An HF and DFT *ab initio* Study on the Mechanism of *ortho*-Directed Lithiation of Hydric and Nonhydric Aromatic Compounds Incorporating Aggregation and Discrete Solvation: The Role of *N,N,N′,N′*-Tetramethylethane-1,2-diamine (TMEDA) in Lithiation Reactions[1])

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An HF and DFT *ab initio* study was set up to decipher the roles of aggregation and solvation in the *ortho*-directed lithiation of aromatics (hydric and nonhydric), as well as to shed light on the much debated question of precomplexation in the mechanism of lithiation. *Ab initio* (HF/6-31-G*) calculations on the lithiation of nonhydric aromatics have uncovered several competitive routes operating as a function of the aggregation state of the organolithium base used. Specifically, two competitive routes were found for the lithiation of the anisole model **2** by organolithium dimers **1-dim**, namely the so-called cyclic-dimer and open-dimer routes, whereas, for organolithium tetramers **1-tet**, the corresponding cyclic route is the only one operative, and, for monomers **1-mon**, several optional routes seem to be available. Precomplexation is, in all cases, a requirement. According to the computational data presented, the mysterious rate acceleration experimentally observed for lithiations carried out in TMEDA can be assigned to an aggregation effect on the intermediate open-dimer species, which subsidiarily give rise to several so-called s-monomer routes, of which the dimerization-driven s-monomer route s-m_{3b} is the one having the lowest energy barrier. The relevant species characteristic of both the open-dimer and s-monomer routes are the so-called open dimers, *i.e.*, high-energy intermediates (actually, spiro dimeric aggregates), resulting from cleavage-induced associative complexation of the aromatic substrate upon the fully solvated organolithium dimer. DFT calculations (B3LYP/6-31+G*) also revealed that the *peri*-lithiation (*i.e.*, Li at C(8)) of 1-naphthol model **3** is a slow process taking place preferentially through the open-dimer route.

1. Introduction. – Independently discovered by *Gilman* and *Bebb* [1], and *Wittig* and *Fuhrmann* [2] sixty years ago, the heteroatom-directed *ortho*-lithiation of aromatics (*Scheme 1*) is currently a prominent synthetic methodology of everyday use in organic-chemistry laboratories [3]. Nevertheless, two large pitfalls in its mechanism still inspire very active debate and controversy. The core of the major dispute refers to the necessity [1][4] or not [5] to invoke the formation of intermediate complexes as a step prior to the actual rate-determining deprotonation [6]. The second concern deals with the actual structure of these complexes (if any) [7], the detailed mechanism of activation [3–5] of the *ortho* (or appropriately located [8]) H-atoms being abstracted, and the hitherto mysterious role played by *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA) as compared with other common donor solvents such as ethers [3g].

In essence, two opposing views exist with regard to the major point in dispute: whilst one group claims that the heteroatom-directed lithiation of aromatics should be strictly considered a kinetically controlled reaction (*i.e.*, a one-step reaction that,

[1]) This paper is dedicated to Prof. *D. Seebach*, a pioneer in the field.

Scheme 1

accordingly, these authors have renamed 'kinetically enhanced metalation') [5], the defenders of the CIPE (complex-induced proximity effects) theory [7] and, ultimately, of the *Roberts* and *Curtin* mechanism [4], call for a stepwise reaction involving a prelithiation complex of imprecise structure (usually written as $Ar{-}X{-}(RLi)_n$) and energy, followed by the rate-limiting intramolecular deprotonation step. In principle, this issue should be amenable to experimental analysis, and, in fact, a number of studies have provided evidence, kinetic [6][9] or otherwise [10], for the existence of prelithiation complexes. However, on closer examination, it turns out that all cited evidences actually refer to benzylic lithiations and none to heteroatom-directed aromatic lithiations. Also in support of this view is *Bauer* and *Schleyer*'s study of the *ortho*-lithiation of anisole [11], which showed that a much presumed prelithiation complex such as $ArOMe \cdot (BuLi)_4$ was in fact an unproductive end-on complex in the mechanistic manifold. Recently, in an effort to clarify this important issue, *Beak* and co-workers evaluated inter- *vs.* intramolecular kinetic isotope effects in three specific examples (two heteroatom-directed aromatic lithiations and one benzylic metalation) [12]. For the benzylic-lithiation case, a clear-cut two-step mechanism involving precomplexation was mandated by the experimental results. However, for the aromatic-lithiation cases, both inter- and intramolecular isotope effects were found to be large (>20) and equal, thus impeding a definitive differentiation between single-step and stepwise mechanisms.

Another kinetic analysis recently published by *Collum* and co-workers [13] on the *ortho*-lithiation of anisole promoted by the action of TMEDA-solvated dimeric butyllithium [14], $(BuLi)_2 \cdot (TMEDA)_2$, also revealed mechanistic details worthy of comment [15]. Thus, the fact that the rate equation included both the $[anisole]^1$ and $[(BuLi)_2 \cdot (TMEDA)_2]^1$ terms but was independent of [TMEDA], as derived from plots of k_{obs} *vs.* [BuLi] and k_{obs} *vs.* [TMEDA] [2]), led the authors to suggest open dimers [16][17] or triple ions [18] as plausible intermediates [19]. *Collum* and co-workers also considered it feasible that more than a single mechanism might well be operating for *ortho*-lithiations, an idea already proposed by *Shimano* and *Meyers* [20] as well as by *Maggi* and *Schlosser* [21], and, more recently, by *Beak* and co-workers [12]. Whatever it might be, in employing BuLi in TMEDA, which is known to exist as a chelated dimer [22], *Collum* and co-workers actually pinpointed solvation and aggregation as the key issues to be studied towards understanding *ortho*-directed lithiations. However, solvation might not be a simple matter to unravel, as recognized by the existence of correlation effects of the chelating amine on the kinetics of the *ortho*-lithiation of anisole [23], and also by the fact that TMEDA can function as a catalyst for the lithiation of anisole, as demonstrated by *Slocum et al.* [24]. Another remarkable

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[2]) Actually there is a slight dependence on [TMEDA] as revealed by the plot k_{obs} *vs.* [TMEDA]; see [15].

observation regarding TMEDA solvation effects is the increase of reactivity of *s*-BuLi-amide prelithiation complexes with the number of TMEDA ligands, as reported by *Smith* and *Beak* [25]. Generally speaking, however, it can be stated that the detailed effects of aggregation [26] and solvation [27] on the reactivity of organometallic compounds is a poorly understood issue [28–32], in spite of the fact that their bulk effects, *i.e.*, the well-known increase of reactivity in the presence of polar solvents, have been described long ago in terms of solvating power [33], basicity [34], or otherwise [35][36].

A number of quantum-chemical studies have dealt with some of the hot issues of heteroatom-directed lithiations. Mechanistic models for the lithiation of nonhydric [11] and hydric [37] aromatics, both based on theoretical MNDO studies, were proposed ten years ago. Both independent studies concluded that *ortho*-positioned H-atoms were apparently activated due to agostic interaction [38] elicited by nearby coordinatively unsaturated Li-atoms [39]. However, the weak point of these proposals, as critics of MNDO argue, was the inadequacy of the semiempirical method employed to detect lithium agostic interactions in light of its well-known overestimation of Li–H and Li–C interactions [40]. Obviously, more reliable theoretical data was needed [41]; *Van Eikema Homes* and *Schleyer* [5] were the first to report high-level *ab initio* calculations on a number of model complexes (lithium aggregation was included in these calculations, but solvation [42], discrete or otherwise, was absent in all cases) for the lithiation of non-hydric compounds. As a consequence of the lack of evidence for the agostic interaction-based mechanism and since precomplexation was considered irrelevant to the Erlangen group [5a], it was eventually suggesed that the classical mechanism should be named, instead, 'kinetically enhanced metalation'. Unfortunately, though, the absence of solvent in *Schleyer*'s analysis impeded the necessary contrasting of theoretical and experimental data such as the recent kinetic work of *Beak*'s and *Collum*'s groups.

Faced with this unsatisfactory state of affairs, a computational approach was planned to clarify the unsettled questions posed by the *ortho*-directed lithiation of hydric and non-hydric aromatics. The plan clearly demanded a refined *ab initio* computational effort, so as to incorporate the two key features of organolithium compounds, namely aggregation and discrete solvation. The availability of experimental mechanistic data for the lithiation of anisole [15] and phenol (the *peri*-lithiation (*i.e.*, Li at C(8)) of 1-naphthol [43] has been shown to involve mixed dimers) facilitated their selection as the initial candidates for this analysis. Herein, I report the results of this extremely laborious approach, for which dimeric methyllithium **1-dim** solvated with two discrete dimethylether (Me_2O), or one TMEDA, molecules per Li-atom[3]) was initially chosen as the model for the aggregated and solvated organolithium base [44]. Eventually, in dealing with tetrameric and monomeric species (see below), models **1-tet** and **1-mon** were employed. Methyl vinyl ether (= methoxyethene; **2** and buta-1,3-dien-2-ol (**3**) were selected as models for the *ortho*-directed lithiations of anisole and 1-naphthol, respectively. Preliminary work with dimeric organolithium compounds with H_2O as ligand (see **1a**) led to unanticipated results (not shown) caused by the

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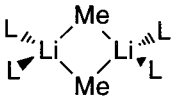
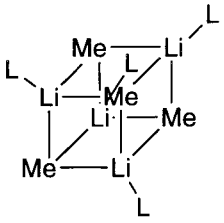
[3]) In THF, BuLi exists as mixture of solvated tetramers and dimers; in TMEDA, BuLi exists as dimers; see [3g][23][14b].

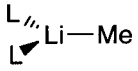
appearance of unrealistic H-bonds involving H_2O and one of the α C-atoms. Since this induced a significant geometric distortion, H_2O was abandoned as ligand [45]. Instead, Me_2O was employed throughout as ligand for the Li-atom (see **1b**), except for the case of **1a-tet**, otherwise too large to examine computationally. TMEDA was also incorporated as ligand (see **1c**) in an effort to learn on its mysterious activating role in lithiation reactions [25][46]. For the sake of generalization, the analysis was eventually extended to the lithiation of *N*,*N*-disubstituted benzamides (one of the best *ortho*-lithiation-directing groups known) [3f][47], for which purpose the model acrylamide (**4**) was selected. Even though aromaticity is absent in the models chosen for the aromatic educts anisole, 1-naphthol, and benzamide, the data obtained for **3** (*vide infra*) fit rather well with that reported by *Schleyer* employing an unsolvated aromatic model [5]. These results are in support of the validity of the models chosen for study.



