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Predicting Directed Lithiations by Means of MNDO-Determined Agostic Interaction Parameters and Proximity Features. Peri Lithiation of Polyhydric Phenolic Compounds

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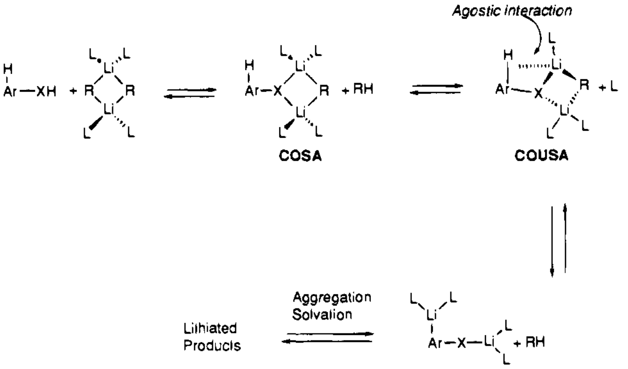
Abstract: The feasibility of the direct lithiation of monohydric compounds (such as a secondary benzamide, phenol, and thiophenol) and dihydric and trihydric phenols has been theoretically examined by using the semiempirical MNDO method. MNDO-determined agostic interaction parameters and proximity features show an outstanding capacity in qualitatively predicting the closeness of the corresponding transition states. According to these parameters, peri lithiation of mono- or polyhydric phenolic compounds (whenever possible) should be kinetically favored over alternative processes. Even second peri lithiations appear to be achievable objectives on account of these indicators. These prognostications have been borne out by experiment for the first time as dihydric phenols of the naphthalene, anthracene, and phenanthrene series yielded peri-substituted products on treatment with nBuLi in *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as solvent, followed by quenching with common electrophiles. Double peri functionalized derivatives of several dihydroxynaphthalenes and phenanthrenes were obtained by directed lithiation of the unprotected compounds. These results strongly suggest the key role that agostic interaction plays on directed lithiations and provide indirect evidence for the intermediacy of such precoordinated species in these reactions.

Introduction

Several key features of the mechanism of the so-called directed lithiation,[1] also named directed ortho metalation (DoM),[2] or kinetically enhanced metalation,[3] have been recently described by Bauer and Schleyer[4] for a number of representative substituted aromatics, as well as for some phenolic compounds.[5] Though it is unclear which is the complexed species actually undergoing metalation in each case, agostic interaction[6] has been invoked in these studies to explain the directing effect of a number of heteroatom-based functional groups. Presumably, a coordinatively unsaturated lithium atom[7] (COUSA) in the intermediate complexes or mixed aggregates[8] interacts to some extent with the adjacent C−H σ bonds, thereby inducing their selective removal by lowering the energy of the corresponding transition-state structure (Scheme 1).[4,5]

Scheme 1



σ complexes of the (X−Y)−M type (in which X = H, C, Si, Sn; Y = H; M = transition metal) are increasingly recognized as fundamental for the understanding of transition metal-promoted reactions involving the activation of σ bonds.[9] Brookhart and Green[10] coined the word agostic for the (C−H)−M interaction in σ complexes involving a transition metal M. A particularly significant consequence of agostic interaction is the increase of acidity of the C−H involved in complexation. Evidence for either strong or weak[11] agostic interaction can be

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[1] (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (c) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (d) Wardell, J. L. *Comprehensive Organic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 1, p 57. (e) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (f) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63. See also ref 2 and 27.

[2] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

[3] Eikema-Hommes, N. J. R. v.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. Eikema-Hommes, N. J. R. v.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903.

[4] Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

[5] Suñer, G. A.; Deyá, P. M.; Saá, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 1467. See also ref 7 and 41.

[6] (a) Bauer, W.; Feigel, M.; Muller, G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 6033. (b) Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597. (c) Bauer, W.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 970. (d) Gregory, K.; Bremer, M.; Bauer, W.; Schleyer, P. v. R.; Lorenzen, N. P.; Kopf, J.; Weiss, E. See also refs 4, 5, and 7.

[7] Strong agostic interactions between a C−H bond and (formally) coordinative saturated lithium atoms have been shown both theoretically and experimentally. See: Saá, J. M.; Deyá, P. M.; Suñer, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093 and ref 6, 9, and 10.

[8] Whether isolable or not (i.e., regardless of its relative energy), an intermediate complex or aggregate is a necessary requirement in moving from starting materials to products. In all cases studied in this work, this intermediate has been found to be a true minimum on the potential energy surface. See ref 18b for a recent survey regarding precoordination in lithiation reactions.

[9] Crabtree, R. H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 789 and references therein.

[10] Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395. Brookhart, M.; Green, M. L. H.; Wang, L. L. *Prog. Inorg. Chem.* **1988**, *36*, 1.

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obtained from neutron diffraction or NMR studies though only when the relative stability of the complexes allows its. Actually, apart of the Ziegler–Natta catalysis,[12] many other reactions promoted by transition metal organometallics are believed to involve agostic complexes either as intermediates or transition states although their existence is based on theoretical evidence only.[13]

Schleyer was the first to recognize the importance of the agostic interaction concept to organolithium chemistry,[14] the existence of short H–Li contacts in the HOESY spectra and/or MNDO-detected agostic interactions being considered strong evidence for it.

By looking at the MNDO-determined agostic interaction (heretofore abbreviated as AI) parameters,[15] we early recognized that lithiation of 1-naphthol at C-8 (peri lithiation)[6] should be the kinetically favored process. In accordance with experiment,[16] calculations revealed that the lowest transition structure ($\Delta H^* = 51.8$ kcal/mol) corresponded to peri lithiation which involved an almost ideal C–H–C angle (172.1°) and a highly symmetrical hydrogen transfer (C–H–C: 1.463 Å and 1.457 Å).[17] The corresponding transition structure for the competitive lithiation at C-2 was found to be 11.9 kcal/mol higher, in line with less pronounced agostic interaction for this case.[5] In other words, it appeared as if phenolic compounds having available peri hydrogens close to the existing OH group were ideally disposed for undergoing lithiation, a process that we envisioned as occurring through a transition state formally analogous to that of a secondary benzamide (Scheme 2). This reasoning led us to speculate the potential use of MNDO-determined agostic interaction parameters as (qualitative) indicators of the proximity[18] of the transition state,[19] i.e., as a very powerful means for predicting whether or not peri lithiation was a kinetic phenomenon of general applicability, even for polyphenols and related substances for which lithiation[20] hitherto requires prior protection.[21]

Scheme 2

Accordingly, we decided to calculate by means of the semiempirical MNDO[22] method the agostic interaction parameters[23] for the lithiation of phenol[24] itself, thiophenol,[25] and a number of dihydric and trihydric phenols of the naphthalene, phenanthrene, and anthracene series in an effort to learn the feasibility of the directed lithiation of polyhydric compounds.[26] For comparison purposes, calculations have been extended to our model compound for peri lithiation, i.e., a secondary benzamide (Scheme 2), a class of functional group well known for its capacity to direct ortho lithiations.[1]

It is worth recalling at this point that phenolic groups stand in the literature[1] as one of the poorest ortho-directing groups for lithiation, the directed lithiation of phenolic (either monohydric, dihydric, or polyhydric) compounds and closely related substances being generally assumed to be unfeasible projects, presumably as a consequence of the reduced acidity of ortho hydrogens and the poor solubility of the corresponding lithium salts, both factors operating against lithiation.[27] This reasoning may induce one to think that insuperable thermodynamic and/or kinetic problems should arise when trying to lithiate hydric compounds, the former related to the tendency of lithium phenoxides to aggregate,[28] and the latter to an increase in ΔG^*. This reasoning is, at least in part, misleading, as the directed lithiation of monohydric phenols,[24] naphthols,[16] and thiols[25] have been carried out in recent years by appropriately selecting the

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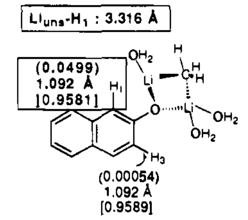
(11) Albinati, A.; Pregosin, P. S; Wombacher, F. *Inorg. Chem.* **1990**, *29*, 1812. Neve, F.; Ghedini, M.; Crispini, A. *Organometallics* **1992**, *11*, 3324.

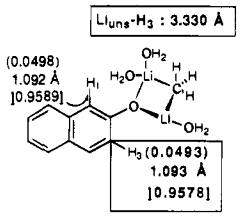
(12) Krauledat, H.; Brintzinger, H. H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1412. Piers, W. E.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 9406. Clawson, L.; Soto, J.; Buchwald, S. L.; Steirgebald, M. L.; Grubs, R. H. *J. Am. Chem. Soc.* **1985**, *107*, 3377.

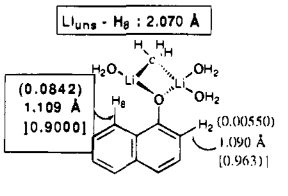
(13) Koga, N.; Morokuma, K. *Chem. Rev.* **1991**, *91*, 823 and references therein.

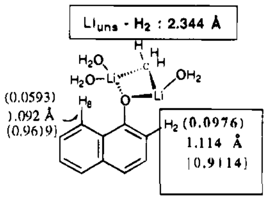
(14) Bauer, W.; Müller, G.; Pi, R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1103.

(15) MNDO determined (using MOPAC 6) AI parameters for both the peri and ortho lithiation of 1-naphthol and the ortho and ortho′ lithiation of 2-naphthol are shown below. Slight differences exist with those previously reported calculated using MOPAC vs 2.1.[5]









(16) Coll, G.; Morey, J.; Costa, A.; Saá, J. M. *J. Org. Chem.* **1988**, *53*, 5345.

(17) One CH_4 molecule was inadvertently omitted in determining (MOPAC vs 2.1) $\Delta H^{\#}$ for 1-naphthol and 2-naphthol, in ref 5. Accordingly, the corrected values for the energies are 11.95 kcal/mol less than those reported. Thus, $\Delta H^{\#}$ for **TS$_1$**, **TS$_2$**, **TS$_3$**, and **TS$_4$** are 61.9, 51.8, 61.7, and 65.1 instead of 73.8, 63.7, 73.6, and 77.0 kcal/mol, respectively, reported in ref 5.

(18) (a) Regio- and stereocontrol in organolithium chemistry has been suggested to be due to complex-induced proximity effects (CIPE). See: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) For a recent demonstration of the intermediacy of a preequilibrium complex during the lithiation of a benzylurea, see: Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 405.

(19) For a recent review on the concept of "proximity" as applied to understanding enzyme kinetics, see: Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206. For an early definition of this concept, see: Bender, M. L.; Chow, Y.-L.; Chloupek, F. *J. Am. Chem. Soc.* **1958**, *80*, 5380. Bruice, T. C. *Annu. Rev. Biochem.* **1976**, *45*, 331.

(20) To the best of our knowledge, no successful[26] examples of the directed lithiation of polyphenols are known. Lithiation of polyphenols has been achieved through halogen–metal exchange; see ref 30 and Timmerman, P.; van Mook, M. G. A.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reindhout, D. N. *Tetrahedron Lett.* **1992**, *33*, 3377. Sunthankar, S. V.; Gilman, H. *J. Org. Chem.* **1951**, *16*, 8. The directed lithiation of 1,2- and 1,3-benzenedithiol has been reported recently. See ref 25a and 25b, respectively.

(21) See, for example: Beaulieu, F.; Snieckus, V. *Synlett* **1992**, 112 and references therein.

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

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

(24) Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571.

(25) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 658. (b) Figuly, G. D.; Loop, C. K.; Martin, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 654. (c) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 665.

(26) Resorcinol has been reported to undergo lithiation by the action of *n*-BuLi in ether (reflux, 21 h). In our hands, no reaction occurred under a variety of conditions. See: Gilman, H.; Willis, H. B.; Cook, T. H.; Webb, F. J.; Meals, R. N. *J. Am. Chem. Soc.* **1940**, *62*, 667.

