

for laser irradiation, a nitrogen-driven piston operating at 20–30 psi is employed. The sequential filling and emptying of the two syringes is controlled via two manually operated 3-way valves. The first of these, located between the reservoirs, syringes, and irradiation cell, controls the direction of the flowing solutions, i.e., from reservoir to syringes to cell. The second valve controls the direction of the pressure-driven piston: retraction to enable filling of the syringes from the reservoir followed by depression to facilitate the solution mixing and subsequent filling of the irradiation cell. The photolysis cell (originally designed for fluorescence work) consists of a quartz block containing a  $20 \times 2 \times 2$  mm<sup>3</sup> rectangular cavity, with one input and one output. Optical detection of transients is carried out along the 20-mm axes with laser irradiation at right angles to the monitoring beam. The quartz block is encased in a brass holder that contains a Teflon insert aligned with the input of the quartz block. Mixing of both solutions is initiated prior to the entrance into the quartz block at the bottom of the Teflon insert. The design of the mixing chamber in the Teflon insert is the same as that originally supplied with the Catek instrument. The output of the cell is connected to an electronic valve that controls the discharge of irradiated solution from the cell. The application of the constant-pressure piston on the front side of the cell in conjunction with an electronic valve on the back side allows

the controlled mixing, static irradiation, and evacuation/refilling of the two solutions within the cell in sequence. The timing procedure for the opening and closing of the electronic valve is coupled to that of the laser system via a Stanford Model DG535 delay unit. Accordingly, solutions are flushed through the cell for 30 ms to ensure a fresh sample for each irradiation. Following the closing of the valve, a delay of 4 ms is applied to allow for complete mixing and for any turbulence to subside. Subsequent laser-flash photolysis is carried out in the usual manner followed by a repeat of the cycle. Under these conditions of applied pressure and time delays, up to 10 irradiations from a single syringe loading can be carried out without risk of secondary photolysis or any ground-state thermal reaction. All solutions flow through Teflon tubing with stainless steel or Teflon connections between glassware. For systems that are highly sensitive to oxygen, an additional sleeve of Teflon tubing, which envelops the thinner diameter flow tubing, carries a blanket of nitrogen. In this way, the deaerated solutions are not exposed to air until they have exited the photolysis cell.

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## The Regioselectivity of the Birch Reduction<sup>1,2</sup>

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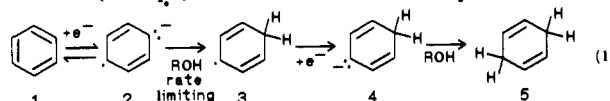
**Abstract:** The reaction mechanism of the Birch reduction was investigated with a view of determining how the regioselectivity is controlled. Regioselectivity is determined in the first step of radical anion protonation and in the second step of cyclohexadienyl carbanion protonation. It was ascertained that the rate-determining step of the Birch reduction of anisole was radical anion protonation, consistent with the observation of Krapcho and Bothner-By in the case of benzene reduction. A new approach to determining the regioselectivity of the two steps of the Birch reduction was devised. This was predicated on an enhanced primary deuterium isotope effect anticipated for radical anion protonation relative to that expected for cyclohexadienyl carbanion protonation. The approach utilized a partially deuterated medium. The method was applied to the reductions of anisole, 1,3-dimethoxybenzene, 3-methoxytoluene, and 2-methoxynaphthalene. The basic assumption of greater selectivity of the radical anion of the first step relative to the carbanion of the second step was explored in the cases of benzene and anisole and confirmed. In the examples studied, ortho protonation of the radical anion was found to predominate. With a view of understanding the regioselectivity of the two steps, quantum mechanical computations were carried out on several facets of the reaction. Electron density distributions of the radical anions were determined as well as the energies of radical products of some radical anion protonations. Similarly, the energies were obtained for the partially protonated radical anion species at several points along the reaction coordinate. In addition, electron densities were obtained for cyclohexadienyl anion. Theory was then correlated with experiment.