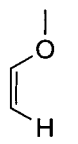
1a-dim L=H_2O
1b-dim L=Me_2O
1c-dim L+L=TMEDA



1-tet L=none
1a-tet L=H_2O



1b-mon L=Me_2O
1c-mon L+L=TMEDA



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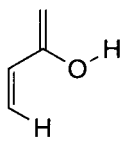

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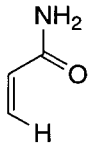

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At the start, one has to accept the possibility that the coordinatively saturated organolithium base (in our case $(MeLi)_2(OMe_2)_4$, **1b-dim**) can form a complex with anisole *en route* towards lithiation. Unfortunately, not much attention has been paid, to date, to the details of complexation in main-group organometallics, in contrast with that involving organotransition metals [48]. The general assumption for the highly ionic organolithium compounds [49] is that complexation likely involves acid-base reactions (presumably occurring through a dissociative mechanism), thereby giving rise to ligand exchange and/or deaggregation phenomena [3c]. Nevertheless, associative mechanisms, though apparently more unusual [50], are gaining general acceptance. Thus, as

suggested by *Gregory*, *Schleyer*, and *Snaith* [51], it is the substrate that may act first as *Lewis* base/nucleophile toward the organolithium reagent, thereby generating the effective reagent. Several research groups, among them those of *Collum*, *Williard*, *Morokuma*, *Nakamura*, and *Schlosser*, have provided evidence for mechanistic schemes of this type for a number of β-elimination reactions promoted by amidolithium derivatives [16][17].

Overall, the present theoretical study has served the main purpose of clarifying somewhat the landscape of aggregation and solvation phenomena in *ortho*-lithiation reactions. In particular, dissociative solvation processes (available for all kinds of aggregates) give rise to a number of lithiation paths, namely the so-called cyclic-oligomer (cyclic-dimer, cyclic-tetramer, *etc.*) routes. On the other hand, cleavage-induced associative solvation (available only for dimeric organolithium compounds) give rise to the open-dimer and the so-called s-monomer lithiation routes[4]). As explained below, analysis of these competing routes allows one to understand the mysterious rate acceleration observed for *ortho*-lithiations carried out in TMEDA. Another important issue was set up in this work: whatever the lithiation route operating for a particular aggregation/solvation case, high-energy intermediate complexes (open dimers or otherwise) appear to be involved.

2. Computational Details. – The study of the *ortho*-lithiation of anisole, 1-naphthol, and benzamide was carried out by determining the structures corresponding to ground-state and transition-state geometries on the reaction-energy hypersurfaces. These were fully optimized by means of gradient techniques [52] at the *Hartree-Fock* (HF) and/or DFT (B3LYP) level of theory, by using split-valence d-polarized 6-31G* basis set [53], enriched, in most cases, with diffuse functions [54]. These functions were employed because they are known to be more effective than polarization functions in reducing electron-density superposition errors for organolithium compounds [55]. Stationary points were fully characterized as minima (all frequencies real) or transition structures (one and only one imaginary frequency) according to the number of imaginary modes resulting from the diagonalization of their Hessian matrices (vibrational analysis) [56]. In addition, visualization of the reactive mode in the transition structures helped in the assignment of the transition structure to the corresponding minima. The zero-point vibrational energies (ZPVE) were computed at the same level and were not scaled. Where appropriate (phenol-lithiation model), electron correlation was incorporated by means of density functional theory (DFT) [57] by using the nonlocal hybrid three-parameter functional developed by *Becke* and denoted as B3LYP exchange-correlation functional [58][59], with the 6-31 + G* basis set [53]. The reliability of the HF *vs.* DFT calculations was checked by examining the HF/6-31G* and B3LYP/6-31 + G* hypersurfaces for the lithiation of naphthol model **3** (*Table 3*, *vide infra*). Somewhat as expected, HF- and DFT-optimized geometries were found to be almost identical, even though energy values differed significantly, more so for transition structures. Due to the extremely high resource-demanding nature of the calculations on nonhydric aromatics **2** and **4**, the reliability of the HF *vs.* B3LYP calculations was checked for two particular cases, namely **6b-ts** and **6b**. Again, it was found that the optimized B3LYP/6-31 + G* geometries were almost identical to those resulting from HF/6-31 + G* optimizations, while energies differed considerably. Fortunately, single-point B3LYP/6-31 + G*//HF/6-31 + G* energy calculations reproduced extremely well the B3LYP/6-31 + G*// B3LYP/6-31 + G* relative energies (104.48 kJ/mol *vs.* 105.27 kJ/mol, respectively, for the **6b** → **6b-ts** conversion). Accordingly, in order to save computer resources, only single-point (B3LYP/6-31 + G*//HF/6-31 + G*) energy calculations were determined for the lithiation of **2** and **4**. Absolute energies (in hartree) are given in *Table 1*. All calculations were performed with the 'Gaussian94' program [60]. The original input structures used for the *ab initio* study were, in most cases, the optimized structures resulting from a semiempirical analysis (the details of which are not reported), here carried out with PM3 as implemented in 'AMPAC' and 'SPARTAN'

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[4]) s-Monomer routes stand for subsidiary monomer routes (*i.e.*, daughters of the open-dimer routes) as opposed to the regular monomer routes.

Table 1. *Absolute Energies* [hartree]

Compound[a])		HF/6-31 + G*// HF/6-31G*	HF/6-31 + G*// HF/6-31 + G*	B3LYP/6-31 + G*// HF/6-31G*	B3LYP/6-31 + G*// HF/6-31 + G*	B3LYP/6-31 + G*// B3LYP/6-31 + G*
1b-dim	$(MeLi)_2L_4$		– 710.447218		– 715.071562	
2	AN		– 191.922602		– 193.122887	
L = Me_2O		– 154.064745	– 154.069430		– 155.032394	– 155.033690
5b + L	$(MeLi)_2L_3$ + L		– 710.440650		– 715.065377	
6b + L	AN · $(MeLi)_2L_3$ + L		– 902.363401		– 908.187570	– 908.195484
7bα	AN · $(MeLi)_2L_4$-odα		– 902.351968		– 908.178207	
7bβ	AN · $(MeLi)_2L_4$-odβ		– 902.346782		– 908.171618	
8bβ + 2L	AN · $(MeLi)_2L_2$-odβ + 2L		– 902.332843		– 908.158070	
7bα-**ts**	AN · $(MeLi)_2L_4$-odα-ts		– 902.304185		– 908.148130	
7bβ-**ts**	AN · $(MeLi)_2L_4$-odβ-ts		– 902.303299		– 908.148863	
6b-ts + L	AN · $(MeLi)_2L_3$-ts + L		– 902.301750		– 908.147778	– 908.155381
8bβ-**ts** + 2L	AN · $(MeLi)_2L_2$-odβ-ts + 2L		– 902.298864		– 908.145055	
1-tet	$(MeLi)_4$		– 188.257685		– 189.811990	
6-tetAN · $(MeLi)_4$			– 380.202303		– 382.954103	
6-tet-ts	AN · $(MeLi)_4$-ts		– 380.131166		– 382905495	
1-tet	AN · $(MeLi)_4L_4$		– 492.411777		– 495.580576	
6a-tet + L	AN · $(MeLi)_4L_3$ + L		– 684.327196		– 688.694470	
6a-tet-ts + L	AN · $(MeLi)_4L_3$-ts + L		– 684.258099		– 688.646339	
1c-dim	$MeLi)_2L_4$		– 784.936394		– 790.453466	
6c	AN · $(MeLi)_2L_4$		unstable		unstable	
7c	AN · $(MeLi)_2L_4$-odα		– 976.840158		– 983.558022	
9c + 1/2(**1c-dim**)	AN · $(MeLi)_1L_2$ + 1/2$(MeLi)_2L_4$		– 976.825114		– 983.538757	
9c-ts + 1/2(**1c-dim**)	AN · $(MeLi)_1L_2$-ts + 1/2$(MeLi)_2L_4$		– 976.778231		– 983.513406	
7c-ts	AN · $(MeLi)_2L_4$-odα-ts		– 976.783731		– 983.521205	
6c-ts	AN · $(MeLi)_2L_4$-ts		not calc.		not calc.	
1b-dim	$(MeLi)_2L_4$	– 710.434406		– 715.071748		– 715.0777106
4	BZ	– 245.820077		– 247.304941		
15b	BZ · $(MeLi)_2L_4$-od	– 956.246261		– 962.366809		
15b-ts	BZ · $(MeLi)_2L_4$-od-ts	– 956.206094		– 962.347435		
3	NA	– 229.777318				– 231.224399
10	NA · $(MeLi)_2L_2L_2$	– 900.122894				– 905.884738
11 + L	NA · $(MeLi)_2L_1L_2$ + L	– 900.114929				– 905.8781527
12	NA · $(MeLi)_2L_1L_3$	– 900.114491				– 905.876107
14 + 2L	NA · $(MeLi)_2L_1L_1$ + 2L	– 900.101964				– 905.867896
13	NA · $(MeLi)_2L_2L_2$-od	– 900.093854				– 905.859358
13-ts	NA · $(MeLi)_2L_2L_2$-od-ts	– 900.053916				– 905.834700
10-ts	NA · $(MeLi)_2L_2L_2$-ts	– 900.051898				–
12-ts	NA · $(MeLi)_2L_1L_3$-ts	– 900.048364				– 905.829264
11-ts + L	NA · $(MeLi)_2L_1L_2$-ts + L	– 900.045566				– 905.827508
14-ts + 2L	NA · $(MeLi)_2L_1L_1$-ts + 2L	– 900.030106				– 905.815237

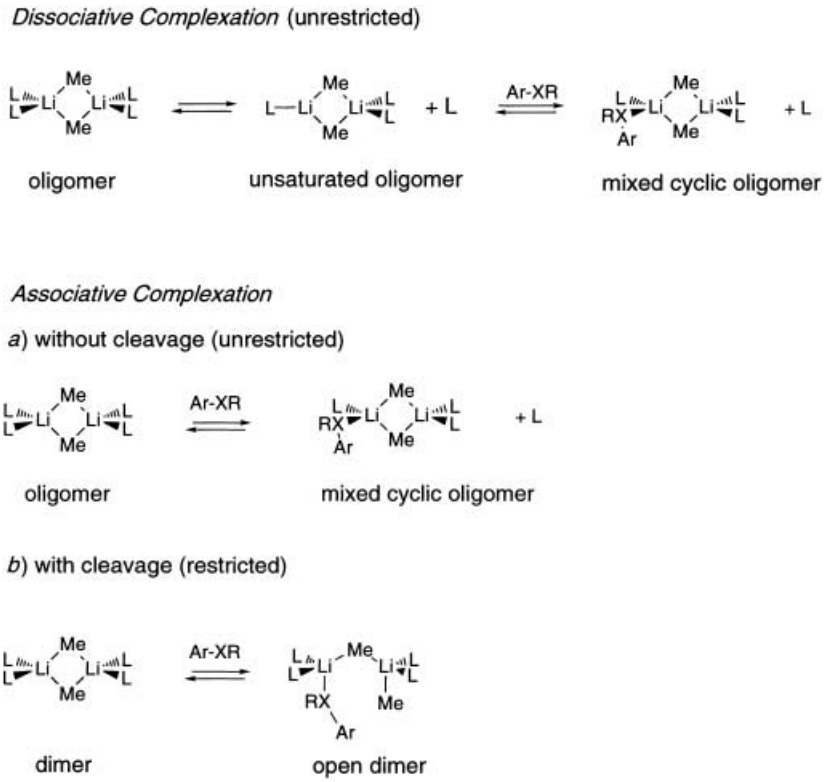
[a]) AN = methoxyethene (**2**) as model for anisole; BZ = acrylamide (**4**) as model for benzamide; NA = buta-1,3-dien-2-ol (**3**) as model for 1-naphthol; od = open dimer; ts = transition structure.

packages [61]. For the sake of generalization, the *ortho*-lithiation of *N,N*-dialkylbenzamides were also briefly examined at the 6-31G(d) level of theory.