(27) Narasimhan, N. S.; Mali, R. S. *Synthesis*, **1983**, 957.

experimental conditions, thus suggesting that solutions to the above problems can be found by the trial and error method.[29] However, no specific methodology has been uncovered yet for the lithiation of the higher members of the polyhydric family of aromatics.[30] Herein we show that theoretically MNDO-determined agostic interaction[9,10] parameters successfully predict that the peri lithiation of monohydric, dihydric, and trihydric phenolic compounds should be feasible projects provided that a peri OH group is present in the substrate. As shown below, these predictions have been borne out experimentally, thus definitely proving that, contrary to customary belief, polyhydric hydroxy aromatics having peri hydrogens within reach, i.e., adjacent to an existing peri phenol group, are very well designed ("preorganized"[31]) substrates to undergo directed lithiation at that position.

Computational Methods

As in previous work by us[5,7] and others,[6] calculations have been performed using dimeric CH_3Li solvated with two H_2O[32] molecules (per lithium) as the working model.[33] Theoretical calculations were carried out at the restricted Hartree–Fock (RHF) level using the MNDO[34] semiempirical SCF–MO method, as implemented in the MOPAC (vs 6.0) package of programs.[35] In spite of the fact that the energy of C–Li and H–Li bonds is overestimated by MNDO,[23,36] this is still the only successful[37] method for studying organolithium compounds which is capable of embracing both discrete solvation[38] and aggregation, two key issues which, in our view, ought to clarify some still poorly understood aspects of lithiation reactions. We have used the reaction coordinate method for extending calculations to the lithiation reaction. As in previous work, we have employed in this study our mixed reaction coordinate.[5] All structures were optimized and further refined by minimization of the gradient norm at least below 0.1 kcal/Å·deg. No symmetry constraints were imposed unless otherwise noted. 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.[39]

Results and Discussion

It should be emphasized that we have arbitrarily chosen to work with mixed dimers, and, of course, ΔG and ΔG^* may vary somewhat if a different aggregate had been considered instead. Nevertheless, since no changes are expected to occur in the aggregation state of reactants during the rate-determining lithiation step (envisioned as an unimolecular, internal reorganization reaction), it can be assumed in a first approximation that calculated ΔG^* values are likely to be also applicable to the corresponding reactions involving higher aggregated species. Care should be taken, however, in evaluating ΔG for reactions that involve either highly aggregated starting materials or products,[40] or when internal aggregation is expected.

Although there is no full agreement as to which are the most significant agostic interaction indicators, those usually employed throughout the literature[6] are the following three: (1) the (increase in) C–H bond length, (2) the (reduced) C–H bond order, (3) the (increase in) positive charge on hydrogen. To these we have added a fourth parameter, namely, the H_{CH}–Li_{unsat} distance, previously employed by us as an indicator of the intensity of the agostic interaction.[5]

The structural consequence of agostic interaction (Scheme 1), i.e., in moving from the coordinatively saturated aggregate (COSA) to the unsaturated one (COUSA), is a somewhat more rigid aggregate already having some key geometric attributes (herein identified as proximity features[18,19]) of the nearby transition state, namely: (1) partially restricted rotation of the rotors (the C–X bond, in particular) that will eventually become frozen out in reaching the transition structure; (2) shorter R–HC_{aryl} distance, approaching that of the transition state value; (3) appropriate trajectory of approach[41] herein measured as the R–H–C_{aryl} angle; and (4) proximity of the C_{ortho}–C_{ipso}–X–Li dihedral angle to that of the transition state. In other words, bonding changes at the COUSA stage, though incipient, should

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(28) The aggregation and mixed aggregation of phenolates has been extensively studied by the group of Jackman. See: Jackmann, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177. Jackmann, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829. Jackmann, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101. Jackmann, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202. Jackmann, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403 and references therein. Aggregation and mixed aggregation in lithium amides has also been extensively studied. See, for example: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Galiano-Roth, A.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602. Zarges, W.; Marsch, M.; Harmes, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1392 and references therein.

(29) In his pioneering work, Gilman reported a very low yield on the lithiation (followed by carboxylation) of phenol itself: Gilman, H.; Arntzen, C. E.; Webb, F. J. *J. Org. Chem.* **1945**, *10*, 374. Forty years later, Posner[24] found conditions for the efficient lithiation of phenol.

(30) Organolithium derivatives of polyhydric compounds have been generated by recourse to halogen–metal exchange. See: Saá, J. M.; Morey, J.; Suñer, G.; Frontera, A.; Costa, A. *Tetrahedron Lett.* **1991**, *32*, 7313. Rotger, M. C.; Costa, A.; Saá, J. M. *J. Org. Chem.* **1993**, *58*, 4083 and references cited therein.

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

(32) Some organolithium compounds crystallize with water as ligand. See: Barr, D.; Raithby, P. R.; Schleyer, P. v. R.; Snaith, R.; Wright, D. S. *Chem. Commun.* **1990**, 643. Mikulcik, P.; Raithby, P. R.; Snaith, R.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 428. Armstrong, D. R.; Barr, D.; Raithby, P. R.; Snaith, R.; Wright, D. S.; Schleyer, P. v. R. *Inorg. Chim. Acta* **1991**, *185*, 163. Lambert, C.; Schleyer, P. v. R.; Pieper, U.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 77.

(33) For a recent application of MNDO calculations (together with HOESY NMR studies) to the structure of some "super bases", see: Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 7482. Best fit with experiment was achieved when real (dimethyl ether) ligands were employed in calculations.

(34) Lithium parametrization: Thiel, W.; Clark, T. Unpublished (W. Thiel, personal communication to S. Olivella, Jan 1982).

(35) (a) MOPAC 6, Dewar, M. J. S. *QCPE*, No. 506. (b) Olivella, S.; Vilarrasa, J. *J. Heterocycl. Chem.* **1981**, *18*, 1189.

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

(37) Dietrich, H.; Mahdi, W.; Wilhelm, D.; Clark, T.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 621. Boche, G.; Decher, G.; Etzrodt, H.; Dietrich, H.; Mahdi, W.; Kos, A. J.; Schleyer, P. v. R. *Chem. Commun.* **1984**, 1493. Wilhelm, D.; Clark, T.; Schleyer, P. v. R.; Dietrich, H.; Mahdi, W. *J. Organomet. Chem.* **1985**, *280*, C6. Schleyer, P. v. R.; Hacker, R.; Dietrich, H.; Mahdi, W. *Chem. Commun.* **1985**, 622. Neugebauer, W.; Geiger, G. A. P.; Kos, A. J.; Stezowski, J. J.; Schleyer, P. v. R. *Chem. Ber.* **1985**, *118*, 1504. Stezowski, J. J.; Hoier, H.; Wilhelm, D.; Clark, T.; Schleyer, P. v. R. *Chem. Commun.* **1985**, 1263. Hacker, R.; Schleyer, P. v. R.; Reber, G.; Müller, G.; Brandsma, L. *J. Organomet. Chem.* **1986**, *316*, C4. McKee, M. L. *J. Am. Chem. Soc.* **1987**, *109*, 559. Hacker, R.; Kauffmann, E.; Schleyer, P. v. R.; Mahdi, W.; Dietrich, H. *Chem. Ber.* **1987**, *120*, 1533. Bausch, J. W.; Gregory, P. S.; Olah, G. A.; Prakasch, G. K.; Schleyer, P. v. R.; Segal, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 3633. Paquette, L. A.; Bauer, W.; Sivik, M. R.; Bühl, M.; Feigel, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 8776. Bauer, W.; O'Doherty, G. A.; Schleyer, P. v. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 7093. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112.

(38) A number of "dielectric continuum" solvation models for quantum mechanical calculations have been developed quite recently. See, for example: (a) Katritzky, A. R.; Karelson, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 1561. (b) Cramer, C. J.; Truhlar, D. G. *Science* **1992**, *256*, 231. Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8552, 8305. (c) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117. (d) Ford, G. P.; Wang, B. *J. Am. Chem. Soc.* **1992**, *114*, 10 563.

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

(40) Organic acids and their corresponding lithium salts exist in different aggregation states. See: Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288.

(41) For recent studies on the trajectories of proton transfer reactions, see: (a) Liotta, D.; Saindane, M.; Waykole, L.; Stephens, J.; Grossman, J. *J. Am. Chem. Soc.* **1988**, *110*, 2667. (b) Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 5421. (c) Duan, X.; Scheiner, S. *J. Am. Chem. Soc.* **1992**, *114*, 5849. For a review of much wider perspective, see: Menger, F. M. *Tetrahedron.* **1983**, *39*, 1013.

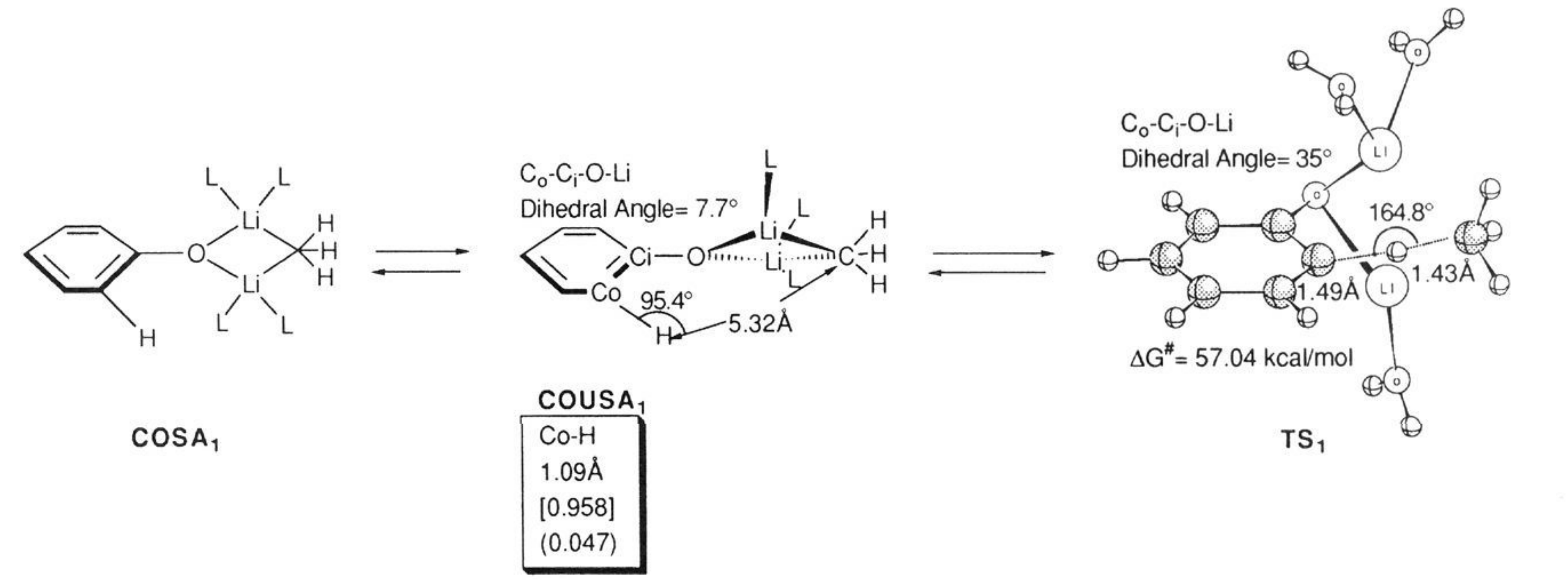

Figure 1. Agostic interaction parameters (C_o−H distance, C_o−H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from phenol and methyllithium **$COUSA_1$** (in box). Relevant proximity features (H−CH_3 distance, C_o−H−CH_3 angle, C_o−C_i−O−Li dihedral angle) directly shown on the **$COUSA_1$** and **TS_1** structures.