### Introduction

The Birch reduction<sup>3</sup> is one of those reactions which constitute the core of organic chemistry. It is of both synthetic utility and mechanistic interest. Though nearly 50 years old,<sup>4</sup> it is very widely used in present-day efforts. Nevertheless, there are major mechanistic aspects of the reduction which have not been resolved. In view of the importance of the Birch reduction, it seemed of particular value to explore these facets.

### Background

The Birch reduction<sup>5</sup> involves protonation of the radical anion formed by addition of one electron to the reacting aromatic. This is followed by rapid addition of a second electron and protonation of the resulting carbanion to afford an unconjugated cyclohexadiene. In this mechanism, protonation of the radical anion by added alcohol is known to be rate limiting in the case of benzene<sup>6a</sup> (see eq 1). The Birch rule,<sup>3b</sup> which predicts a kinetic



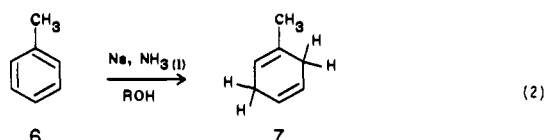
(1) (a) This is part 228 of our general series. (b) Part 227: Zimmerman, H. E.; Baker, M. R.; Bottner, R. C.; Morrissey, M. M.; Murphy, S. *J. Am. Chem. Soc.* 1993, 115, 459–466.

(2) For a preliminary communication describing our initial efforts, see: Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* 1990, 112, 1280–1281.

(3) (a) Birch, A. J. *J. Chem. Soc.* 1944, 430–436. (b) Birch, A. J.; Subba Rao, G. *Adv. Org. Chem.* 1972, 8, 1–64 and references cited therein. (c) Rabideau, P. W. *Tetrahedron* 1989, 45, 1579–1603. (d) Rabideau, P. W.; Marciniow, Z. In *Organic Reactions*; Pacquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1992; Vol. 42, Chapter 1.

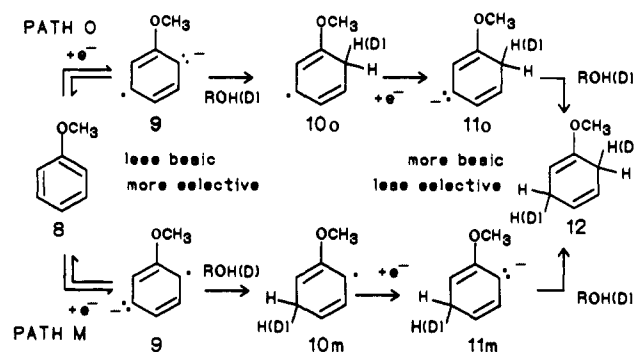
(4) (a) Indeed, there were earlier reductions of aromatics with sodium in ammonia; however, some of these efforts<sup>4b</sup> argued for an erroneous mechanism. Other work<sup>4c</sup> provided only one example and without suggestion of the product structure: (b) Hückel, W.; Bretschneider, H. *Liebigs Ann. Chem.* 1939, 540, 157–189. (c) Wooster, C. B.; Godfrey, K. L. *J. Am. Chem. Soc.* 1937, 59, 596–597.

preference for that regioisomer with the maximum number of alkyl and/or alkoxy groups on the residual double bonds, is quite successful. Note, for example, the case of the toluene reduction in eq 2.<sup>6a</sup>



(5) Birch, A. J.; Nasipuri, D. *Tetrahedron* 1959, 148–153.

Scheme I. Possible Mechanisms for the Birch Reduction of Anisole



Using anisole as an example and on the basis of product structure alone, one can write two possible reaction mechanisms: mechanism O and mechanism M, one proceeding by initial ortho protonation of the radical anion and the other going by initial meta protonation. On the basis of qualitative reasoning, Birch<sup>5</sup> proposed mechanism M which presumed the meta position of the radical anion to have the highest electron density in the radical anion.<sup>7</sup> However, simple Hückel calculations<sup>8</sup> on a series of alkoxy-substituted aromatics revealed that it is the position ortho to the maximum number of substituents which is most electron rich in the radical anion. This led to our suggestion that mechanism O was followed<sup>8</sup> (note Scheme I).