3. Results and Discussion. – 3.1. ortho-*Lithiation of Nonhydric Aromatics by the Action of Dimeric or Oligomeric Organolithium Bases: Ether* vs. *TMEDA*. Both dissociative and associative routes (*Scheme 2*) for the complexation of anisole model **2** with **1-dim** have been examined computationally at the HF/6-31 + G* level, both for **1b-dim** (L = Me_2O) and, to some extent, for **1c-dim** (L + L = TMEDA). At the outset,

it was clear that complexation *via* dissociative routes should be unrestricted, *i.e.*, available to all kinds of aggregates. However, cleavage-induced associative complexation, which leads to open oligomers (*Scheme 2*, route *b*) and, subsidiarily, to monomeric species (see below for details), is restricted to organolithium dimers only.

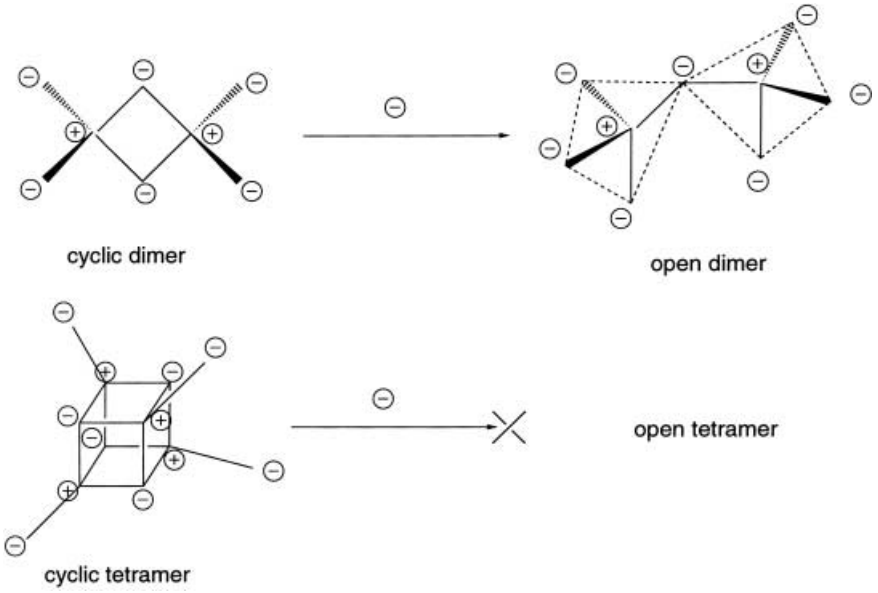
Scheme 2. *Complexation Modes for Organolithium Oligomers*



This behavior is a consequence of the intrinsic ionic nature of organolithium compounds. According to this model [62], one can surmise (see the cartoon-like structures of *Scheme 3*) that building a fully solvated organolithium dimer comes down to locating just six negative charges (two C-atoms and four O-atoms) in the immediate surroundings of two positive charges (Li-atoms). Analogously, for building a solvated tetramer, one needs to distribute eight negative charges in the immediate surroundings of four positive ones disposed as a tetrahedron. According to this oversimplified view, the associative complexation of an incoming base to each of these ionic aggregates can simply be redrawn as follows: can we add one extra negative charge without pulling apart the system? And if so, where should the extra negative charge be located? The answer is simple: to locate seven negative charges in the immediate vicinity of two positive ones, one of the common edges (a Me–Li bond) must be cleaved, thus giving rise to a dimeric species where the fully solvated monomers are joined through one vertex only. The result is a sort of spiro-ionic aggregate, for which I propose to keep the

name open dimer. In view of their activated nature (see below), open dimers are likely to play a central role in polar organometallic chemistry other than that already described [16][17]. On the other hand, it is worth emphasizing at this point that one cannot build open tetramers (or higher oligomers) in this manner, *i.e.*, there is no way to locate nine negative charges in the immediate vicinity of four positive ones in a 'stable' manner. Extra negative charges are required to break a tetrameric species, or higher aggregates. Actually, according to PM3 calculations, open tetramers, resulting from attack of a substrate upon the solvated, tetrameric organolithium compound, are not stationary points. They simply revert back to the cyclic oligomeric species. One can imagine open oligomers resulting from simultaneous complexation of two or more ligands. No calculations have been obtained, however, for these extremely large species.

Scheme 3. *Cartoon-Like Point-Charge Models for Associative Complexation of a fully Solvated Dimer or Tetramer*. Dashed lines on the open dimer are shown to emphasize its spiro-aggregated nature.



First, I examined the *ortho*-lithiation of **2** by the action of **1b-dim** *via* the cyclic-dimer and open-dimer routes, the former originating on dissociative and the latter on associative complexation. Presumably, the dissociative complexation **1b-dim** → **5b** (not shown) + L is behind the overall ligand-exchange process **1b-dim** + **2** → **6b** + L leading to mixed dimeric species **6b** ($\Delta E = +16.74$ kJ/mol). On the other hand, the associative complexation that leads to open-dimer (od) species **7** by cleavage of the original dimeric structure is, as expected, much more energy costly (46–58 kJ/mol) than that reported by *Nakamura et al.* for unsolvated open dimers [17b]. Further dissociative processes upon open-dimer species **7** yielded unsaturated open dimer **8**. In particular, the following relevant stationary points were located and fully characterized (*Fig. 1*, *Table 2*) in the solvation hypersurface of the anisole *ortho*-lithiation **1b-dim** + **2**:

coordinatively saturated mixed-solvated dimer AN · $(MeLi)_2$3L **6b**, coordinatively saturated open dimers AN · $(MeLi)_2$4L-odβ **7b**β and AN · $(MeLi)_2$4L-odα **7b**α, and coordinatively unsaturated open dimer species AN · $(MeLi)_2$2L-odβ **8b**β, all derived from associative processes. All these species are higher in energy than the initial reactants and, therefore, neither one of them is expected to be experimentally observed or detected. It should be mentioned that this is not in contradiction with *Bauer*'s observation of the formation of an anisole · $(BuLi)_4$ complex when BuLi in toluene (mostly hexameric, unsolvated) is mixed with anisole. In fact, calculations with tetramers (**1-tet**) agree well with this experiment (see below). Open dimers AN · $(MeLi)_2$4L-odβ **7b**β and AN · $(MeLi)_2$4L-odα **7b**α are the result of attack of the O-atom lone pairs (α or β) of anisole model **2** upon one of the Li-atoms of fully saturated dimeric methyllithium **1b-dim**. Even though, formally, these species should be enantiomeric (the O-atom is the only apparent stereogenic center), the existence of multiple interactions involving many other atoms actually makes them diastereomeric and, therefore, quite different in energy at this point of the reaction coordinate (see, however, below).

The optimized geometries of the transition structures corresponding to the so-called open-dimer route, namely **7b**α**-ts** and **7b**β**-ts**, were the lowest in energy (*Fig. 1*, *Table 2*). They have approximately the same energy (172.34 *vs.* 174.64 kJ/mol, or 121.63 *vs.* 119.70 kcal/mol according to single-point B3LYP calculations) as, strictly speaking, both should be enantiomeric species. Even though, to the best of our knowledge, no

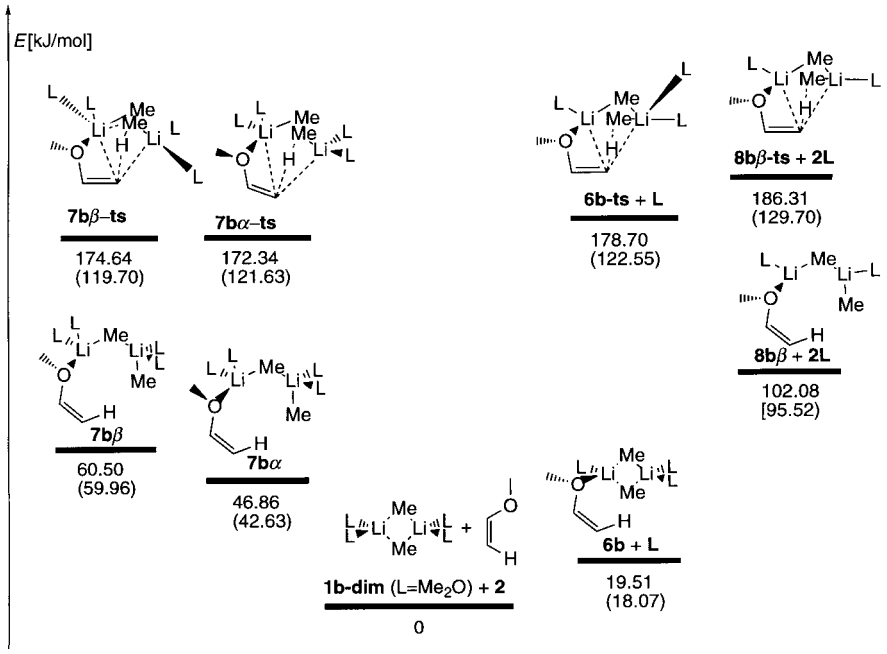


Fig. 1. *Schematic representation of the* ortho-*lithiation hypersurface* **1b-dim** + **2** (cyclic-dimer and open-dimer routes). Energy values in kcal/mol relative to **1b-dim** + **2** refer to HF/6-31 + G*//HF/6-31 + G* and B3LYP/6-31 + G*//HF/6-31 + G* (in parentheses) calculations.