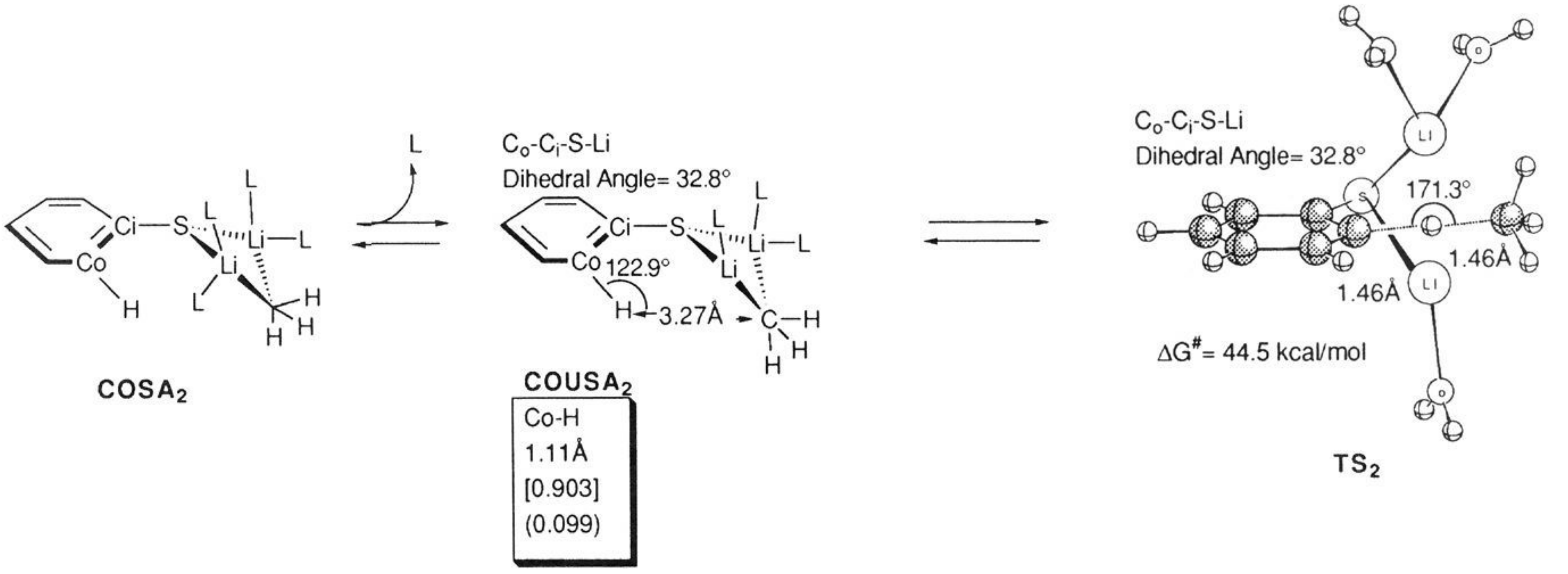

Figure 2. Agostic interaction parameters (C_o−H distance, C_o−H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from thiophenol and methyllithium **$COUSA_2$** (in box). Relevant proximity features (H−CH_3 distance, C_o−H−CH_3 angle, C_o−C_i−S−Li dihedral angle) directly shown on the **$COUSA_2$** and **TS_2** structures.

be indicative of the vicinity of the transition state. Accordingly, we decided to incorporate proximity features into the discussion, nevertheless, being conscious of the fact that examination of the AI parameters and proximity features can only give a gross indication of ΔG^* values because the major energy changes must occur on the proximity of the transition state where the slope is highest and all permanent and temporary forces (bonding changes) operate altogether. For comparison purposes we choose an arbitrary TS structure having no free rotors about the key bonds, a mean CH_3−HC distance of 1.46 Å, a trajectory angle in the range of 170−180°, and a C_{ortho}−C_{ipso}−X−Li dihedral angle of 35°.

Monohydric Compounds. Calculations revealed important features in regard to the mechanism of lithiation of mono- and polyhydric compounds, the first being that phenol **1** and thiophenol **2** are quite differently prepared to undergo ortho lithiation. Thus, whereas almost negligible AI was noticed for the case of phenol itself, as exemplified by the parameters shown in Figure 1 for **$COUSA_1$**, those for thiophenol **2** were found to be quite strong (Figure 2). Most likely, this is a consequence of the larger C−S and S−Li bonds which can thus act as larger poles for bringing the CH_3 (of the CH_3Li unit on the mixed aggregate) closer to the hydrogen atom to be removed. Sulfur is also responsible for the fact that the mixed aggregate unit is tilted 63.2° above the plane formed by the ring and sulfur atoms, whereas the whole molecule is almost planar in the case of phenol. In fact, thiophenol **2** is a clear-cut case having not only stronger AI parameters[42] but also advanced proximity features (Table 1) as exemplified by a good trajectory of approach (CH_3−H−C angle = 122.9°) and CH_3−HC distance of only 3.27 Å. Accordingly, the transition structure **TS_2** was found to be significantly more advanced (ΔG^* = 44.5 kcal/mol) than that of phenol (**TS_1**, ΔG^* = 57.0 kcal/mol). These results are in good qualitative agreement with experimental findings: lithiation of thiophenol can be carried out with *n*BuLi in an apolar solvent,[25] whereas that of phenol itself requires especial, stronger (*t*-BuLi/THP) conditions.[24]

As for the case of phenol **1**, ortho (either C-3 or C-1) lithiation of 2-naphthol **3** exhibited also negligible AI parameters, and, accordingly, high ΔG^* values (56.48 and 59.09 kcal/mol, respectively) were obtained for these processes. On the other hand, peri lithiation of 1-naphthol **4** is highly favored,[15] as exemplified (Table 1) by strong AI parameters and excellent proximity features: (1) a fairly rigid C−O rotor; (2) a CH_3−HC distance of 3.471 Å; (3) a close-to-ideal trajectory of

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[42] Bulky substituents vicinal to the phenol group can cause a significant increase of the AI parameters, thereby facilitating lithiation by simply pushing in the adjacent mixed aggregate toward the vicinal C−H bond. See: Morey, J.; Costa, A.; Deyá, P. M.; Suñer, G. A.; Saá, J. M. *J. Org. Chem.* **1990**, *55*, 3902.

Table 1. Proximity Features ($H_{C\text{ortho or peri}}-CH_3$ Distance, C–H–CH_3 Angle and C–C–O–Li Dihedral Angle) of the Coordinatively Unsaturated Mixed Aggregates (COUSA) for the Lithiation of Hydric Compounds[a]

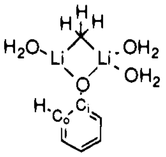
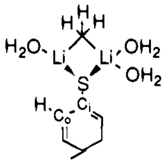
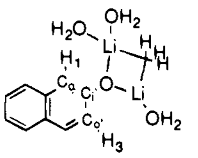
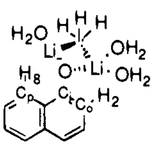
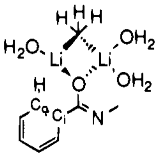
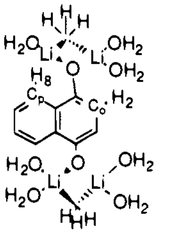
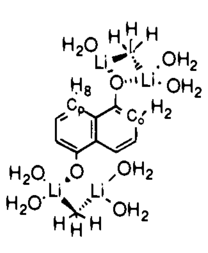
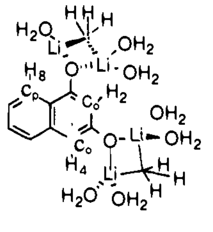
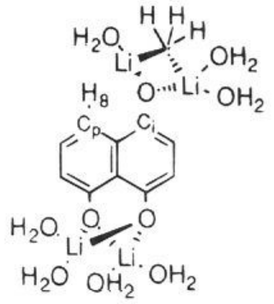
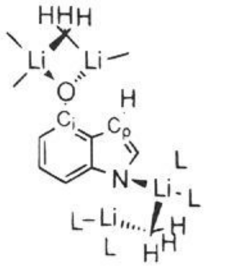
Coordinatively Unsaturated Mixed Aggregate (COUSA)	**COUSA** HC_O or p-CH_3 Distance (Å)	**COUSA** C_O or p-H-CH_3 Angle	**COUSA** C-C-O-Li Dihedral Angle	**Transition State** ΔG* (Kcal/mol)	**Transition State** C_O or p-H-CH_3 Distances(Å)	**Transition State** C_O or p-H-CH_3 Angle	**Transition State** C-C-O-Li Dihedral Angle
	5.321	95.4°	7.7°(C_OC_iOLi)	57.04	1.491 (H-C_O) 1.434 (H-CH_3)	164.8°	35°(C_OC_iOLi)
	3.266	122.9°	46.5°(C_OC_iOLi)	44.49	1.457 (H-C_O) 1.438 (H-CH_3)	171.3°	32.8°(C_OC_iOLi)
	H_3 5.314	96.3°	7.4°($C_{O'}C_iOLi$)	56.48	1.491 (H-$C_{O'}$) 1.434 (H-CH_3)	165.6°	34.2°($C_{O'}C_iOLi$)
	H_1 5.274	96.6°	13.3°(C_OC_iOLi)	59.59	1.500 (H-C_O) 1.433 (H-CH_3)	164.9°	34.8°(C_OC_iOLi)
	H_8 3.471	144.9°	30.2°(C_PC_iOLi)	46.12	1.463 (H-C_P) 1.457 (H-CH_3)	172.1°	29.6°(C_PC_iOLi)
	H_2 3.507	94.2°	46.7°(C_OC_iOLi)	55.82	1.494 (H-C_O) 1.435 (H-CH_3)	165.0°	34.9°(C_OC_iOLi)
	3.467	118.7°	18°(C_OCNOLi)	47.89	1.460 (H-C_O) 1.463 (H-CH_3)	170.4°	26.9°(C_OCNOLi)
	H_8 3.566	149.2°	28.7°(C_PC_iOLi)	44.89	1.469 (H-C_P) 1.452 (H-CH_3)	172.3°	28.7° (C_PC_iOLi)
	H_2 (stationary point not found)						
	H_8 3.363	132.1°	30.2°(C_PC_iOLi)	47.39	1.472 (H-C_P) 1.480 (H-CH_3)	173°	32.7°(C_PC_iOLi)
	H_2 3.978	119.9°	16.1°(C_OC_iOLi)	57.74	1.503 (H-C_O) 1.428 (H-CH_3)	164.8°	35.4°(C_OC_iOLi)
	H_8 3.383	135.4°	33.4°(C_PC_iOLi)	46.67	1.461 (H-C_P) 1.462 (H-CH_3)	173.1°	33.4°(C_PC_iOLi)
	H_2 5.384	94.7°	0°(C_OC_iOLi)	66.84	1.539 (H-C_O) 1.406 (H-CH_3)	164.9°	34°(C_OC_iOLi)

Table 1 (Continued)

Coordinatively Unsaturated Mixed Aggregate (COUSA)	**COUSA** HC_o or p-CH_3 Distance (Å)	**COUSA** C_o or p-H-CH_3 Angle	**COUSA** C-C-O-Li Dihedral Angle	**Transition State** ΔG* (Kcal/mol)	**Transition State** C_o or p-H-CH_3 Distances(Å)	**Transition State** C_o or p-H-CH_3 Angle	**Transition State** C-C-O-Li Dihedral Angle
	3.475	140.6°	24.8°(C_pC_iOLi)	48.75	1.469 (H-C_p) 1.451 (H-CH_3)	180°	36.7°(C_pC_iOLi)
	3.330	135.0°	24.2°(C_pC_iOLi)	55.58	1.463 (H-C_p) 1.412 (H-CH_3)	180°	30.15(C_pC_iOLi)

[a] The corresponding values for the transition structures are given for comparison.