The literature has not been consistent in favoring one or the other of these two mechanisms. A preference for mechanism M (i.e., meta protonation) has been based on Birch's arguments by another author.<sup>9</sup> One more quantitative study was by Burnham,<sup>10</sup> who considered a frontier electron approach in an ESR study. However, in this publication the relatively similar odd-electron densities observed were taken as signifying similar charge densities, which is not correct. In any event, the conclusion was a prediction of little selectivity between the two mechanisms. In a later article,<sup>11</sup> the same author used a transition-state model employing a UHF computation<sup>11b</sup> and concluded that mechanism M was preferred. Although our suggestion of ortho protonation was initially rejected,<sup>3b</sup> in a recent publication Birch and Radom<sup>12</sup> suggest protonation at both sites with a slight preference for ortho, that is, both mechanisms O and M operating. The results were derived from molecular electrostatic potential computations at the STO-3G level. Another publication by these authors<sup>13a</sup> considered the relative stabilities of the cyclohexadienyl radicals formed in the protonation step and found a thermodynamic preference for the ortho-protonated radical anion. These computations used RHF computations and geometry optimization on only the cyclohexadienyl parent structure.

In view of the multiplicity of opinions concerning the reaction mechanism, it was of considerable interest to pursue the problem

further. A particularly challenging goal was an experimental test of the mechanism. In addition, we wished to investigate the theoretical issues.

### The Approach

The approach devised to solve this problem relies on the greater primary deuterium isotope effect expected for the protonation of less basic anions relative to more basic anions. Thus, one would anticipate that protonation of the radical anion (e.g., 9) of the first step of the Birch reduction mechanism should exhibit greater isotope selectivity than protonation of the cyclohexadienyl carbanion (e.g., 11) of the second step. This assumption is predicated on the known greater basicity of the carbanions relative to the corresponding radical anions<sup>14</sup> and also the greater rates of protonation of the carbanions compared to the radical anions.<sup>15</sup>

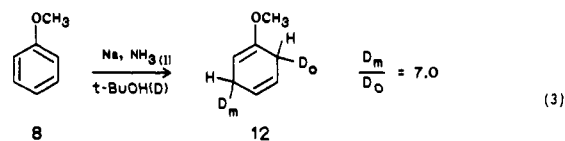
Accordingly, in the Birch reduction of anisole, for example, if mechanism O in Scheme I is followed, the radical anion will protonate ortho and this protonation will be selective with a reluctance to pick up deuterium. In contrast, in the second step where the more basic and reactive cyclohexadienyl carbanion is being protonated meta, less isotope selectivity will result. The consequence then is that the ortho position of the product will be deficient in deuterium relative to meta.

Conversely, if mechanism M is operating, then the first protonation, being more selective and in the meta position, will result in lower deuterium introduction meta. The protonation of the carbanion of the second step, being relatively unselective, will afford a higher amount of deuterium at the ortho site. Using this approach, we began our studies with the example of the anisole reduction.

### Results

**Study of the Birch Reduction of Anisole: The Isotope Selectivity Test.** The initial decision was to employ a standard set of conditions with *tert*-butyl alcohol as the proton donor, ca. 1–2% total deuterium content, sodium as the reducing metal, and a temperature of  $-78^{\circ}\text{C}$ . The low temperature was selected to minimize difficulties with ammonia evaporation. The metal was added last in order to minimize the possibility of dianion formation. Introduction of deuterium was by use of deuterated *tert*-butyl alcohol.<sup>16</sup>