Table 2. *Computed Energies for Stationary Points in the Hypersurface of the* ortho-*Lithiation of Anisole Model* **2** *by the Action of Solvated* (L = Me_2O) *Dimeric Methyllithium* **1b-dim** (cyclic-dimer and open-dimer routes)

Compound[a])		HF/6-31 + G*//HF/6-31 + G* Relative energy [kJ/mol]	B3LYP/6-31 + G*//HF/6-31 + G* Relative energy [kJ/mol]
1b-dim	$(MeLi)_2L_4$		
2	AN		
5b + L	$(MeLi)_2L_3$ + L		
2 + **1b-dim**	AN + $(MeLi)_2L_4$	0	0
2 + **5b** + L	AN + $(MeLi)_2L_3$ + L	17.24	16.23
6b + L	AN · $(MeLi)_2L_3$ + L	19.51	18.07
7bα	AN · $(MeLi)_2L_4$-odα	46.86	42.63
7bβ	AN · $(MeLi)_2L_4$-odβ	60.50	59.96
8bβ + 2L	AN · $(MeLi)_2L_2$-odβ + 2L	102.08	95.52
7bα-**ts**	AN · $(MeLi)_2L_4$-odα-ts	172.34	121.63
7bβ-**ts**	AN · $(MeLi)_2L_4$-odβ-ts	174.64	119.70
6b-ts + L	AN · $(MeLi)_2L_3$-ts + L	178.70	122.55
8bβ-**ts** + 2L	AN · $(MeLi)_2L_2$-odβ-ts + 2L	186.31	129.70

AN = methoxyethene (**2**) as a model for anisole; od = open dimer; ts = transition structure.

kinetic rate has been experimentally obtained for the lithiation of anisole in ether, these results fit rather well with the experimental data obtained by *Collum* and co-workers for the lithiation of anisole in TMEDA (see below) [13]. On the other hand, the energy barrier corresponding to the so-called cyclic-dimer route (transition structure **6b**-**ts** + L), was found to be only slightly higher in energy (178.70 kJ/mol, or 122.55 kJ/mol according to single-point B3LYP calculations), thereby suggesting that only coordinatively saturated species may actually pass through the so-called transition region in these reactions [63]. In line with this reasoning, we found that lithiation of coordinatively unsaturated **8b**β (unsaturated open-dimer route) involving transition structure **8b**β-**ts** is somewhat more energy costly (186.31 kJ/mol, or 129.70 kJ/mol according to B3LYP calculations). In other words, in spite of the very close structural resemblance of both **6b-ts** and **8b**β-**ts** with **7b**β-**ts**, there is a considerable increase in energy associated with the removal of every discrete solvent molecule around the Li-atoms. In this regard, it is worth emphasizing that the second-sphere Me_2O molecules in **7b**β-**ts** are not simple spectator ligands. In fact, on closer examination (see below for the TMEDA case), it can be recognized that each of the two faraway Me_2O molecules in **7b**β-**ts** are involved in weak H-bonding (2.8–2.9 Å) with H-atoms of the first-sphere Me_2O ligands. This unusual feature accounts, at least in part, for the overall 11.67 kJ/mol difference (10.00 according to single-point B3LYP calculations) when compared with the otherwise identical transition structure **8b**β-**ts**.

In ether solution, however, real organolithium bases exist mostly as tetramers [3g]. For these oligomeric species, the cleavage-induced associative mode for complexation (open-tetramer route; route *b* in *Scheme 2*) is not accessible [62]. The consequence is self-evident: the open-tetramer route cannot operate. Accordingly, it is safe to conclude that lithiation of anisole in ether likely takes place *via* the so-called cyclic-tetramer route represented by **1b-dim** + **2** → **6b** + L → **6b-ts** + L → lithiated products. Due to the enormous computational resources required for a direct analysis of this route, an extrapolation method was chosen for prediction. Thus, lithiation of **2** by the action of both unsolvated, tetrameric methyllithium **1-tet** (a model for tetrameric butyllithium in

a noncoordinating solvent such as toluene) [11], and solvated ($L = H_2O$), tetrameric methyllithium **1a-tet** were analyzed at the HF/6-31 + G* level (*Fig. 2*, *Table 3*). In agreement with expectations, transition structures **6-tet-ts** and **6a-tet-ts** were found at 186.77 kJ/mol (127.61 kJ/mol according to single-point B3LYP calculations) and 200.25 kJ/mol (150.0 kJ/mol according to single-point B3LYP calculations) above the corresponding complexed species **6-tet** and **6a-tet**. In other words, both energy barriers are considerably higher (up to 25 kJ/mol) than those found for the cyclic-dimer and open-dimer routes (see *Fig. 1* and *Table 2*). One can, thus, tentatively conclude that, in ether solvents, *ortho*-lithiations involving tetramers evolve *via* the cyclic-tetramer route, which is likely more energy costly (≥ 25 kJ/mol) than those involving dimers.

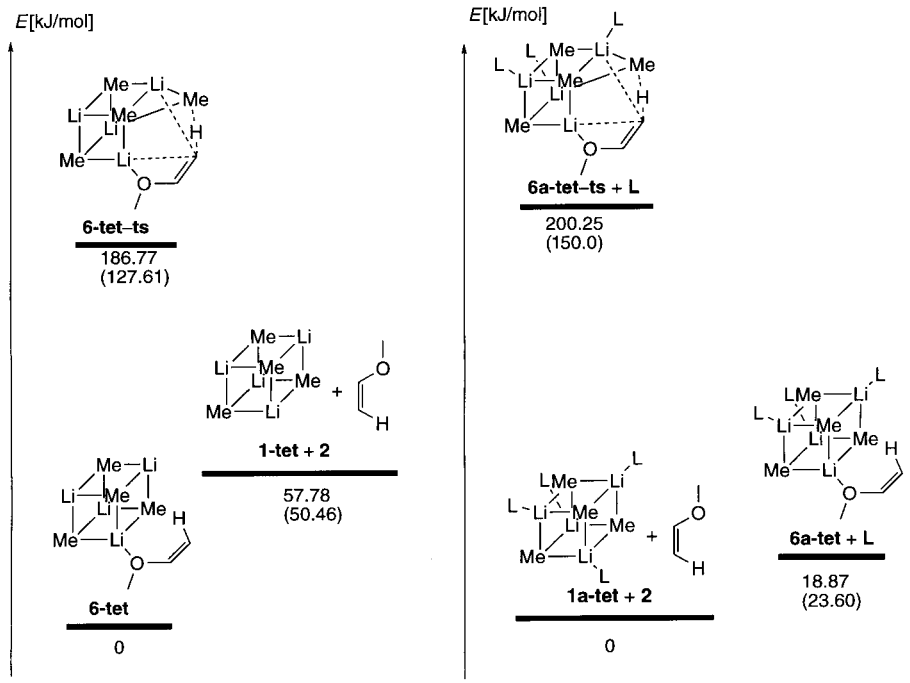


Fig. 2. *Schematic representation of the* ortho-*lithiation hypersurfaces* **1-tet + 2** *and* **1a-tet + 2** (cyclic-tetramer routes). Energy values in kcal/mol relative to both **6-tet** and **1a-tet + 2** refer to HF/6-31 + G*//HF/6-31 + G* and B3LYP/6-31 + G*//HF/6-31 + G* (in parentheses) calculations.

From the structural viewpoint, several remarkable geometric features of the open-dimer species are worthy of detailed comment. The first refers to the formation of the open-dimer species **7b** itself. This operation involves the conversion of a low-energy aggregate (in our case the rhombus dimer **1b-dim**) to a high-energy, angular complex **7b** that scarcely bears any resemblance to the unsolvated linear complexes LiMe···LiMe described years ago by *Schleyer* and co-workers [64]. In fact, contrary to the strongly bound units of *Schleyer*'s linear dimer (Me···Li = 2.3 Å; Li···CLi angle *ca.* 180°), the two monomeric units in **7b** are loosely held together by both a largely broken Me–Li bond (2.80–2.77 Å, *Fig. 3*), and two strong CH···Li interactions (H···Li distances in

Table 3. *Computed Energies for Stationary Points in the Hypersurface of the* ortho-*Lithiation of Anisole Model* **2** *by the Action of Both Unsolvated, Tetrameric Methyllithium* **1-tet** *and Solvated* (L = H_2O), *Tetrameric Methyllithium* **1a-tet** (cyclic-tetramer route)

Compound[a])		HF/6-31 + G*//HF/6-31 + G* Relative energy [kJ/mol]	B3LYP/6-31 + G*//HF/6-31 + G* Relative energy [kJ/mol]
1-tet	$(MeLi)_4$		
2	AN		
2 + **1-tet**	AN + $(MeLi)_4$	57.78	50.46
6-tet	AN · $(MeLi)_4$	0	0
6-tet-ts	AN · $(MeLi)_4$-ts	186.77	127.61
1a-tet	$(MeLi)_4L_4$		
2	AN		
2 + **1a-tet**	AN + $(MeLi)_4L_4$	0	0
6a-tet + L	AN · $(MeLi)_4L_3$ + L	18.87	23.60
6a-tet-ts + L	AN · $(MeLi)_4L_3$-ts + L	200.25	150.00

[a]) AN = methoxyethene (**2**) as a model for anisole; ts = transition structure.

the range of 2.2–2.4 Å, *Fig. 3*) of the type described by *Stucky* and co-workers [65], later on termed Li···H agostic interactions [38] by *Power* and co-workers [66], *Snaith* and co-workers [67], and others [68]. An additional feature of distinction between **7b** and *Schleyer*'s linear dimer and trimer is the flexibility (see below) of the Li···Me···Li angle (113.1° for **7b**β and 131.9° for **7b**α, *Fig. 3*). In other words, open dimers should be described as spiro dimeric aggregates of highly ionic species, having just one vertex in common, as shown in the cartoon-like structures of *Scheme 3*. Presumably, their spiro nature facilitates a smooth approach to the transition structure of lithiation reactions by working as a knee-like joint. Finally, as judged from a detailed analysis of structural features (Li···H distance, C–H bond length and H–C–O angle) of **1b-dim**, **7b**, and transition structures **7b-ts**, it is clear that the discrete solvent molecules around Li-atoms do not play a specific structural role in the lithiation reaction other than determining the aggregation state of the organolithium species in solution.

In TMEDA solution, BuLi exists as dimeric species [11][15]. Thus, the possibility that both open- and cyclic-dimer routes could take part in the *ortho*-lithiation of anisole in TMEDA urged us to carry out a limited study at the HF/6-31 + G* level (*Fig. 4*, *Table 4*), aiming at understanding the special effect of TMEDA in lithiation reactions [27]. As for the previous study of **1b-dim**, I have examined associative and dissociative coordination modes for the **1c-dim** + **2** pair. Mixed dimer **6c**, the starting compound of the so-called cyclic-dimer route, was found not to be a stable species at HF/6-31 + G*: it simply dissociates back into **2** and coordinatively unsaturated **5c** (not shown). On the other hand, associative coordination of **2** with **1c-dim** brings about a major structural change upon the rhombus-like dimer $(MeLi)_2(TMEDA)_2$, namely, its conversion to open dimer **7c**[5]), which requires 49.37 kJ/mol[6]). Again, besides the largely broken

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[5]) At the HF/3-21G* level, two enantiomeric species, namely **7c**α and **7c**β were located, the O-atom being the chiral center. However, at the HF/6-31 + G* level, both converged into a single species, namely **7c**, in which the O-atom is planar, *i.e.*, is using sp^2 orbitals to bind the adjacent C-, Li-, and C-atoms.

[6]) TMEDA has been proposed long ago to induce cleavage of alkyllithium aggregates into dimeric and/or monomeric species; see [28a]. However, no proof for the formation of monomeric species has ever been found; see [14b].