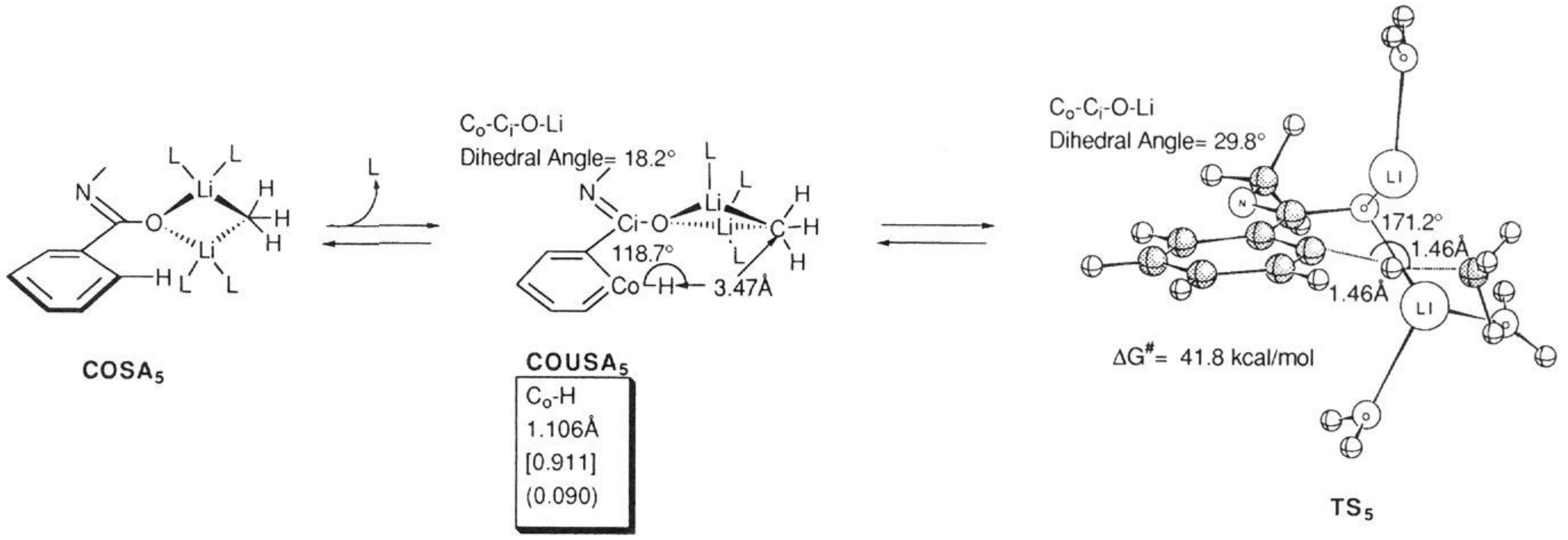


Figure 3. Agostic interaction parameters (C_o-H distance, C_o-H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from *N*-methylbenzamide and methyllithium **COUSA₅** (in box). Relevant proximity features ($H-CH_3$ distance, C_o-H-CH_3 angle, C_o-C_i-O-Li dihedral angle) directly shown on the **COUSA₅** and **TS₅** structures.

approach (CH_3-H-C angle = 144.9°) and (4) a $C_{ortho}-C_{ipso}-O-Li$ dihedral angle that is already quite close (30.2°) to the final (29.6°) transition state value. In striking contrast, the corresponding dihedral angles for the ortho (C-2) lithiation of phenol **1** (7.7°) and 2-naphthol **3** (7.4° and 13.3° for the lithiation at C-3 and C-1, respectively) deviate significantly from the final values in the corresponding transition states (35° for **TS₁**, 34.2° for **TS₃ₒ₋₃**, and 34.8° for **TS₃ₒ₋₁**).

At the outset we envisaged lithiation of a secondary benzamide as a good model for understanding the startling peri lithiation of 1-naphthol (Scheme 2). So, it came as no surprise to find that the agostic interaction parameters for peri lithiation of 1-naphthol **4** (Figure 3) were quite similar (actually somewhat better) to those obtained for the imidate species **COUSA₅** presumably involved in the lithiation of a secondary benzamide.[43] Here, too, the system features (Table 1) (1) considerable restriction about the C−O and $C_{ipso}-C_N$ rotors; (2) a short (3.47 Å) CH_3-HC distance; (3) a good trajectory of approach as measured by the CH_3-H-C angle of 118.7°; and (4) a $C_{ortho}-C_{ipso}-O-Li$ dihedral angle (18.0°) somewhat close to that of the nearby transition structure (26.9°). In agreement with this reasoning, the MNDO calculated ΔG* for the peri lithiation of 1-naphthol (45.6 kcal/mol) was found to be not too far apart from that of the lithiation of *N*-methylbenzamide (ΔG* = 47.9 kcal/mol), the geometries of the corresponding transition state structures **TS₄ₚ** and **TS₅** being also very close to one another (Figure 3). It must be emphasized, though, that because of the well-known tendency of MNDO to overestimate steric interactions (thereby underestimating conjugation) the calculated ΔG* for the lithiation of *N*-methylbenzamide is abnormally high. By simply restricting the dihedral $C_oC_iC_NN$ angle to 0°, the calculated ΔG* reduces to 41.8 kcal/mol, no doubt owing to the much better trajectory of approach (CH_3-H-C angle = 152.0°).[44]

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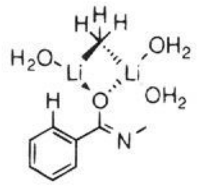
(43) The X-ray structure of *N*-isopropylbenzamide lithium salt has been recently described. See: Maetzke, T.; Hidber, C. P.; Seebach, D. *J. Am. Chem. Soc.* **1990**, *112*, 8248.

(44) In fact, when calculations on benzamide **5** were performed with a restricted dihedral angle of $C_oC_iC_NN$ = 0°, the following data (compare with those on Table 1) were obtained:

Coordinatively Unsaturated Mixed Aggregate (COUSA)	**COUSA** HC_{ortho} or peri-CH_3 Distance (Å)	**COUSA** C_{ortho} or peri-H-CH_3 Angle	**COUSA** C-C-O-Li Dihedral Angle	**Transition State** ΔG* (Kcal/mol)
	3.463	152.0°	32.3°(C_OC_NOLi)	41.79

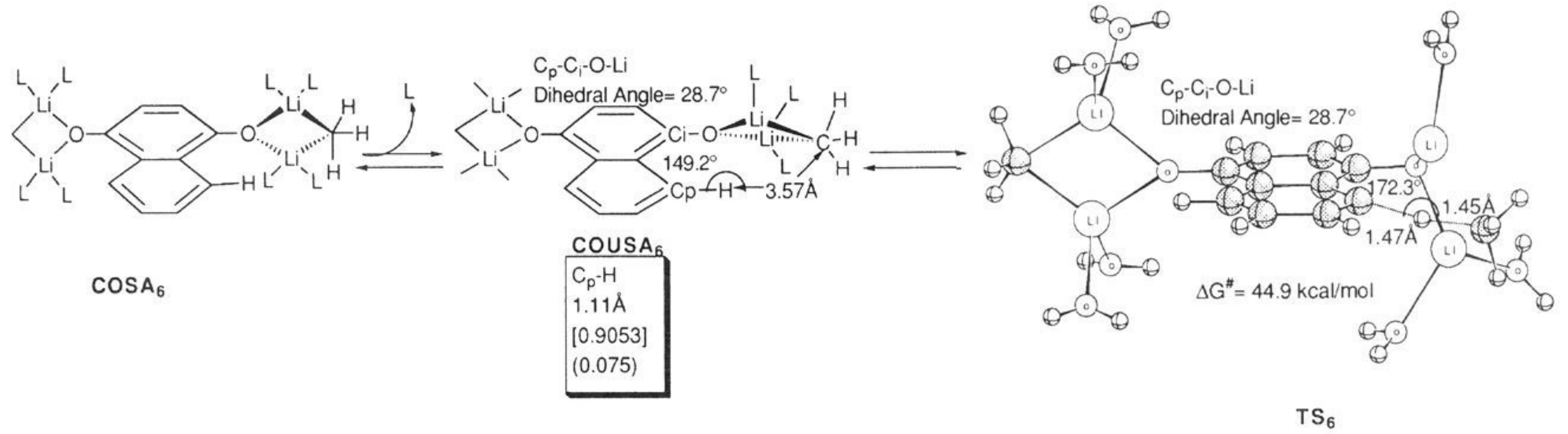


Figure 4. Agostic interaction parameters (C_p−H distance, C_p−H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from 1,4-dihydroxynaphthalene and methyllithium **COUSA$_6$** (in box). Relevant proximity features (H−CH_3 distance, C_p−H−CH_3 angle, C_p−C_i−O−Li dihedral angle) directly shown on the **COUSA$_6$** and **TS$_6$** structures.

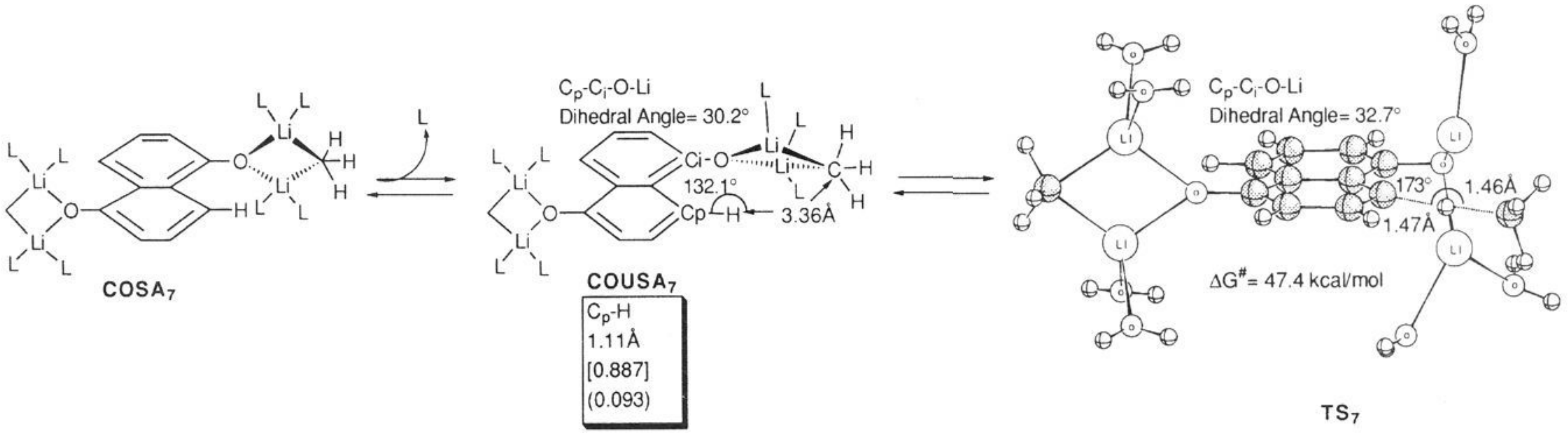


Figure 5. Agostic interaction parameters (C_p−H distance, C_p−H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from 1,5-dihydroxynaphthalene and methyllithium **COUSA$_7$** (in box). Relevant proximity features (H−CH_3 distance, C_p−H−CH_3 angle, C_p−C_i−O−Li dihedral angle) directly shown on the **COUSA$_7$** and **TS$_7$** structures.

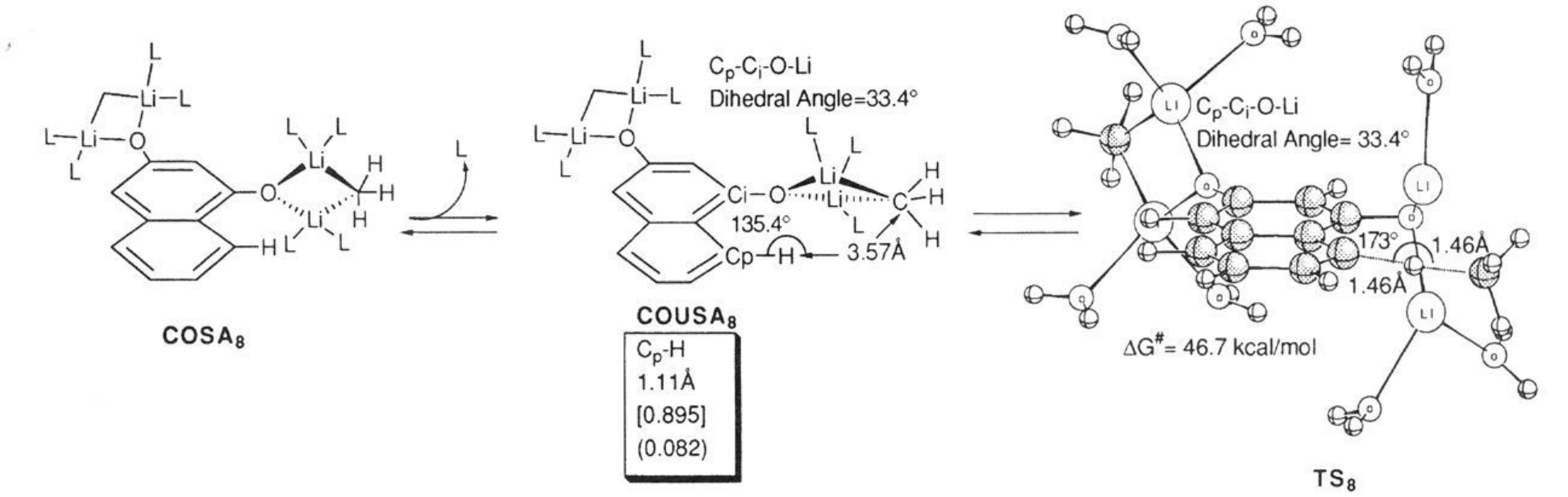


Figure 6. Agostic interaction parameters (C_p−H distance, C_p−H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from 1,3-dihydroxynaphthalene and methyllithium **COUSA$_8$** (in box). Relevant proximity features (H−CH_3 distance, C_p−H−CH_3 angle, C_p−C_i−O−Li dihedral angle) directly shown on the **COUSA$_8$** and **TS$_8$** structures.

