving either lithium or other metals. As suggested by Jorgensen's mnemonics for binding between neutral compounds, central criteria for success should be that attractive forces are maximized whereas repulsive ones are minimized.

Acknowledgment. Time allocation for calculations was generously provided by the Centre de Càlcul de la Universitat de les Illes Balears. Financial support by the DGICYT (PB90-0040) is gratefully acknowledged. We are indebted to Professor S. Olivella (U. de Barcelona, Spain) for valuable suggestions and comments during the course of our work, as well as for making his modified version of MOPAC available to us, and to Dr. A. Costa and P. Ballester for helpful discussions.

Registry No. 1a, 151-10-0; **1b**, 372-18-9; **1c**, 456-49-5; $[CH_3Li(H_2O)_2]_2$, 143631-78-1.

Supplementary Material Available: Tables of Cartesian coordinates of the optimized molecular structures (22 pages). Ordering information is given on any current masthead page.

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Computational Evaluation of the Coupled Oscillator Model in the Vibrational Circular Dichroism of Selected Small Molecules

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Received April 8, 1992

Abstract: A comparison is made between the predictions of the dynamic coupling or coupled oscillator model of vibrational circular dichroism (VCD) and those of the a priori magnetic field perturbation (MFP) theory as formulated by Stephens. For two independent formaldehyde molecules at reasonably large separations, both calculations are in agreement for the C=O VCD; but deviations develop at short separations. In addition, calculated results for seven different cyclopropane- or cyclobutane-based molecules made chiral by trans-dideuterio substitution are presented. For identical C–H and C–D stretch oscillators, the hydrocarbons studied gave MFP computed VCD spectra that are qualitatively predictable with the coupled oscillator model, but the MFP magnitudes were uniformly larger and exhibited a progressive degree of inequality. However, the coupled oscillator model failed for some oxygen-containing molecules studied, implying that its application is far from universal.

Introduction

The simplest model for vibrational circular dichroism (VCD) is known variously as the dynamic coupling, exciton coupling, or degenerate coupled oscillator (DCO) mechanism,[1,2] whereby monomer-like excitations of local transition dipoles are mixed to form properly phased molecular excitations. Effects of dipolar mixing are most evident for degenerate oscillators, those related by a symmetry operation, but dynamic coupling can contribute to the VCD of any pair of oscillators. If these degenerate local oscillators are non-coplanar, a VCD spectrum results which has a positive and a negative lobe of the same intensity (often termed a "conservative couplet") that usually result in a characteristic derivative shape whose intensity and sign is dependent on the relative angle between the oscillators and consequently on the geometry of the molecule.

Over the last 15 years, a number of reported VCD spectra, especially for C_2 symmetry molecules, have evidenced such band shapes.[3-5] Consequently, with some success, efforts have been

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