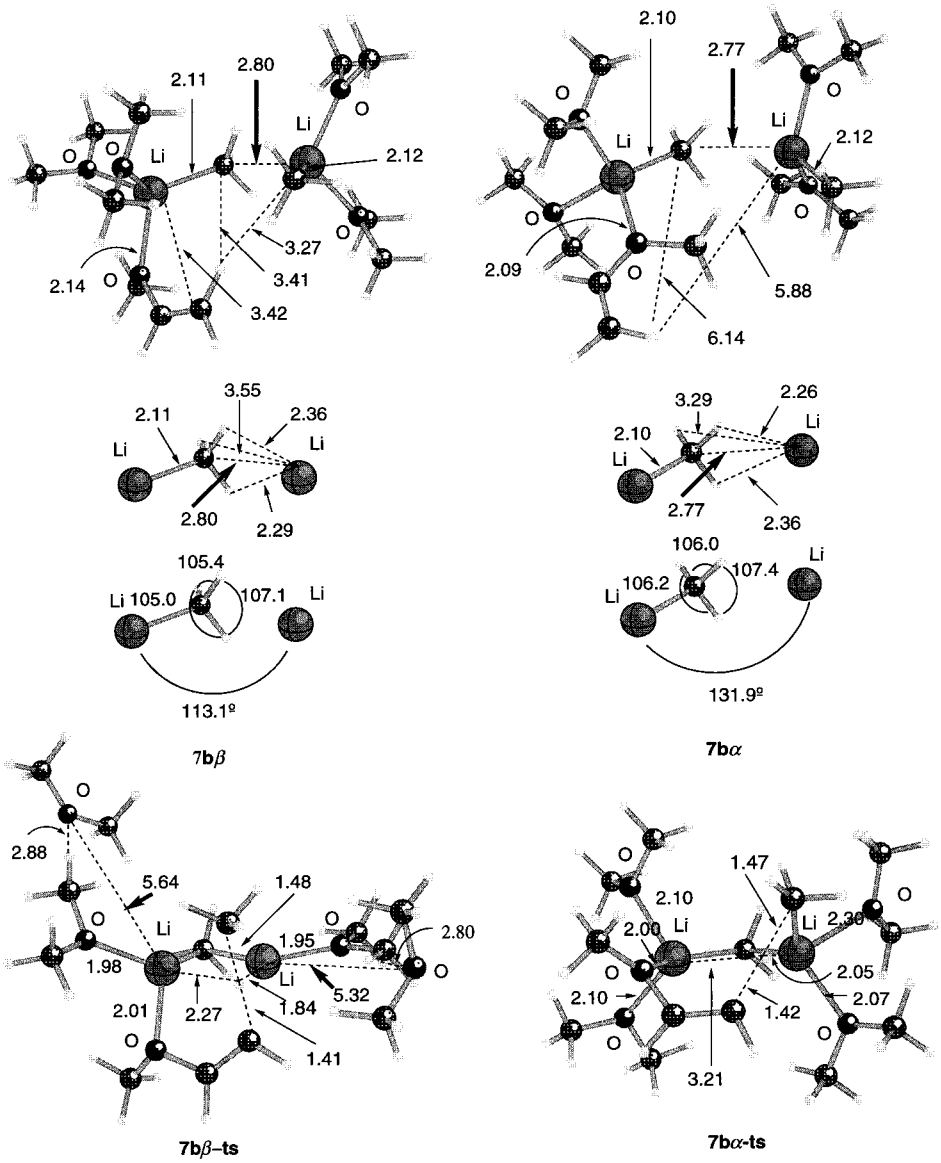

Fig. 3. *Ball- and stick structures of stationary points* **7b**α, **7b**β, **7b**α**-ts**, *and* **7b**β**-ts** *from HF/6-31 + G* calculations.* Relevant distances are given in Å and angles in degrees.

C–Li bond (2.67 Å), two major CH···Li agostic interaction [38] forces [65–68] seemed to be responsible for the geometrical appearance of open dimer **7c** (H···Li distances in the range of 2.24–2.25 Å and a Li···CLi angle of 140.5°, *Fig. 5*). The corresponding transition structure **7c-ts** (open-dimer route) was eventually found at 197.61 kJ/mol (144.77 kJ/mol as according to single-point B3LYP calculations) above

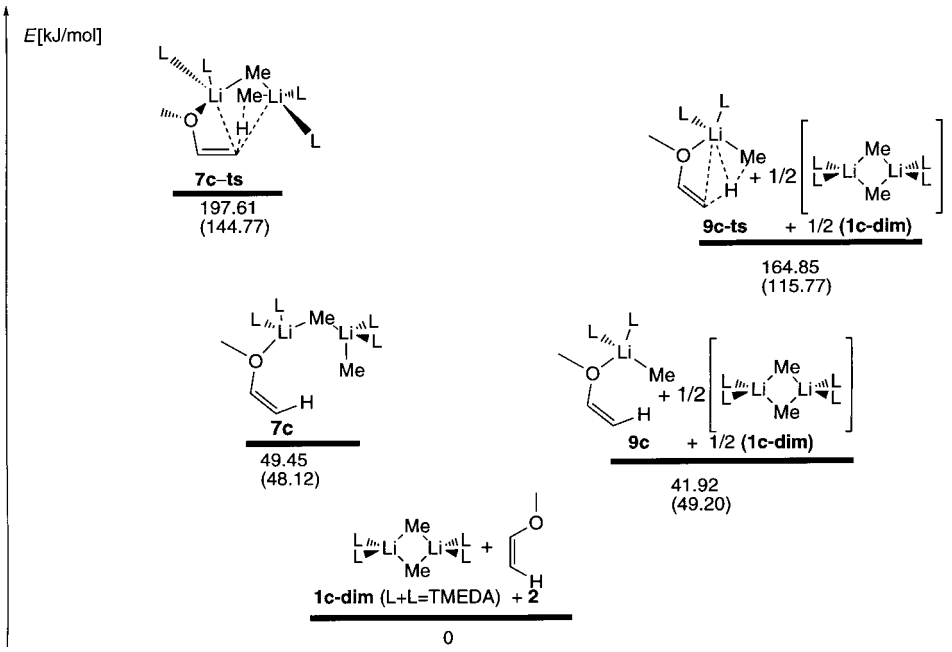

Fig. 4. *Schematic representation of the* ortho-*lithiation hypersurface* **1c-dim** + **2** (open-dimer and s-monomer routes). Energy values in kcal/mol relative to **1c-dim** + **2** refer to HF/6-31 + G*//HF/6-31 + G* and B3LYP/6-31 + G*//HF/6-31 + G* (in parentheses) calculations.

the starting compounds **1c** + **2**. This was quite a surprise because this energy barrier was *ca*. 25 kJ/mol higher than that found for the same process in Me_2O (**1b** + **2**) and, still more impressive, almost identical to that of the cyclic-tetramer route represented by the transition structure **6a-tet-ts** (*Table 3*). Clearly, TMEDA does not stabilize transition structures better than Me_2O itself does! To put it in other words, TMEDA might even be a poorer solvent than ether for *ortho*-lithiations, in agreement with *Collum*'s experimental observations [63][18b]. Even though the transition structure of the cyclic-dimer route **6c-ts** was not calculated, TMEDA appears not to play any particularly stabilizing structural role other than that played by other ligating solvents. In fact, as in the case of Me_2O, I see no specific role for the η^2 or η^1 ligated TMEDA molecules in **7c** or **7c-ts**, as judged from the analysis of such structural features as Li···H distances, C–H bond lengths, and H–C–N angles in **1c-dim**, **7c**, and **7c-ts**. It could be argued that single-point B3LYP energy calculations showed the existence of strong electron-correlation effects[7]), but since these values are quite similar for both Me_2O and TMEDA (*Tables 3* and *4*), it is safe to conclude that there is no special structural effect associated with the transition structures of lithiations carried out in TMEDA.

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[7]) Only somewhat shortened Li···H distances (by *ca*. 0.1 Å) were detected in moving from **1c** and **7c** to **7c-ts**, which could be interpreted as suggestive of a very weak Li···H agostic interaction. Unfortunately, optimization at the B3LYP/6-31 + G* was not attempted due to the enormous size of the calculation.

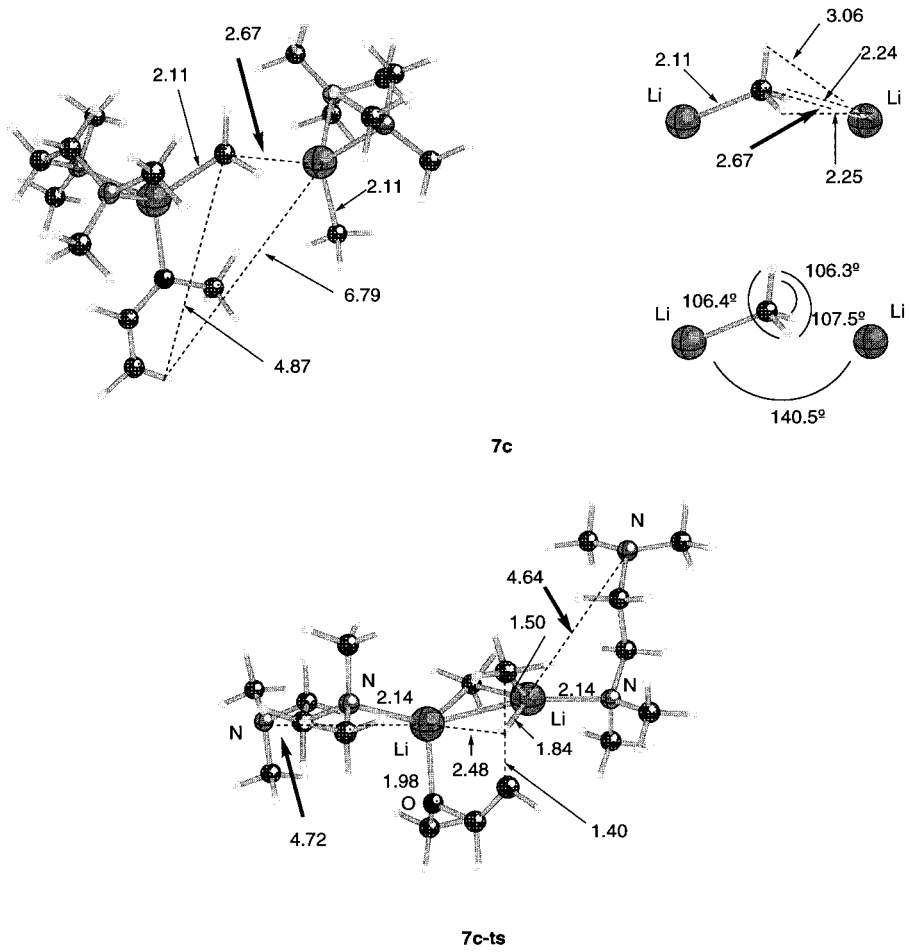

Fig. 5. *Ball and stick structures of stationary points* **7c** *and* **7c-ts** *from HF/6-31 + G* calculations.* Relevant distances are given in Å and angles in degrees.