Polyhydric Compounds. Because of the strong AI parameters and proximity features observed for **COUSA$_4$** and **COUSA$_5$**, we conceived the idea that peri lithiation of phenolic compounds having an adjacent peri OH,[45] or related functional group, should be a general phenomenon even for polyhydric analogues such as, for example, 1,4-, 1,5-, and 1,3-dihydroxynaphthalenes **6**, **7**, and **8**, and, more importantly, we expected that lithiation could be anticipated with the help of agostic interaction and proximity parameters. Not unexpectedly, the MNDO-determined AI parameters, calculated on the corresponding coordinatively unsaturated species, were found to be as strong as for the case of 1-naphthol (Figures 4, 5, and 6). Furthermore, as illustrated in Table 1, substrates **COUSA$_{6p}$**, **COUSA$_{7p}$**, and **COUSA$_{8p}$** appear to be also highly preorganized species as judged by quite short CH_3−HC distances (3.56, 3.36, and 3.38, respectively), excellent trajectory angles (149.2°, 132.1°, and 135.4°), and dihedral angles (28.7°, 30.2°, and 33.4°, respectively). In accordance with these data, the corresponding transition state structures **TS$_{6p}$**, **TS$_{7p}$**, and **TS$_{8p}$** ($\Delta G^* = 44.9$, 47.4, and 46.7 kcal/mol, relative to the coordinatively saturated mixed aggregates **COSA**) were found to be very similar to that of 1-naphthol ($\Delta G^* = 46.1$ kcal/mol).[46] Moreover, in all cases, the corresponding AI parameters and proximity features (Table 1) for ortho lithiation (at C-2) suggested significantly less advanced TSs, as previously shown for the case of 1-naphthol.[15]

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(45) Lithiation of 1-naphthol methyl ether and MOM protected 1-naphthol, occurs predominantly at C-2. See: Kawikawa, T.; Kubo, I. *Synthesis* **1986**, 431. Narasimhan, N. S.; Mali, R. S. *Tetrahedron* **1975**, *31*, 1005. Shirley, D. A.; Cheng, C. F. *J. Organomet. Chem.* **1969**, *20*, 251. For the peri lithiation of naphthylamines, see: Kirby, A. J.; Percy, J. M. *Tetrahedron* **1988**, *44*, 6093. Jastrzebski, J. T. B. H.; Van Koten, G.; Goubitz, K.; Arlen, C.; Pfeffer, M. *J. Organomet. Chem.* **1983**, *246*, C75. Narasimhan, N. S.; Ranade, A. C. *Indian J. Chem.* **1969**, 539.

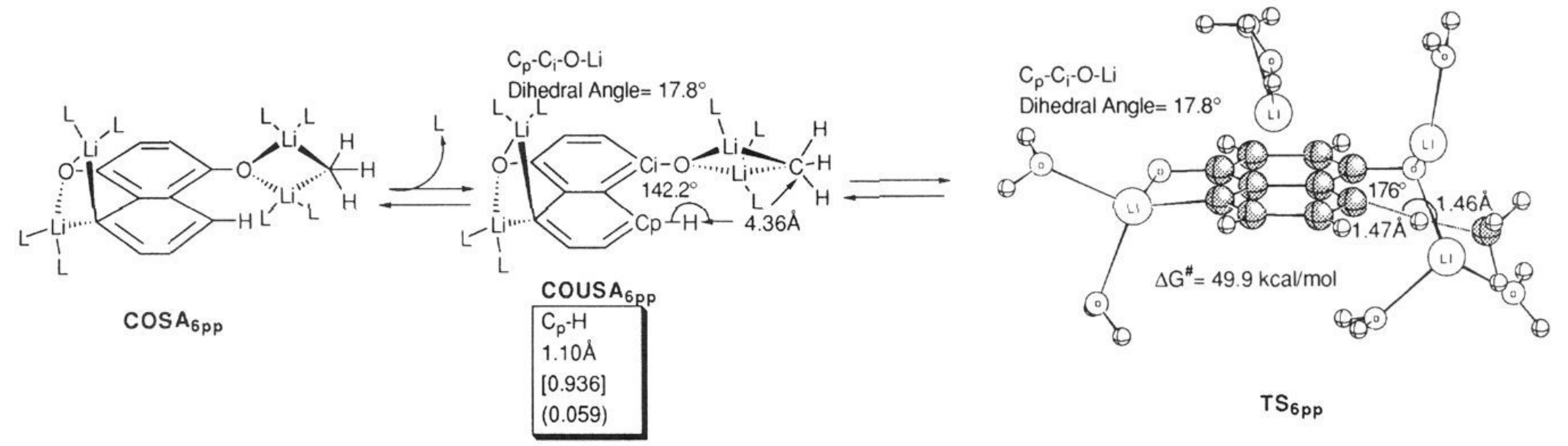

Figure 7. Double peri lithiation. Agostic interaction parameters (C_p-H distance, C_p-H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from phenol and methyllithium **COUSA$_{6pp}$** (in box). Relevant proximity features ($H-CH_3$ distance, C_p-H-CH_3 angle, C_p-C_i-O-Li dihedral angle) directly shown on the **COUSA$_{6pp}$** and **TS$_{6pp}$** structures.

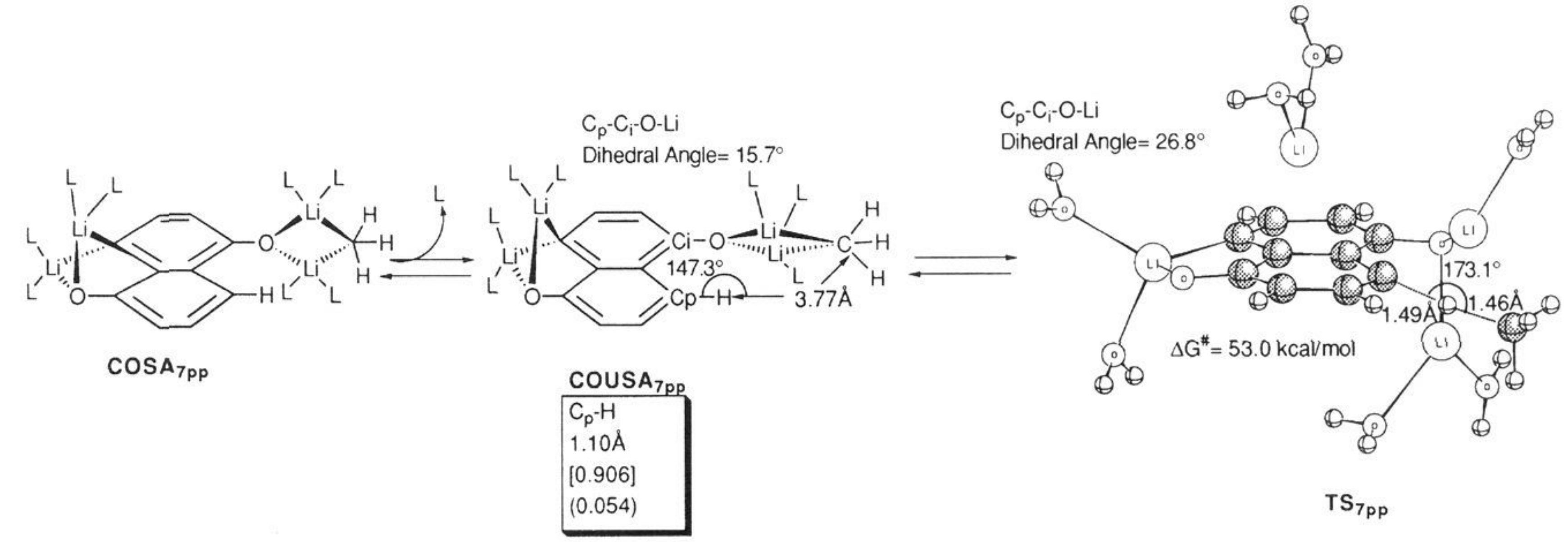

Figure 8. Double peri lithiation. Agostic interaction parameters (C_o-H distance, C_o-H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from 1,5-dihydroxynaphthalene and methyllithium **COUSA$_{7pp}$** (in box). Relevant proximity features ($H-CH_3$ distance, C_p-H-CH_3 angle, C_p-C_i-O-Li dihedral angle) directly shown on the **COUSA$_{7pp}$** and **TS$_{7pp}$** structures.

In fact, calculations revealed the transition state structures **TS$_{6o}$**, **TS$_{7o}$**, and **TS$_{8o}$** lying at very high energy values ($\Delta G^* = 57.6$, 57.7, and 59.7 kcal/mol), i.e., 10−13 kcal/mol higher than peri lithiation. These data fully confirmed the above analysis and the ensuing prognostication: *peri lithiation of polyhydric phenols of the naphthalene, phenanthrene, and anthracene series and, presumably, of closely related compounds as well, having at least one such grouping in a peri position, should be experimentally practicable* provided that (1) the expected solubility problems could be surmounted and (2) aggregation effects would not significantly modify the otherwise very high activation energies. Success was thus being linked to finding a suitable media for avoiding extensive aggregation and precipitation,[28] and we set out to find such reaction conditions.

In the event we found that 1,4-, 1,5-, 1,3- and 1,6-dihydroxynaphthalenes **6**, **7**, **8**, and **9**, 10,10′-dihydroxy-9,9′-biphenanthryl (**10**),[47] and 9,10-dihydroxyanthracene (**11**)[48] underwent peri lithiation in a totally regioselective manner by working with excess *n*-BuLi (best results were obtained when using 3 equiv per OH unit, approximately) in TMEDA as solvent,[49] as demonstrated by the isolation of the corresponding peri functionalized products[50] from quenching with trimethylsilyl chloride, dimethyl disulfide, dimethylformamide (DMF), or ethyl chloroformate. Products derived from lithiation at C-2 were not detected in the crude reaction mixtures. In addition to these results, the following two experimental observations fully confirmed that only peri-lithiated products are obtained when submitting polyhydric phenolic compounds to the above standard conditions of lithiation: (1) 2-naphthol **3** did not react (recovered unchanged) under the above nBuLi/TMEDA conditions (regioselective lithiation of **3** under tBuLi/THP occurs at C-3[16]); (2) 1-naphthol **4**, under the above reaction conditions, underwent peri lithiation only (monosubstituted derivative **4b** was obtained in high yield[16]), also in contrast with the observations using tBuLi/THP.[5]

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(46) Ab initio (3-21G) calculations revealed that the N,C$_8$-dilithiated naphthylamine is 14.4 and 27.3 kcal/mol lower in energy than the corresponding N,C$_2$ and N,N-dilithiated analogues, respectively. See: Armstrong, D. R.; Barr, D.; Clegg, W.; Drake, S. R.; Singer, R. J.; Snaith, R.; Stalke, D.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1707.

(47) Yamamoto, K.; Fukushima, H.; Okamoto, I. *Chem. Commun.* **1984**, 1111. Toda, F.; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607.

(48) (a) Dimmel, D. R.; Shepard, D. *J. Org. Chem.* **1982**, *47*, 22. (b) Koerner, N.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 1373.