The reduction of anisole under these conditions proceeded to afford only the single unconjugated dihydroanisole as reported originally by Birch<sup>3a</sup> (note eq 3). Deuterium NMR established that only the methylene carbons incorporated deuterium. In order



to resolve the two methylene peaks, the  $\text{Pr}(\text{FOD})_3$  shift reagent was employed. This had the effect of nicely separating the peaks and also the advantage of providing firm identification of the two. Not only did the  $\text{Pr}(\text{FOD})_3$  reagent shift the *o*-methylene absorption to higher field than the less proximate *m*-methylene peak but  $\text{Eu}(\text{FOD})_3$  also led to similar behavior but with the shift being downfield. Hence the *o*- and *m*-methylene peaks in the NMR were identified. Nevertheless, since identification of the methylene peaks was critical, proton NMR decoupling was carried out. Irradiation of the *m*-methylene frequency of the undeuterated material led to the high-field, enol ether, vinyl triplet resolving into a sharp singlet, while the other dihydroanisole peaks were

(6) (a) Krapcho, A. P.; Bothner-By, A. A. *J. Am. Chem. Soc.* **1959**, *81*, 3658–3666. (b) Private communication from Professors Aksel Bothner-By and Paul Krapcho.

(7) The suggestion was made that, since the ortho and para positions of anisole are electron rich, the added electron should avoid these positions.

(8) (a) Zimmerman, H. E. *Tetrahedron* **1961**, *16*, 169–176. (b) It was also noted that ortho protonation leads to a more delocalized radical. See: Zimmerman, H. E. In *Molecular Rearrangements*; de Mayo, P., Ed.; Interscience Publishers: New York, 1963; p 352.

(9) Smith, H. *Chemistry in Nonaqueous Ionizing Solvents*; Interscience Publishers: New York, 1963; Vol. 1, Part 2, p 255.

(10) Brown, J. K.; Burnham, D. R.; Rogers, N. A. *J. Tetrahedron Lett.* **1966**, 2621–2626.

(11) (a) Burnham, D. R. *Tetrahedron* **1969**, *25*, 897–904. (b) From the publication it is not possible to ascertain what type of UHF computation was employed, although this appears to be "two-dimensional".

(12) Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 3370–3376.

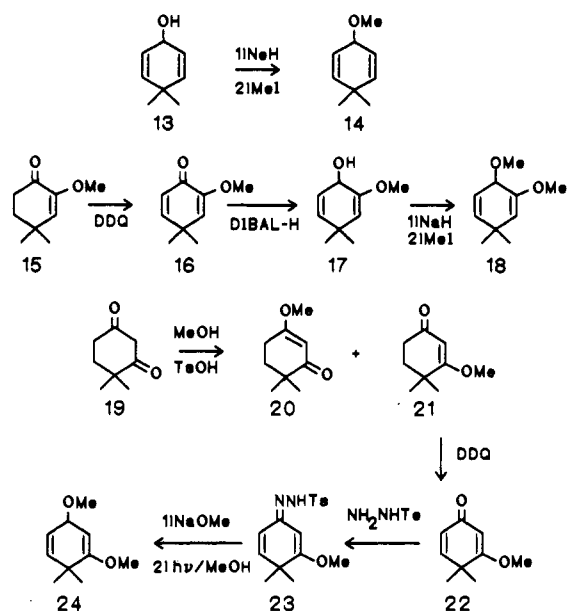
(13) (a) Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 4074–4080. (b) Similar STO-3G computations without geometry optimization by Birch and Radom<sup>13a</sup> found a 11.2 kcal/mol preference for the ortho-protonated species.

(14) Parker, V. D.; Tilset, M.; Hammerich, O. *J. Am. Chem. Soc.* **1987**, *109*, 7905–7506.

(15) (a) Bank, S.; Bockrath, B. *J. Am. Chem. Soc.* **1971**, *93*, 430–437. (b) Bank, S.; Bockrath, B. *J. Am. Chem. Soc.* **1972**, *94*, 6076–6083.

(16) Isotopic exchange between alcohol and ammonia was assumed to be rapid relative to the reaction rate in all of this work. Evidence for the validity of this rapid equilibration was that variation in the initial amount of deuterated alcohol did not alter deuterium incorporations that were normalized to 1% deuterium available. Regardless, measured aromatic reduction selectivities should remain in the same direction.

Scheme II. Synthesis of Carbanion Precursors



unaffected. See the Experimental Section for these NMR details.