If TMEDA does not, as it seems, to play any special structural effect, then its role ought to be non other than to convert the already reactive dimers[8]) and open dimers into more reactive monomers [71][3g]. I have tried to find out how this can be by carefully comparing the theoretically derived kinetic laws of several alternative mechanistic routes with that obtained experimentally [13], as illustrated below.

3.2. ortho-*Lithiation of Nonhydric Aromatics in TMEDA: The Monomer Route* vs. *the s-Monomer Routes.* – Fully TMEDA-solvated, monomeric species **9c** and its corresponding **9c-ts** were optimized and fully characterized at the HF/6-31 + G* level of calculation. The difference in energy (122.93 kJ/mol; *Fig. 4*, *Table 4*) clearly indicated that this elementary step was one of the lowest in energy.

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[8]) The higher reactivity of dimers *vs.* higher aggregates has been experimentally demonstrated [70].

Table 4. *Computed Energies for Stationary Points in the Hypersurface of the* ortho-*Lithiation of Anisole Model* **2** *by the Action of Solvated* (L + L = TMEDA) *Dimeric Methyllithium* **1c-dim** (cyclic-dimer, open-dimer, and s-monomer routes)

Compound[a])		HF/6-31 + G*//HF/6-31 + G* Relative energy [kJ/mol]	B3LYP/6-31 + G*//HF/6-31 + G* Relative energy [kJ/mol]
1c-dim	$(MeLi)_2L_4$		
2	AN		
2 + **1c-dim**	AN + $(MeLi)_2L_4$	0	0
6c	AN · $(MeLi)_2L_4$	–	–
7c	AN · $(MeLi)_2L_4$-odα	49.45	48.12
9c + 1/2(**1c-dim**)	AN · $(MeLi)_1L_2$ + 1/2$(MeLi)_2L_4$	41.92	49.20
9c-ts + 1/2(**1c-dim**)	AN · $(MeLi)_1L_2$-ts + 1/2$(MeLi)_2L_4$	164.85	115.77
7c-ts	AN · $(MeLi)_2L_4$-odα-ts	197.61	144.77
6c-ts	AN · $(MeLi)_2L_4$-ts	–	–

[a]) AN = methoxyethene (**2**) as a model for anisole; od = open dimer; ts = transition structure.

First, I examined the prototypical monomer route m (*Eqns. 1–3*)[9]), which involves deaggregation of the fully solvated dimer **1c-dim** into two coordinatively unsaturated monomers **1c-mon**. Clearly, the theoretically derived kinetic rate law for this route does not fit the experimental rate equation obtained by *Collum* and co-workers [13]. Accordingly, it was discarded. Three other conceivable mechanistic pathways that can integrate the above elementary step into their routes, namely the s-monomer routes s-m, were then analyzed. As shown in *Scheme 4*, these routes subsidiarily derive from the so-called open-dimer route **1c-dim** + **2** → **7c**. In other words, the key monomeric complex **9c** can originate by cleavage of the labile C–Li bond of open dimer **7c** in a number of possible ways: substrate-promoted, solvent-promoted, or dimerization-promoted, herein termed the s-monomer routes s-m_1, s-m_2, and s-m_3. For the sake of analysis, only their kinetically relevant elementary steps will be given, together with thermochemical data, where appropriate.

From a kinetic viewpoint, the substrate-promoted s-m_1 route (*Eqns. 4–6*) is indistinguishable from the prototypical monomer route m above and, therefore, it can be discarded, too[10]). It is conceivable, though, that this route could be operative if substrate **2** were in large excess relative to **7c**, a case described by *Slocum et al.* years ago as TMEDA-catalyzed *ortho*-lithiations [25a]. At difference with those above, the solvent-promoted (s-m_2) and the dimerization-driven (s-m_3) routes share a kinetically relevant feature: only 'one half' of the dimer enters the rate-determining step, while the 'other half' simply reacts after the rate-determining step with the lithiated product initially produced. The solvent-promoted route s-m_2 (*Eqns. 7–9*) was also rejected for

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[9]) Prototypical monomer route m

1c-dim → 2 × **1c-mon** (1)

1c-mon + **2** → **9c** (2)

9c → **9c-ts** → lithiated product (3)

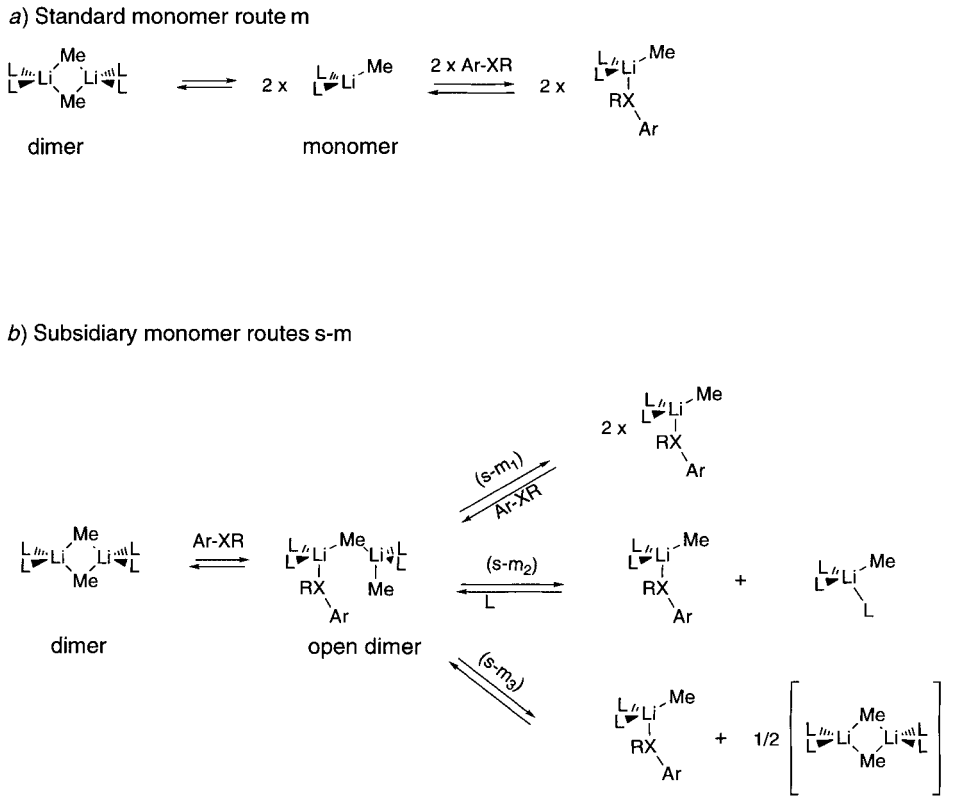
[10]) Substrate-promoted s-monomer route s-m_1

1c-dim + **2** → **7c** (4)

7c + **2** → 2 × **9c** (5)

9c → **9c-ts** → lithiated product (6)

Scheme 4. *Accessible Monomer Routes.* See text for detailed analysis.



two reasons[11]). First, because, as required by its rate equation, there should be a direct dependence on the concentration of solvent, which is at discrepancy with *Collum*'s kinetic data. Second, because the overall energy barrier associated with this route (117.19 kJ/mol) is almost as high as that found for the cyclic-tetramer route ($L = Me_2O$), obviously not accounting for the experimentally observed acceleration effect of TMEDA in lithiation reactions. The overall energy barrier (164.85 kJ/mol, *Table 4*) for the dimerization-driven routes s-m_{3a} (*Eqns. 10–13*) and s-m_{3b} (*Eqns. 14–18*) is significantly lower than any of those previously found, thus accounting for the abundant experimental observations concerning rate acceleration of lithiation reac-

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[11]) Solvent-promoted s-monomer route s-m_2

1c-dim + **2** → **7c**	$\Delta E = +11.82$ kcal/mol	(7)
7c + s → **9c** + **1c-mon** · s	$\Delta E = +5.89$ kcal/mol	(8)
9c → **9c-ts** → initial lithiated product	$\Delta E = +29.42$ kcal/mol	(9)

tions induced by TMEDA[12]). Their key driving force is the exothermic dimerization of the coordinatively unsaturated monomer **1c-mon** to **1c-dim**. In the former (s-m_{3a}), cleavage of open dimer **7c** is spontaneous, whereas in the latter (s-m_{3b}), cleavage is induced by solvent. The slight dependence of rate on the concentration of TMEDA found by *Collum* and co-workers makes a strong suggestion in favor of the s-m_{3b} route [13]. Therefore, I propose the following detailed series of kinetically relevant elementary steps (where appropriate, stoichiometry is included to facilitate reading) as those responsible for the lithiation of anisole in TMEDA:

$$\mathbf{1c\text{-}dim} + \mathbf{2} \rightarrow \mathbf{7c} \tag{14}$$

$$\mathbf{7c} + \mathrm{s} \rightarrow \mathbf{9c} + \mathbf{1c\text{-}mon} \cdot \mathrm{s} \tag{15}$$

$$\mathbf{1c\text{-}mon} \cdot \mathrm{s} \rightarrow \mathbf{1c\text{-}mon} + \mathrm{s} \tag{16}$$

$$1/2(\mathbf{1c\text{-}mon} + \mathbf{1c\text{-}mon} \rightarrow \mathbf{1c\text{-}dim}) \tag{17}$$

$$\mathbf{9c} \rightarrow \mathbf{9c\text{-}ts} \rightarrow \text{initial lithiated product} \tag{18}$$

At the risk of being repetitive, I must insist that, after the rate-determining step, the initial lithiated product must consume the 'other half' dimer 1/2(**1c-dim**), thus eventually giving rise to the final lithiated product (presumably a mixed dimeric species). In this manner, the overall reaction is appropriately balanced. More importantly, the rate equation derived from this mechanism (*Eqn. 20 via Eqn. 19*)[13]), fits rather well that experimentally obtained by *Collum* and co-workers [13] by simply assuming that the concentration of **1c-mon** is approximately constant for each concentration of TMEDA: $v = k_{obs}[\mathbf{1c\text{-}dim}][\mathbf{2}]$. The two main conclusions of *Collum*'s work are thus fully explained: *a*) the rate of the reaction has a first-order dependance on the concentration of anisole and the concentration of TMEDA-solvated organolithium dimer, and *b*) there is a slight dependence of rate on the concentration of TMEDA.

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[12]) Two closely related dimerization-driven s-monomer routes s-m_3 are possible, though hard to distinguish. While the former route s-m_{3a} is characterized by the spontaneous cleavage of **7c**,

$\mathbf{1c\text{-}dim} + \mathbf{2} \rightarrow \mathbf{7c}$	$\Delta E = +11.82$ kcal/mol	(10)
$\mathbf{7c} \rightarrow \mathbf{9c} + \mathbf{1c\text{-}mon}$	$\Delta E = +9.44$ kcal/mol	(11)
$1/2(\mathbf{1c\text{-}mon} + \mathbf{1c\text{-}mon} \rightarrow \mathbf{1c\text{-}dim})$	$\Delta E = -22.55$ kcal/mol	(12)
$\mathbf{9c} \rightarrow \mathbf{9c\text{-}ts} \rightarrow$ initial lithiated product	$\Delta E = +29.42$ kcal/mol	(13)

in the latter route s-m_{3b}, cleavage of **7c** is induced by solvent s.