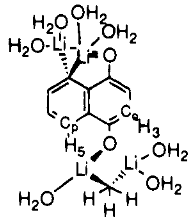
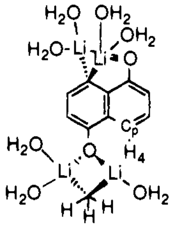
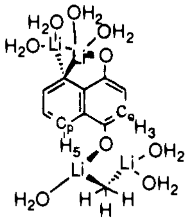
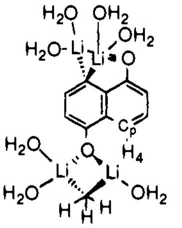
(49) For a recent reassessment of the ligand capacity of TMEDA, see: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448, and references therein.

(50) The regiospecific synthesis of substituted naphthalenes has received great attention in recent years. See, for example: Buchwald, S. L.; King, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 258. Batt, D. G.; Jones, D. G.; La Greca, S. *J. Org. Chem.* **1991**, *56*, 6704. Loewenthal, H. J. E.; Gottlieb, L. *J. Org. Chem.* **1992**, *57*, 2631. Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010 and references therein.

(51) Balasubramaniyan, V. *Chem. Rev.* **1966**, *66*, 5670.

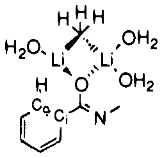
(52) The assistance of Dr. S. García-Granda and I. Cándano-González (University of Oviedo, Spain) in obtaining the X-ray crystal structure of **6bb** is gratefully acknowledged. Details of the X-ray crystallographic analysis are available upon request from the Director of the Cambridge Crystallographic Data Center, 12 Union Rd, Cambridge, CB2 1EZ, U.K. Empirical formula $C_{22}H_{40}O_2Si_4$: $M_r = 448.90$; triclinic, space group $P1$; $a = 6.422(3)$ Å, $b = 10.096(6)$ Å, $c = 22.33(1)$ Å; $\alpha = 86.80(5)°$, $\beta = 89.64(5)°$, $\gamma = 71.55(4)°$; $V = 1371.3(1)$ Å^3; $Z = 2$, $D_x = 1.09$ mg m^{-3}, Mo Kα radiation (graphite crystal monochromator, $\lambda = 0.730\,71$ Å) $\mu = 2.25$ cm^{-1}; $F(000) = 487.94$; $T = 293$ K. Final conventional $R = 0.057$ and $R_w = 0.055$ for 1524 observed reflections and 254 variables.

Table 2. Proximity Features ($H_{C_{ortho}\ or\ peri}-CH_3$ Distance, C–H–CH_3 Angle and C–C–O–Li Dihedral Angle) of the Coordinatively Unsaturated Mixed Aggregates (COUSA) for the Second Lithiation of Hydric Compounds.

Coordinatively Unsaturated Mixed Aggregate (COUSA)	COUSA HC_o or p-CH_3 Distance (Å)	COUSA C_o or p-H-CH_3 Angle	COUSA C-C-O-Li Dihedral Angle	Transition State ΔG* (Kcal/mol)	Transition State H-C_o or p-CH_3 Distances(Å)	Transition State C_o or p-H-CH_3 Angle	Transition State C-C-O-Li Dihedral Angle
	H5 4.359	142.2°	19.2°(C_pC_iOLi)	49.91	1.461 (H-C_p) 1.466 (H-CH_3)	175.5°	17.8°(C_pC_iOLi)
	H3 3.830	121.7°	33.3°(C_oC_iOLi)	56.18	1.509 (H-C_o) 1.420 (H-CH_3)	166.1°	30.3°(C_oC_iOLi)
	H4 3.776	147.3°	15.7°(C_pC_iOLi)	52.99	1.486 (H-C_p) 1.457 (H-CH_3)	173.1°	26.8°(C_pC_iOLi)
	H6 3.626	121.6°	36.2°(C_oC_iOLi)	59.31	1.515 (H-C_o) 1.420 (H-CH_3)	165.5°	30.9°(C_oC_iOLi)
	H5 4.359	142.2°	19.2°(C_pC_iOLi)	49.91	1.461 (H-C_p) 1.466 (H-CH_3)	175.5°	17.8°(C_pC_iOLi)
	H3 3.830	121.7°	33.3°(C_oC_iOLi)	56.18	1.509 (H-C_o) 1.420 (H-CH_3)	166.1°	30.3°(C_oC_iOLi)
	H4 3.776	147.3°	15.7°(C_pC_iOLi)	52.99	1.486 (H-C_p) 1.457 (H-CH_3)	173.1°	26.8°(C_pC_iOLi)
	H6 3.626	121.6°	36.2°(C_oC_iOLi)	59.31	1.515 (H-C_o) 1.420 (H-CH_3)	165.5°	30.9°(C_oC_iOLi)

[a] The corresponding values for the transition structures are given for comparison.

Table 3. Proximity Features ($H_{C_{ortho}\ or\ peri}-CH_3$ Distance, C–H–CH_3 Angle and C–C–O–Li Dihedral Angle) of the Coordinatively Unsaturated Mixed Aggregate (COUSA) for the Lithiation of *N*-Methylbenzamide[a]

Coordinatively Unsaturated Mixed Aggregate (COUSA)	COUSA HC_o or p-CH_3 Distance (Å)	COUSA C_o or p-H-CH_3 Angle	COUSA C-C-O-Li Dihedral Angle	Transition State ΔG* (Kcal/mol)	Transition State H-C_o or p-CH_3 Distances(Å)	Transition State C_o or p-H-CH_3 Angle	Transition State C-C-O-Li Dihedral Angle
	3.463	152.0°	32.3°(C_oCNOLi)	41.79	1.459 (H-C_{ortho}) 1.465 (H-CH_3)	171.3°	29.8°(C_oCNOLi)

[a] The corresponding values for the transition structure are given for comparison.

Even more remarkable is the fact that compounds having two peri positions available such as 1,4- and 1,5-dihydroxynaphthalenes **6** and **7**, 10,10′-dihydroxy-9,9′-biphenanthryl (**10**), and 9,10-dihydroxyanthracene (**11**) underwent double (peri) lithiation, as demonstrated by the isolation of crystalline O,O,C,C tetrakis(trimethylsilyl) derivatives **6bb**, **7bb**, **11bb**, and **10cc** or **10dd**. Best yields were found when using 10 equiv of *n*-BuLi (sonication required), lesser amounts giving rise to significantly reduced yields. The structures of these highly encumbered compounds[51] result from their spectroscopic properties, and in one particular case, namely that of **6bb**, it was fully confirmed by X-ray analysis.[52] Interestingly, we found that MNDO-determined AI parameters (Figures 7 and 8) and proximity features (Table 2) also anticipate these results. The unexpectedly low energy of transition structures TS_{6pp} and TS_{7pp} found to lie at 49.9 and 53 kcal/mol, relative to the corresponding lithiated precursors, also agree with these observations. Curiously enough, the corresponding ΔG^* values for monolithiation at C-2 of 1,4- and 1,5-dihydroxynaphthalenes **6** and **7** were found to lie at significantly higher energy values: $\Delta G^* = 57.6$ and 57.4 kcal/mol, respectively, thus implying that even second peri lithiations should be kinetically favored processes over monolithiation at C-2. In fact, these results were borne out by experiment! It can be argued, though, that products of double lithiation could, in fact, derive from a monolithiation–electrophile quench–monolithiation sequence instead of resulting from the generation of a O,O,C,C-tetralithiated species by two subsequent monolithiations (sequential double metalation), and final quench. On the basis of the above MNDO calculated ΔG^* values, it is tempting to conclude that these O,O,C,C-tetralithiated species may actually result from sequential double lithiation, but, of course, the final decision awaits experimental proof.[53] This intriguing but, otherwise, synthetically attractive possibility is supported by recent work by Beak and co-workers who demonstrated the unusual capacity of alkoxides to induce sequential double lithiations, thereby giving rise to O,C,C-trilithio derivatives.[54] The well-known peri lithiation of 1-lithionaphthalene reported by Schleyer et al.[6c] provides additional support to our hypothetical O,O,C,C-tetralithiated species. On the other hand, the possibility that a O → C silyl migration had occurred during quenching was discarded on the basis of prior work which proved that such migration does not take place on naphthyl silyl ethers.[55]

The scope and limitations to these otherwise apparently general peri lithiation reactions of polyhydric compounds can be gleaned from the following facts. On the one hand, vicinal dihydroxy aromatics appear to be inert to the standard reaction conditions, as shown by the fact that 1,2-naphthalenediol **13** was recovered unchanged when treated under the above reaction conditions. Apparently, this is due to precipitation which precludes further reaction to occur. Interestingly, we have found some evidence for peri lithiation in the case of a triphenolic compound. Thus, the easily available 1,4,5-trihydroxynaphthalene **12** under the above reaction conditions (14 equiv of *n*-BuLi) yielded 2,8-bis(methylthio)juglone **12cc** after quenching with dimethyl disulfide, together with 2-methylthiojuglone and 2,3-bis(methylthio)juglone.[56] However, quenching with other electrophiles such as DMF, ClCOOMe, or $(CH_3)_3SiCl$ yielded only recovered starting material (as such or as carbonate or silyl ether). These contradictory results clearly suggest caution at further extending the peri lithiation concept to higher polyhydric compounds, even though calculations indicate that this should be the case as shown by moderately high AI parameters (Figure 9) and proximity features (Table 1) and an incredibly low ΔG^* value of 48.7 kcal/mol for the direct lithiation of a 1,4,5-trihydroxynaphthalene **12**.

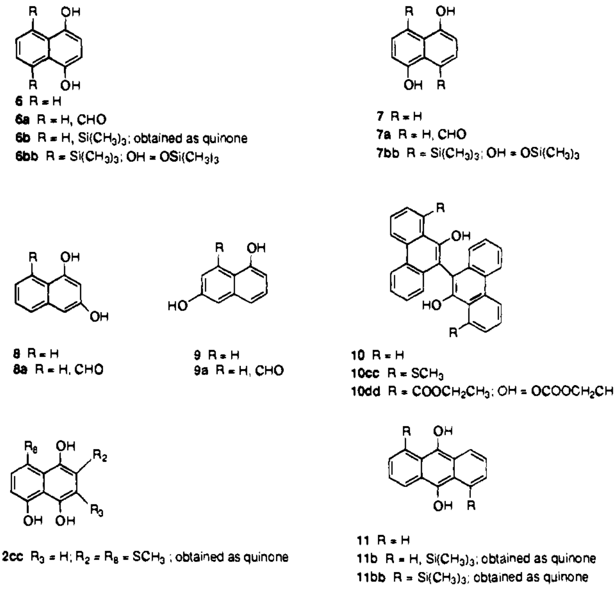

6 R = H
6a R = H, CHO
6b R = H, $Si(CH_3)_3$; obtained as quinone
6bb R = $Si(CH_3)_3$; OH = $OSi(CH_3)_3$
7 R = H
7a R = H, CHO
7bb R = $Si(CH_3)_3$; OH = $OSi(CH_3)_3$
8 R = H
8a R = H, CHO
9 R = H
9a R = H, CHO
10 R = H
10cc R = SCH_3
10dd R = $COOCH_2CH_3$; OH = $OCOOCH_2CH_3$
12cc R_3 = H; R_2 = R_8 = SCH_3 ; obtained as quinone
11 R = H
11b R = H, $Si(CH_3)_3$; obtained as quinone
11bb R = $Si(CH_3)_3$; obtained as quinone

Figure 9.

In trying to fully understand the details of lithiation reactions, we have recently classified the major bonding changes being set up in reaching the transition structures as: bond-breaking processes ($C_{\text{ortho or peri}}$-H, CH_3–Li, CH_3–Li) and bond-forming processes ($C_{\text{ortho or peri}}$-Li_1, $C_{\text{ortho or peri}}$-Li_2, and CH_3-H).[7] Simultaneous to these major processes, a number of minor forces between atoms not to become actually bonded in the final products (nonneighbor interactions) are temporarily established.[7] Of course, this is an oversimplified picture as other significant, temporary bond changes occur which affect atoms far away from those actually suffering permanent (either formation or cleavage) bond changes.[3]

The predictive capacity of agostic interaction parameters and proximity features to evaluate lithiation reactions lies in the fact that, to a certain extent, the above forces are already present at the COUSA stage. Minor forces operate only to a limited extent at this point of the reaction coordinate as demonstrated by partitioning the total energy.[35b] Only general trends are provided, and, therefore, care should be taken in applying these principles in a quantitative manner. In this regard, a particular telling example is that of the lithiation of hydroxyindole **14** for which MNDO calculated ΔG^* (Table 1) was found to be 55.6 kcal/mol,[57] in spite of having good AI parameters and proximity features (CH_3–HC distance 3.30 Å, trajectory angle 135.0°, and a dihedral C_pC_iOLi angle of 24.2°). In this case the extra energy cost needed for breaking the H–C_{peri} bond is clearly associated with the fact that C_{peri} develops significant negative charge along the reaction coordinate, and therefore some (C_{peri}–H) ionic bonding is retained at the proximity of the transition state. To a different extent, the same occurs in the case of the ortho lithiation of phenol and polyphenols. However, being larger systems, polyhydric naphthalenes and analogues having –OH groups ortho or para to the peri position can dissipate somewhat better the excess charge, thus suggesting that even phenolic or polyphenolic systems having larger aromatic polycyclic systems could undergo direct lithiation.