Furthermore, in reductions with *tert*-butyl alcohol, the deuterium NMR analysis showed that there was a strong preference for deuteration of the meta position. The ratio of meta to ortho deuteration was  $7.0 \pm 0.7$ . Thus, the reduction in the deuterated medium may be written as in eq 3.

This disinclination for deuteration of the ortho position immediately indicates that it is the ortho carbon which is being protonated at the radical anion stage of the Birch mechanism. However, the kinetics is complex, and we delay full analysis until the Discussion Section.

**Validity of the Selectivity Hypothesis: Synthetic Aspects.** The conclusions we reached depend totally on the original hypothesis that the less basic species, that is, the radical anions, exhibit a more selective primary isotope effect than the rather basic and reactive carbanion counterparts. Therefore, it was deemed important to devise an experimental verification. To this end, several carbanion precursors were synthesized; these syntheses are outlined in Scheme II. Thus benzylic and allylic ethers are known to afford carbanions via the radical anions on treatment with alkali metals, such as sodium, potassium, and sodium/potassium alloy, in solvents ranging from ether to liquid ammonia.<sup>17</sup> Our intent was the generation of the cyclohexadienyl anions which are the second intermediates of the Birch reduction. In studying the Birch reduction of benzene, the cyclohexadienyl carbanion itself was not utilized. Instead, the closely related dimethyl derivative derived from methyl ether 14 was investigated, since the nonmethylated precursors proved unstable.

In the case of the Birch reduction of anisole, two potential carbanion intermediates, 11m and 11o, were needed. Again, the dimethyl analogs were used. Thus the precursor methyl ethers 18 and 24 were prepared. The synthesis of 24 required a route not involving methylation of the corresponding allylic alcohol, since the doubly allylic alcohol with a  $\beta$ -methoxy group proved rather sensitive. The carbene approach in Scheme II successfully led to the required ether 24.

**Validity of the Selectivity Hypothesis: Carbanion Generation and Reaction.** The three allylic ethers—14, 18, and 24—were subjected to reaction with sodium and *tert*-butyl alcohol in liquid ammonia, enriched with deuterium, under the standard Birch

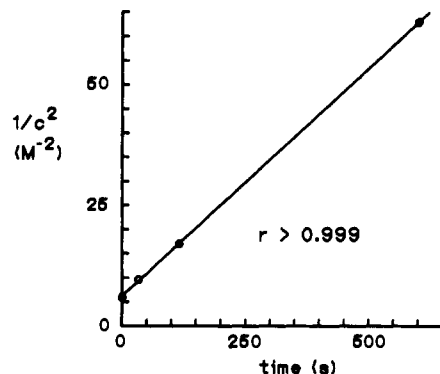
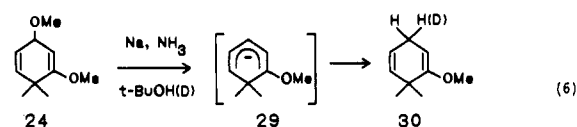
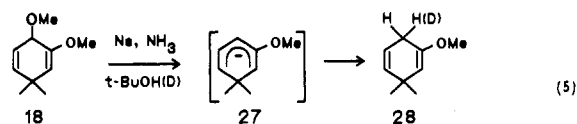
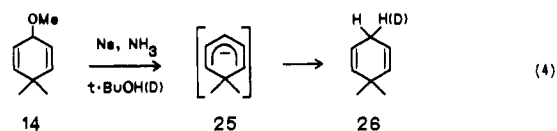


Figure 1. Kinetics of the Birch reduction of anisole.

conditions described above. The observed transformations are outlined in eqs 4–6. One regioisomer of the reductive cleavage was observed in each case. Reduction product 26 was a known compound whose NMR and physical properties matched those reported.<sup>18</sup> Products 28 and 30 had NMR spectra in accord with the structures (note the Experimental Section).