$\mathbf{1c\text{-}dim} + \mathbf{2} \rightarrow \mathbf{7c}$	$\Delta E = +11.82$ kcal/mol	(14)
$\mathbf{7c} + \mathrm{s} \rightarrow \mathbf{9c} + \mathbf{1c\text{-}mon} \cdot \mathrm{s}$	$\Delta E = +5.89$ kcal/mol	(15)
$\mathbf{1c\text{-}mon} \cdot \mathrm{s} \rightarrow \mathbf{1c\text{-}mon} + \mathrm{s}$	$\Delta E = +3.55$ kcal/mol	(16)
$1/2(\mathbf{1c\text{-}mon} + \mathbf{1c\text{-}mon} \rightarrow \mathbf{1c\text{-}dim})$	$\Delta E = -22.55$ kcal/mol	(17)
$\mathbf{9c} \rightarrow \mathbf{9c\text{-}ts} \rightarrow$ initial lithiated product	$\Delta E = +29.42$ kcal/mol	(18)

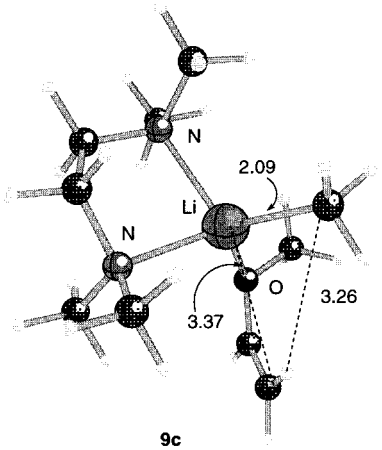
[13]) The following equation results by considering that the first four elementary steps are pre-equilibrium steps:

$$v = k_5 K_1 K_2 K_3 [\mathbf{1c\text{-}dim}][\mathbf{2}]/[\mathbf{1c\text{-}mon}] \tag{19}$$

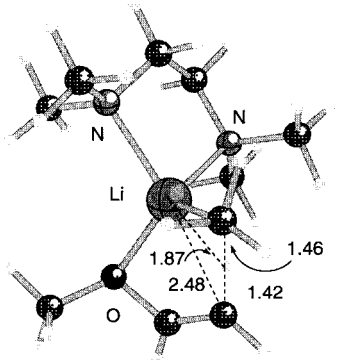
By assuming that [**1c-mon**] is a constant for each and every concentration of TMEDA, the following equation results:

$$v = k_{obs}[\mathbf{1c\text{-}dim}][\mathbf{2}] \tag{20}$$

From the structural viewpoint (*Fig. 6*), a relevant geometrical feature of the key species **9c** and **9c-ts** involved in the rate-determining step needs to be mentioned. At difference with **7c-ts**, the lithium atom in **9c-ts** appears to be fully coordinated to both N-atoms of TMEDA, as well as to each of the three atoms involved in the lithiation reaction (Me−H−C). This clearly suggests that steric congestion in **7c-ts** may be causing an additional energetic cost.



9c



9c-ts

Fig. 6. *Ball and stick structures of stationary points* **9c** *and* **9c-ts** *from HF/6-31+G* calculations.* Relevant distances are given in Å and angles in degrees.

For the sake of analyzing the role of different solvents, I have also examined the energetics of the analogous monomer route in Me_2O (**1b-dim** + **2** → **7b**; **7b** + s → **9b** + 1/2 **1c-dim**; **9b** → products). No noticeable solvent effect upon the energetics of the process was found, *i.e.*, the energy barrier for lithiation in Me_2O was found to lay

163.09 kJ/mol above the starting compounds **1b-dim** + **2**, *i.e.*, a somewhat lower amount than that found above for lithiation in TMEDA (163.12 kJ/mol). The remarkable corollary follows: if one could find an ether solvent in which organolithiums could exist solely as dimers, then lithiation reactions in this solvent should be as effective as those carried out in TMEDA!

All the above data clearly point out the major role that solvents play in *ortho*-directed lithiation of nonhydric aromatics: that of determining the aggregation state of the organolithium species.

3.3. ortho/peri-*Lithiation of Hydric Aromatics.* To examine the role of other substituents as *ortho*-directing groups in lithiation reactions, I planned the study of the lithiation of hydric aromatics. Our long-standing interest in the lithiation of phenolic compounds [72] led us to choose buta-1,3-dien-2-ol (**3**) as the model for the *peri*-lithiation (*i.e.*, Li at C(8)) of 1-naphthol. This process is known to take place in TMEDA and has also been shown to involve intermediate mixed dimers [43]. The above results for the lithiation of anisole showed that open-dimer routes, whether in Me_2O or TMEDA, were not too different in energy. Accordingly, I selected the fully solvated ($L = Me_2O$) mixed dimer $NA \cdot (MeLi)_2L_2L_2$ **10** as the actual model for the *peri*-lithiation of 1-naphthol in TMEDA. Eventually, as single-point B3LYP/6-31 + G* energy calculations on the HF/6-31G* optimized structures revealed quite large energy changes, final optimization was eventually carried out at the B3LYP/6-31 + G* level. However, the optimized geometries were found to be almost identical at both levels of theory.

The following relevant stationary points were found on the solvation hypersurface of **10**, namely unsaturated dimers $NA \cdot (MeLi)_2L_1L_2$ **11** and $NA \cdot (MeLi)_2L_1L_3$ **12**, doubly unsaturated dimer **14**, open dimer **13** (*Fig. 7*, *Table 5*), and their transition structures **13-ts** (181.08 kJ/mol), **10-ts** (186.40 kJ/mol), **12-ts** (195.69 kJ/mol), **11-ts** (203.01 kJ/mol), and **14-ts** (243.59 kJ/mol). Thus, according to HF/6-31G* calculations, the open-dimer route (**10** → **13** → **13-ts** → products) and the cyclic-dimer route (**10** → **10-ts** → products) appeared to be the lowest-energy routes operating for the lithiation of hydric compounds in TMEDA. However, optimization at the B3LYP/6-31 + G* level

Table 5. *Computed Energies for Stationary Points in the Hypersurface of the* peri-*Lithiation of 1-Naphthol Model* **3** *by the Action of Solvated* ($L = Me_2O$) *Dimeric Methyllithium* **1b-dim** (cyclic-dimer and open-dimer routes)

Compound[a])		HF/6-31G*//HF/6-31G* Relative energy [kJ/mol]	B3LYP/6-31G*//B3LYP/6-31G* Relative energy [kJ/mol]
1b-dim	$(MeLi)_2L_4$		
3	NA		
10	$NA \cdot (MeLi)_2L_2L_2$	0	0
11 + L	$NA \cdot (MeLi)_2L_1L_2 + L$	20.92	17.28
12	$NA \cdot (MeLi)_2L_1L_3$	22.05	22.68
14 + 2L	$NA \cdot (MeLi)_2L_1L_1 + 2L$	54.94	44.18
13	$NA \cdot (MeLi)_2L_2L_2$-od	76.23	66.65
13-ts	$NA \cdot (MeLi)_2L_2L_2$-od-ts	181.08	131.38
10-ts	$NA \cdot (MeLi)_2L_2L_2$-ts	186.40	–
12-ts	$NA \cdot (MeLi)_2L_1L_3$-ts	195.69	145.64
11-ts + L	$NA \cdot (MeLi)_2L_1L_2$-ts + L	203.01	132.97
14-ts + 2L	$NA \cdot (MeLi)_2L_1L_1$-ts + 2L	243.59	182.46

[a]) NA = buta-1,3-dien-2-ol (**3**) as model for 1-naphthol; od = open dimer; ts = transition structure.

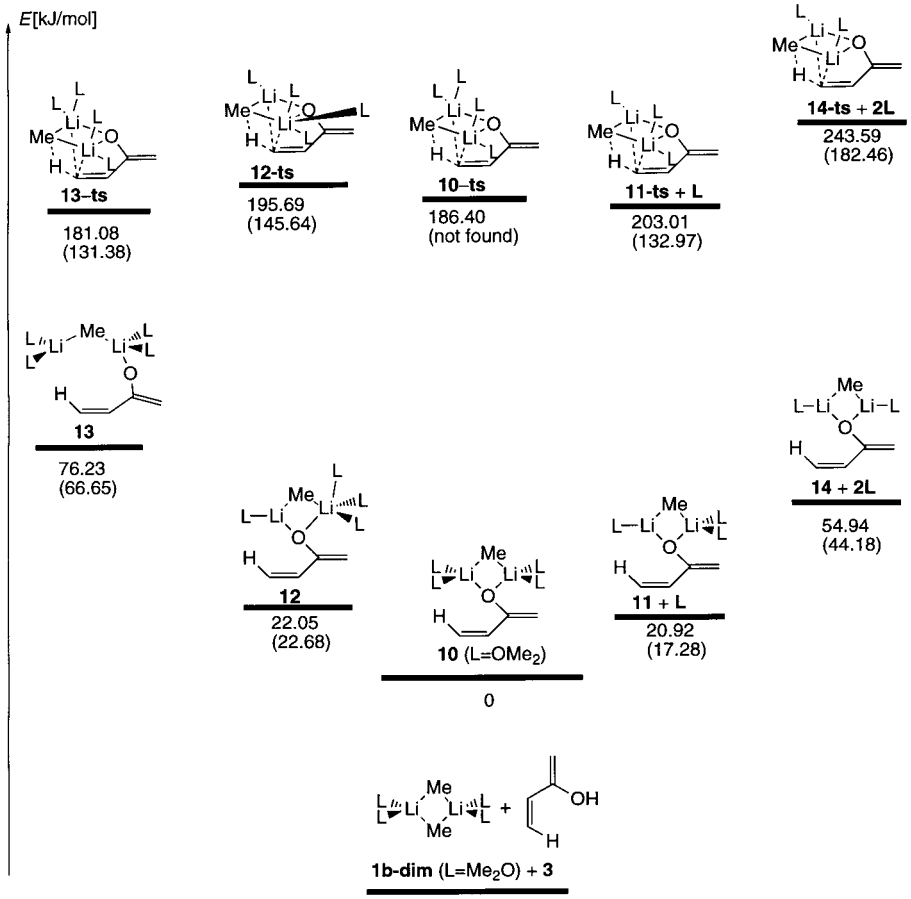


Fig. 7. *Schematic representation of the* peri-*lithiation hypersurface* **1b-dim** + **3**. Energy values in kcal/mol relative to **10** refer to HF/6-31 + G*//HF/6-31 + G* and B3LYP/6-31 + G*//B3LYP/6-31 + G* (in parentheses) calculations.

led to two interesting observations. First, the highly symmetric (square bipyramidal) transition structure **10-ts** was found not to be a stationary point at this level of calculation as, eventually, it converged into the less symmetric (rectangular bipyramid) **13-ts**. Second, the open-dimer route appeared to be the lowest-energy path (131.38 kJ/mol), followed very closely by the cyclic-dimer route represented by transition structure **11-ts** (132.97 kJ/mol). These not-too-high energy barriers agree well with the experimental fact that phenol lithiations work well in TMEDA or with the help of special additives [72], likely because these conditions favor the formation of dimeric species [43]. In accordance with our previous findings (the tetramer route is more costly than the dimer or monomer routes), one can speculate on the actual reasons behind the generally accepted low capacity of phenolates to direct lithiations: it is likely the consequence of the higher aggregation state of the phenolates in ether solution [73].