In examining the whole spectrum of data obtained, it can be concluded that peri lithiation is highly favored over other alternatives, the reason being that the mixed aggregate species (at the COUSA stage) is ideally disposed for achieving hydrogen

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[53] Second metalations directed by the first metallic substituent. See: West, R.; Jones, P. C. *J. Am. Chem. Soc.* **1968**, *90*, 2656. Mulvaney, J. E.; Gardlund, Z. G.; Gardlund, S. L.; Newton, D. J. *J. Am. Chem. Soc.* **1966**, *88*, 476. Mulvaney, J. E.; Newton *J. Org. Chem.* **1969**, *34*, 1936. Neugebauer, W.; Kos, A.; Schleyer, P. v. R. *J. Organomet. Chem.* **1982**, *228*, 207. Neugebauer, W.; Clark, T.; Schleyer, P. v. R. *Chem. Ber.* **1983**, *116*, 3283. D. J. Wilhelm, D.; Clark, T.; Schleyer, P. v. R.; Courtneidge, J. L.; Davies, A. G. *J. Am. Chem. Soc.* **1984**, *106*, 361.

[54] Gallagher, D. J.; Garret, C. G.; Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1991**, *56*, 853.

[55] 1-Naphthol trimethylsilyl ether is known not to undergo silyl O–C migration on treatment with the stronger *tert*-butyllithium: Simchen, G.; Pfletschinger, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 428.

[56] A blank reaction of **12** with 3.3 equiv of *n*-BuLi followed by quenching with dimethyl disulfide yielded 2-methylthiojuglone in low yield. Thiols add to juglones at C-3. See: Laugraud, S.; Guignant, A.; Chassaguard, C.; d'Angelo, J. *J. Org. Chem.* **1988**, *53*, 1557 and references therein.

[57] Lithiation of 4-hydroxyindole 4 under the general conditions above (10 equiv of *n*-BuLi) followed by quenching with different electrophiles yielded recovered starting material. Using dimethyl disulfide as quencher, 15–25% yield of 3-methylthio-4-hydroxyindole was obtained together with recovered starting material. *N*-lithio indole is known to react at C-3 with different electrophiles. See, for example: Raban, M.; Chern, L.-J. *J. Org. Chem.* **1980**, *45*, 1688. Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 758.

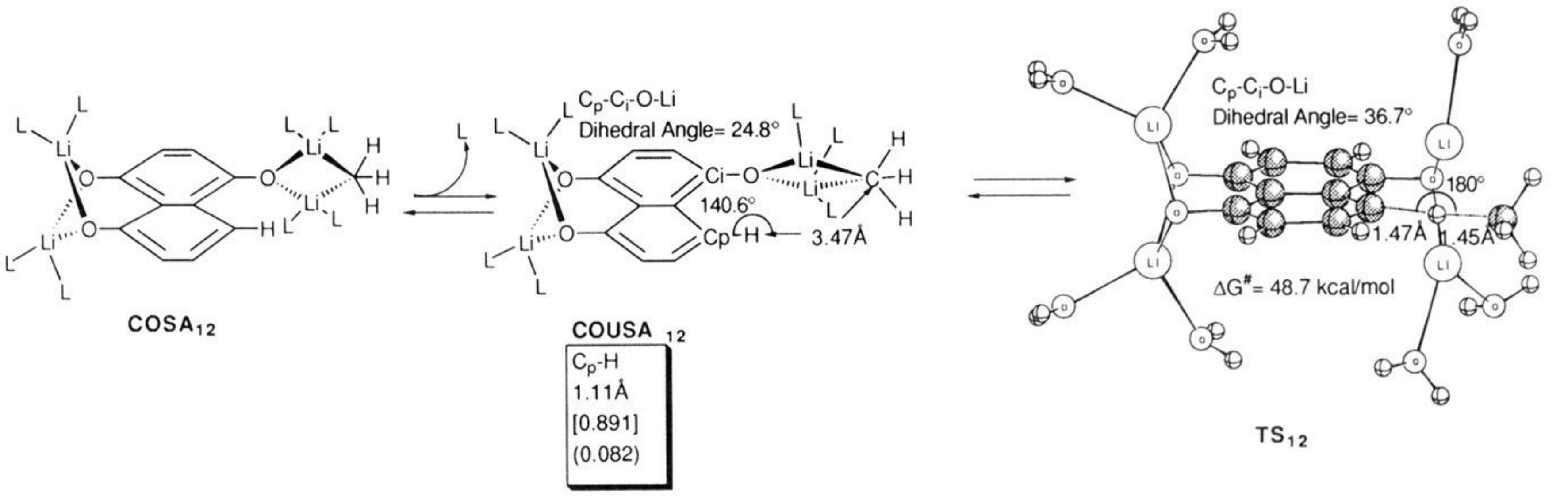

Figure 10. Agostic interaction parameters (C_p−H distance, C_p−H bond order, positive charge on H) for the coordinatively unsaturated mixed aggregate from 1,4,5-trihydroxynaphthalene and methyllithium $\mathbf{COUSA_{12}}$ (in box). Relevant proximity features (H−CH_3 distance, C_p−H−CH_3 angle, C_p−C_i−O−Li dihedral angle) directly shown on the $\mathbf{COUSA_{12}}$ and $\mathbf{TS_{12}}$ structures.

removal through a rigid seven-membered ring in which the trajectory of attack is excellent and the key atoms (CH_3−HC) involved in the lithiation process are in close proximity. Lithiation of secondary benzamides can be formally considered as the prototype of the herein described peri lithiations involving seven-membered ring transition structures. On the other hand, ortho lithiations of mono- or polyhydric compounds are clearly disfavored because the trajectory of attack and CH_3−HC distances are poorer, except for the case of thiophenol. In this latter case both features are quite good, no doubt as a consequence of the larger S−C and S−Li bonds and the reduced (when compared to the corresponding oxygen species) negative charge on the ortho carbon.

In summary MNDO-determined agostic interaction parameters and proximity features are very helpful in predicting directed lithiations of unprotected polyhydric phenolic compounds.[58] The (single or double) peri lithiation of dihydroxy and trihydroxy aromatics, in particular, stands as a unique example of this principle. From the preparative viewpoint, it must be stressed that the direct lithiation of polyphenolic and related compounds, described herein for the first time, facilitates the access to a number of otherwise difficult-to-synthesize mono and doubly peri functionalized aromatics. In our view, these results further stress the key role that agostic interaction must play in the mechanism of the directed lithiations of either hydric or nonhydric species.[59] We expect that (old) novel directing groups for aromatic and nonaromatic lithiations may be rationally (re)designed using this principle.

Experimental Section

General Methods. All melting points are uncorrected and were taken on a capillary melting point apparatus. Proton and carbon-13 NMR spectra were obtained at 300 MHz in $CDCl_3$, and referenced to the chloroform peak at 7.26 ppm and the central chloroform peak at 77.7 ppm, respectively. Electron impact mass spectra were recorded at 70 eV ionizing energy. Column chromatographies were performed on Merck silica gel (Kieselgel 40) and eluted with hexane, ether−hexane, or ether−cyclohexane mixtures. TLC was performed on silica plates purchased from Scharlau (Glasschrom Si F_{254} 0.5 mm).

Diphenolic compounds **10** and **11** were prepared as described in the literature by Toda[47] and Dimmel,[48a] respectively. Compound **12** was prepared by standard sodium dithionite reduction of commercially available juglone. The remaining phenolic substances were obtained from commercial sources and used as received. TMEDA was freshly distilled from calcium hydride. Commercial 2.5 M butyllithium in hexane was employed as received. All operations involving organolithium compounds were carried out under argon.

The standard workup procedure employed throughout involved careful addition of aqueous hydrochloric acid, followed by extraction with three to five 25-mL portions of Et_2O, drying of the organic phase over anhydrous Na_2SO_4, and evaporation *in vacuo*. The residue was usually flash chromatographed on silica gel prior to crystallization. Unless otherwise noted, the purity of new compounds for which combustion analysis could not be obtained was judged to be ≥90% on the basis of their ^1H and ^{13}C NMR spectra (available as supplementary material). Where appropriate, COSY spectra are also given as supplementary material.

Lithiation of Polyhydric Phenolic Compounds. General Procedure. A solution (or suspension) of the phenolic compound (1 mmol) in dry TMEDA (1.5 mL) was placed in an oven-dried round-bottomed flask, under argon, and capped with a septum. To this solution the appropriate amount of commercial 2.5 M *n*-BuLi in hexane (6, 10, or 14 equiv for mono-, di-, or trihydric compounds, respectively, unless otherwise noted) was added via syringe, at room temperature. The mixture was sonicated in a commercial cleaning bath for 2 h (the bath reaches 40−50 °C) and then cooled to 0 °C (to −40 °C in the case of quenching with DMF or ethyl chloroformate) and the selected electrophile (excess) carefully added. Stirring was continued for 4 h (24 h in the case of quenching with DMF). The standard extractive workup was followed by column chromatography and final crystallization from the appropriate solvent.

5-Formyl-1,4-dihydroxynaphthalene (6a) obtained from **6** in 85% as a red-brick solid: mp 182−185 °C (cyclohexane); ^1H NMR δ 10.24 (s, 1 H), 10.15 (s, 1 H), 9.09 (s, 1 H), 8.43 (dd, 1 H, J = 8.4 Hz and 1.5 Hz), 7.84 (dd, 1 H, J = 7.2 Hz and 1.5 Hz), 7.32 (dd, 1 H, J = 8.4 Hz and 7.2 Hz), 6.75 (s, 2 H) ppm; ^{13}C NMR δ 197.6, 147.0, 146.9, 137.4, 132.9, 131.6, 126.4, 123.4, 122.0, 114.4, 110.9 ppm; IR ν 3320, 1665, 1590, 1540, 1475, 1220, 1180, 1150, 760 cm^{-1}; MS *m*/*e* (%) 188 (M^+, 100), 171 (27), 149 (27), 131 (24), 103 (17), 77 (20). HRMS: Calcd for $C_{11}H_8O_3$, 188.0473. Found: 188.0474.

5-Trimethylsilyl-1,4-naphthoquinone (6b) was obtained from **6** in 60% yield (after oxidation of the crude, unstable 5-trimethylsilyl-1,4-bis(trimethylsilyloxy)naphthalene with CAN/MeCN) as a yellow crystalline solid: mp 44−7 °C (pentane); ^1H NMR δ 8.13 (dd, 1 H, J = 7.7 Hz and 1.4 Hz), 8.00 (dd, 1 H, J = 7.7 Hz and 1.4 Hz), 7.71 (t, 1 H, J = 7.7), 6.97 (s, 2H), 0.34 (s, 6 H) ppm; ^{13}C NMR δ 186.9, 186.4, 143.5, 141.6, 139.7, 138.6, 136.9, 133.4, 133.3, 128.2, 0.6 ppm; IR ν 1660, 1560, 1400, 1380, 1320, 1295, 1240, 1095, 1030, 880, 770 cm^{-1}; MS, *m*/*e* (%) 230 (M^+, 0.4), 215 (100), 187 (19), 157 (16), 149 (27), 128 (6), 77 (2). HRMS: Calcd for $C_{11}H_8O_3$: 230.076 308. Found: 230.075 133.