3.4. ortho-*Lithiation of* N,N-*Disubstituted Benzamides.* As a final probe to test the *ortho*-lithiation mechanistic model just derived from the above study with both a poor (phenolic OLi) and an ordinary (OMe) *ortho*-directing group, I extended the analysis to the lithiation of *N,N*-disubstituted benzamides (one of the best *ortho*-lithiation-directing groups known) [3f][46]. For this purpose the reaction between the model acrylamide (**4**) and Me_2O-solvated dimeric methyllithium **1b-dim** was selected for a short study at the HF/6-31G* level, and according to the open-dimer route only (*Fig. 8*). Expectations were on the side that amides, being highly polarized functional groups, should be able to induce easier cleavage to open-dimer species and, presumably, easier lithiation, too. All these expectations were fulfilled by the results of calculations. Thus, as shown in *Fig. 8* and *Table 6*, cleavage-induced associative complexation between **1b-dim** and **4** lead to open dimer **15b**. This species was found at 21.59 kJ/mol (at the HF/6-31G*//HF/6-31G* level of calculation) above the starting compounds only, in contrast with the 46–58 kJ/mol for **7b** or **7c** shown above. This result clearly suggests that intermediates of this type might possibly be experimentally detected, under appropriate circumstances [46]. The corresponding transition structure **15b-ts** was found at 127.03 kJ/mol higher than **1b-dim** + **4** (76.82 kJ/mol according to B3LYP/6-31 + G*// HF/6-31G* calculations). Thus, the relevant conclusions that can be extracted from this brief study are twofold. First, associative complexation appears

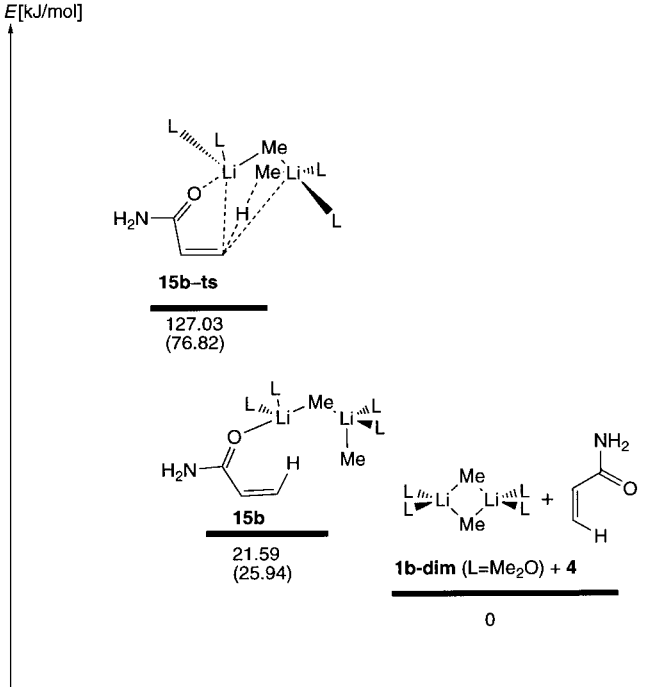


Fig. 8. *Schematic representation of the* ortho-*lithiation hypersurface* **1b-dim** + **4**. Energy values in kcal/mol relative to **1b-dim** + **4** refer to HF/6-31 + G*//HF/6-31 + G* and B3LYP/6-31 + G*//HF/6-31 + G* (in parentheses) calculations.

Table 6. *Computed Energies for Stationary Points in the Hypersurface of the* ortho-*Lithiation of* N,N-*Disubstituted Benzamide Model* **4** *by the Action of Solvated* (L = Me_2O) *Dimeric Methyl-Lithium* **1b-dim** (open-dimer route, only)

Compound[a])		HF/6-31G*//HF/6-31G* Relative energy [kJ/mol]	B3LYP/6-31G*//HF/6-31G* Relative energy [kJ/mol]
1b-dim	$(MeLi)_2L_4$		
4	BZ		
4 + **1b-dim**	BZ + $(MeLi)_2L_4$	0	0
15b	BZ · $(MeLi)_2L_4$-od	21.59	25.94
15b-ts	BZ · $(MeLi)_2L_4$-od-ts	127.03	76.82

[a]) BZ = acrylamide (**4**) as a model for *N,N*-disubstituted benzamide; od = open dimer; ts = transition structure.

to be a must for *ortho*-lithiations, and second, the acceleration effect on the lithiation reactions by directing groups such as −OMe, $-CONR_2$, or −OLi is well-estimated by the mechanistic manifold described above.

From the structural viewpoint (*Fig. 9*), it is worth noting that the key Me ··· Li bonding between both monomeric units in open dimer **15b** appears to be somewhat stronger than in previous cases (**7**, **13**), as suggested by both the shorter C ··· Li (2.64 Å) and H ··· Li (2.27, 2.27, and 2.87 Å) bonding distances and a larger Li ··· CLi angle (153.5°). Thus, the low energy associated with open dimer **15b** is likely a consequence of the fact that a stronger O−Li bond is created when the highly polarized carboxamide group attacks the organolithium dimer (associative complexation). In addition to this, the low energy associated with transition structure **15b-ts** appears to be, at least in part, a consequence of the larger ring size involved in the transition geometry. According to this reasoning, the highly polar carboxamides, *O*-carbamates, as well as the phosphamido and sulfonamido groupings should be the more efficient directing groups, as in fact they are [3].

4. Conclusions. – The HF and DFT computational results reported in this work clearly illustrate the fundamental role that aggregation phenomena play in the *ortho*-directed lithiation of aromatics. In particular, calculations show that solvation *per se* does affect not much the transition-structure energies. Rather, the role played by solvents can be circumscribed to that of determining the predominant aggregation state for each organolithium species. Accordingly, the actual number and variety of mechanistic routes available (the mechanistic manifold) for a particular substrate/organolithium pair can be related to the relative importance of associative and dissociative routes in the solvation scheme. Thus, on the one hand, dissociative routes give rise to the so-called cyclic-oligomer (cyclic-dimer, cyclic-tetramer, *etc.*) routes, which are available for all kinds of aggregates. On the other hand, associative routes appear to be operative only for dimeric organolithiums (open-dimer route), and lead to open dimers, which can undergo further cleavage to monomeric species. Thus, in addition to the prototypical monomer route (m), we found that a number of subsidiary routes of the open-dimer route (the so-called s-monomer routes or s-m routes) may actually operate in heteroatom-directed *ortho*-lithiation reactions. Moreover, calculations show that whatever the solvent, the so-called open-dimer, cyclic-dimer, and cyclic-tetramer routes are more energy-costly (in the ranking order given) than the

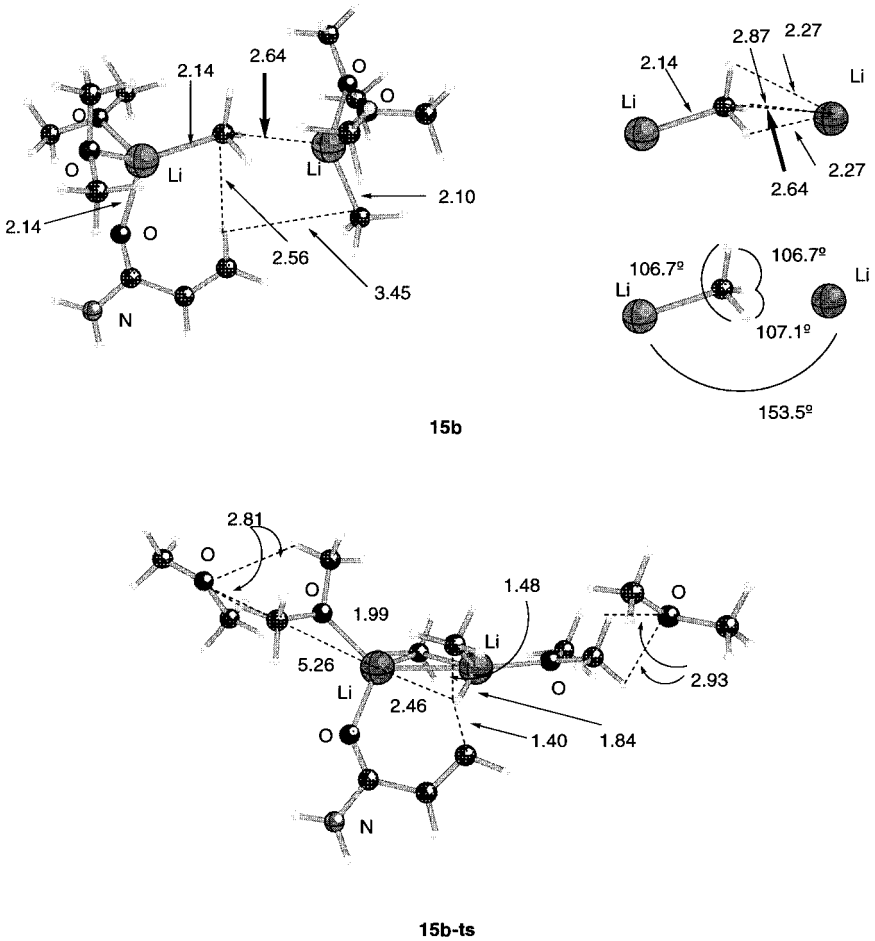


Fig. 9. *Ball and stick structures of stationary points* **15b** *and* **15b-ts** *from HF/6-31 + G* calculations.* Relevant distances are given in Å and angles in degrees.

dimerization-driven s-monomer routes. Predictions are, therefore, trivial: the mysterious rate acceleration observed for *ortho*-lithiations carried out in the presence of TMEDA can simply be related to the well-known fact that dimers are the only species in solution. In this situation, the cyclic-dimer, open-dimer, and s-monomer routes compete, the lowest energy of all being the dimerization-driven s-monomer route s-m_{3b}. In addition to this, the present study also provides theoretical evidence for the requirement of precomplexation (associative or dissociative) in *ortho*-directed lithiation of aromatics. Associative complexation appears to be specific for dimers and leads to open dimers, which can be perceived as a new sort of spiro-aggregate of organolithium compounds, having unique bonding features (agostic interactions) at the spiro junction.

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