5,8-Bis(trimethylsilyl)-1,4-bis(trimethylsilyloxy)naphthalene (6bb) was obtained from **6** in 75% yield as a colorless crystalline solid: mp 184−5 °C (methanol); ^1H NMR δ 7.77 (s, 2 H), 6.86 (s, 2 H), 0.49 (s, 18 H), 0.40 (s, 18 H) ppm; ^{13}C NMR δ 147.1, 136.3, 133.5, 132.4,

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(58) While writing this manuscript we became aware of the recent work by P. Beak and co-workers in predicting relative rates of the lithiation of benzyl alcohols and tertiary benzamides by considering C−C−C−O dihedral angles and H−O distances of the substrate materials. See: Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10 628.

(59) Manuscript in preparation.

110.4, 3.4, 1.4 ppm; IR ν 2950, 1600, 1450, 1360, 1250, 1120, 1050, 900, 820, 760, 730 cm^{-1}; MS, *m/e* (%) 448 (M$^+$, 100), 345 (75), 271 (32), 211 (28), 197 (32), 147 (32), 73 (93). Anal. Calcd for $C_{22}H_{40}O_2Si_4$: C, 58.86; H, 8.98. Found: C, 58.97; H, 9.34.

8-Formyl-1,5-dihydroxynaphthalene (7a) was obtained from **7** in 96% yield as a yellowish crystalline solid: mp 253−4 °C (lit.[60] mp 254−5 °C); ^{1}H NMR δ 12.15 (s, 2 H), 9.43 (s, 1 H), 7.75 (d, 1 H, *J* = 8.1 Hz), 7.72 (dd, 1 H, *J* = 8.4 Hz and 1.5 Hz), 7.29 (t, 1 H, *J* = 8.4 Hz), 6.96 (dd, 1 H, *J* = 8.4 Hz and 1.5 Hz), 6.84 (d, 1 H, *J* = 8.1 Hz) ppm; ^{13}C NMR δ 194.9, 163.2, 155.3, 145.7, 127.5, 127.4, 123.5, 123.1, 115.9, 113.9, 107.5 ppm; MS *m/e* (%): 188 (M$^+$, 100), 187 (79), 171 (47), 131 (57), 115 (13), 103 (24), 77 (25).

4,8-Bis(trimethylsilyl)-1,5-bis(trimethylsilyloxy)naphthalene (7bb) was obtained from **7** in 70% yield as a colorless crystalline solid: mp 230−232 °C (methanol); ^{1}H NMR δ 7.65 (d, 2H, *J* = 7.86 Hz), 6.86 (d, 2 H, *J* = 7.86 Hz), 0.48 (s, 18 H), 0.37 (s, 18 H) ppm; ^{13}C NMR δ 154.1, 133.9, 133.8, 126.6, 111.5, 3.6, 1.3 ppm; IR ν 1585, 1510, 1380, 1305, 1260, 1250, 1145, 985, 850, 830 cm^{-1}; MS *m/e* (%) 448 (M$^+$, 7), 345 (23), 257 (83), 147 (13), 73 (100). Combustion anal. Calcd for $C_{20}H_{40}O_2Si_4$: C, 58.86; H, 8.98. Found: C, 58.63; H, 8.98.

8-Formyl-1,3-dihydroxynaphthalene (8a) was obtained from **8** in 60% yield as a yellow solid: mp 151−153 °C (toluene); ^{1}H NMR δ 11.95 (s, 2 H), 9.78 (s, 1 H), 7.95 (dd, 1 H, *J* = 8.4 Hz and 1.5 Hz), 7.87 (dd, 1 H, *J* = 7.2 Hz and 1.5 Hz), 7.50 (dd, 1 H, *J* = 8.4 Hz and 7.2 Hz), 6.79 (d, 1 H, *J* = 2.7 Hz), 6.75 (d, 1 H, *J* = 2.7 Hz) ppm; ^{13}C NMR δ 198.1, 158.0, 156.8, 139.5, 137.9, 137.8, 133.0, 125.1, 116.4, 107.0, 104.0 ppm; IR ν 3320, 2620, 1780, 1540, 1300, 1170, 840, 750 cm^{-1}; MS *m/e* (%) 188 (M$^+$, 100), 149 (43), 131 (43), 84 (34), 66 (31). HRMS: Calcd for $C_{11}H_8O_3$: 188.0473. Found: 188.0470.

8-Formyl-1,6-dihydroxynaphthalene (9a) was obtained from **9** in 65% yield as a solid: mp 230−1 °C (toluene); ^{1}H NMR δ 10.46 (s, 1 H), 10.09 (s, 1 H), 9.18 (s, 1 H), 7.35 (d, 1 H, *J* = 2.7 Hz), 7.07 (d, 1 H, *J* = 2.7 Hz), 6.96 (t, 1 H, *J* = 7.8 Hz), 6.87 (dd, 1 H, *J* = 7.8 Hz and 0.9 Hz), 6.52 (dd, 1 H, *J* = 7.8 Hz and 0.9 Hz) ppm; ^{13}C NMR δ 196.8, 156.2, 154.6, 154.1, 137.9, 134.9, 127.9, 127.2, 118.5, 117.7, 110.5 ppm; IR ν 3300, 1650, 1540, 1470, 1380, 1340, 1280, 1255, 115, 750 cm^{-1}; MS *m/e* (%) 188 (M$^+$, 100), 187 (44), 171 (26), 131 (62), 115 (9), 103 (26), 77 (26). Combustion anal. Calcd for $C_{11}H_8O_3$: C, 70.23; H, 4.25. Found: C, 69.97; H, 4.26.

1,1′-Bismethylthio-9,9′-biphenanthryl-10,10′-diol (10cc) was obtained in 56% yield by lithiation of 9,9′-biphenanthryl-10,10′-diol (**10**) as a yellow solid; mp 98−99 °C (ether); ^{1}H NMR δ 9.94 (s, 1 H), 8.82 (d, 1 H, *J* = 7.9 Hz), 8.70 (d, 1 H, *J* = 8.4 Hz), 7.70 (d, 1 H, *J* = 6.8 Hz), 7.64 (t, 1 H, *J* = 7.9), 7.48 (t, 1 H, *J* = 6.8), 7.30 (m, 2 H), 2.33 (s, 3 H) ppm; ^{13}C NMR δ 150.4, 144.9, 134.4, 133.4, 132.6, 128.4, 127.8, 127.3, 127.1, 125.9, 124.9, 124.6, 123.8, 115.0, 22.2 ppm; IR ν 3450, 1640, 1620, 1440, 1380, 760 cm^{-1}; MS *m/e* (%) 478 (M$^+$, 100), 460 (37), 432 (11), 326 (23), 205 (31), 178 (39). HRMS: Calcd for $C_{30}H_{22}O_2S_2$: 478.106 12. Found: 478.105 83.

1,1′-Bis(ethoxycarbonyl)-9,9′-biphenanthryl-10,10′-ethoxycarbonyloxy (10dd) was obtained in 58% yield by lithiation of 9.9′-biphenanthryl-10,10′-diol (**10**) as a white solid: mp 202−3 °C (ether); ^{1}H NMR δ 8.89 (d, 2 H, *J* = 7.5 Hz), 8.74 (d, 2 H, *J* = 7.9 Hz), 7.78 (t, 2 H, *J* = 7.9 Hz), 7.70 (d, 2 H, *J* = 7.2 Hz), 7.64 (m, 2 H), 7.38 (d, 4 H, *J* = 3.9), 4.43 (q, 4 H, *J* = 7.1), 4.32 (q, 4 H, *J* = 7.2), 1.36 (t, 6 H, *J* = 7.2), 0.66 (t, 6 H, *J* = 7.1) ppm; ^{13}C NMR δ 171.1, 152.3, 143.4, 132.8, 131.5, 130.9, 129.1, 128.7, 127.8, 127.5, 127.3, 127.2, 124.9, 124.5, 123.9, 123.1, 65.0, 62.4, 14.4, 13.8 ppm; IR ν 1740, 1710, 1640, 1280, 1230, 1210, 1025, 770 cm^{-1}; MS *m/e* (%): 674 (M$^+$, 1), 630 (6), 602 (8), 512 (27), 466 (10), 438 (100), 412 (14), 383 (12). HRMS: Calcd for $C_{40}H_{34}O_{10}$: 674.215 19. Found: 674.215 88.

1-Trimethylsilyl-9,10-anthraquinone (11b) was obtained by lithiation of 9,10-dihydroxyanthracene (**11**)[48a] in 65% yield as a yellowish crystalline solid, mp 139−141 °C (pentane), together with **11bb** (30% yield; see below for physical and spectroscopic properties): ^{1}H NMR δ 8.37 (dd, 1 H, *J* = 7.7 Hz and 1.4 Hz), 8.31 (m, 2 H), 8.06 (dd, 1 H, *J* = 7.7 Hz and 1.4 Hz), 7.79 (m, 2 H), 7.76 (t, 1 H, *J* = 7.7 Hz), 0.40 (s, 9 H) ppm; ^{13}C NMR δ 184.8, 183.87, 143.5, 138.2, 137.8, 134.3, 134.0, 133.9, 133.6, 133.1, 132.8, 128.3, 127.3, 126.9, 0.0 ppm; IR ν 1670, 1310, 1280, 1250, 950, 850, 705 cm^{-1}; MS *m/e* (%) 280 (M$^+$, 1), 265 (100), 235 (35), 207 (5), 163 (5), 125 (9). HRMS: Calcd for $C_{17}H_{16}O_2Si$: 280.091 96. Found: 280.088 08.

1,5-Bis(trimethylsilyl)-9,10-anthraquinone (11bb) was obtained by lithiation of 9,10-dihydroxyanthracene (**11**) in 30% yield as a yellowish crystalline solid, mp 151−3 °C (pentane) together with **11b** (65% yield; see above for physical and spectroscopic properties): ^{1}H NMR δ 8.36 (dd, 2 H, *J* = 7.7 Hz and 1.3 Hz), 8.04 (dd, 2 H, *J* = 7.7 Hz and 1.3 Hz), 7.75 (t, 2 H, *J* = 7.7 Hz), 0.39 (s, 18 H) ppm; ^{13}C NMR δ 184.7, 142.9, 140.83, 137.4, 134.3, 132.5, 128.2, −0.01 ppm; IR ν 1670, 1570, 1320, 1260, 1250, 870, 840, 720 cm^{-1}; MS *m/e* (%) 280 (M$^+$, 1), 265 (100), 235 (35), 207 (5), 163 (5), 125 (9). HRMS: Calcd for $C_{20}H_{24}O_2Si_2$: 352.131 49. Found: 352.127 47.

5-Hydroxy-2,8-bis(methylthio)-1,4-naphthoquinone (12cc) was obtained in 33% yield from the lithiation of 1,4,5-trihydroxynaphthalene (**12**) under the above general conditions except for the use of 14 mmol of BuLi per mmol of substrate (substantially reduced yields were obtained using lesser amounts of BuLi) as a dark red crystalline solid: mp 154−8 °C (EtOH); ^{1}H NMR δ 12.19 (s, 1 H), 7.65 (d, 1 H, *J* = 9.3 Hz), 7.3 (d, 1 H, *J* = 9.3 Hz), 6.55 (s, 1 H), 2.55 (s, 3 H), 2.40 (s, 3 H) ppm; ^{13}C NMR δ 186.9, 181.2, 160.5, 159.1, 140.1, 132.2, 126.4, 125.9, 125.6, 115.8, 16.5, 14.8; IR ν 3500, 1640, 1620, 1460, 1400, 1390, 1240, 1220, 880, 825, 805 cm^{-1}; MS *m/e* (%): 266 (M$^+$, 100), 251 (31), 249 (17), 236 (10), 233 (42), 218 (10), 69 (7). HRMS: Calcd for $C_{12}H_{10}O_3S_2$: 266.007 138. Found: 266.007 742.

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Supplementary Material Available: Tables containing *Z* matrices and gradient NORMs of the optimized molecular structures and the ^{1}H and ^{13}C NMR spectra of **6a**, **6b**, **8a**, **10cc**, **10dd**, **11b**, **11bb**, and **12cc**, the COSY spectra of **11b**, and the HMBC (heteronuclear multiple-bond correlation) spectra of **12cc** (66 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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