**Validity of the Selectivity Hypothesis: Deuterium Incorporation Overall vs Incorporation in Carbanion Protonation.** The basic aim was to ascertain the fraction of deuterium incorporated in the second step of the Birch reduction compared to deuterium incorporated in both steps of the mechanism. This comparison was made for the cases of two compounds, benzene and anisole. For each of these, the deuterium introduced in the carbanion reactions was compared with the amount of deuterium incorporated in the overall Birch reduction. All extents of deuterium incorporation were normalized to 1.0% of deuterium available. For benzene, the deuterium content in the carbanion step, as modeled by protonation in the ether cleavage approach above, was 0.10% (corresponding to an isotope effect of 9.9), while 0.13% of deuterium was incorporated in the overall Birch reduction product. Similarly, the protonations of the 2-methoxy (27) and 3-methoxy (29) carbanions led to 0.21 and 0.49% (corresponding to isotope effects of 4.9 and 2.1) of deuterium incorporated, respectively. This compares with 0.39% deuterium incorporated in the overall Birch reduction of anisole. This evidence permitted us to assess carbanion vs radical anion selectivity (*vide infra*).

**Reaction Kinetics.** Our approach to determining the reaction regioselectivity was predicated on the assumption that it is the radical anion which is being protonated in the first step of the Birch reduction. This is inherent in the finding of Krapcho and Bothner-By<sup>6a</sup> of third-order kinetics for the reduction of benzene. This led these authors to the conclusion that the rate-limiting step of the Birch reduction is radical anion protonation. However, although relative rates were measured for several aromatics, the kinetic order was not determined for the reactants in this study.<sup>6b</sup>

(17) (a) The basic reaction seems to have been discovered by Ziegler<sup>17b</sup> in the formation of cumenylsodium from cumenyl methyl ether. (b) Ziegler, K.; Schell, B. *Ann. Chem.* **1924**, *437*, 227–255. (c) For other examples, see refs 3a and 6. (d) Clemo, G. R.; King, T. J. *J. Chem. Soc.* **1948**, 1661–1666. (e) Hallsworth, A. S.; Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 1969–1974. (f) Zimmerman, H. E.; Zweig, A. *J. Am. Chem. Soc.* **1961**, *83*, 1196–1213.

(18) Jacobson, G. M.; Soteropoulos, P.; Bahadori, S. *J. Org. Chem.* **1988**, *53*, 3247–3255.

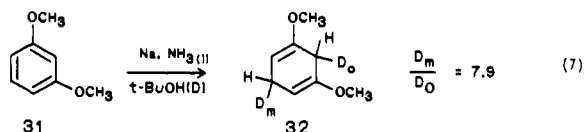
Hence it was necessary to determine the rate law for anisole. The kinetics was obtained under the present reaction conditions. Details are given in the Experimental Section, and Figure 1 shows the plot of the inverse square of concentration vs time, a treatment which tests the assumption of third-order kinetics. The resulting linearity with a correlation coefficient greater than 0.999 thus confirms the accepted mechanism, which is first order in metal, anisole, and *tert*-butyl alcohol. A fourth-order plot gave a correlation coefficient of only 0.991 (note the Experimental Section); the possibility of a fourth-order mechanism had been of real concern, since the Birch reduction does, indeed, proceed via a dianion process under certain conditions (vide infra) and for molecules with high electron affinities.<sup>19</sup> Finally, the kinetic determination led to a third-order rate constant of  $k = 0.024 \text{ L}^2 \text{ mol}^{-2} \text{ s}^{-1}$ .

**Variation of Reaction Conditions: Temperature, Alcohol, and Metal.** Some of the isotope effects appeared surprisingly large; however, it seemed likely that these were merely artifacts of the low temperature used. Thus it was of concern to pursue the effect of temperature on the reactions. At  $-33 \text{ }^\circ\text{C}$  the meta to ortho selectivity for anisole, which was 7.0 at  $-78 \text{ }^\circ\text{C}$ , diminished to  $3.8 \pm 0.2$ . The isotope effect in protonation of the dimethylcyclohexadienyl anion **25**, which was 9.9 at  $-78 \text{ }^\circ\text{C}$ , decreased to  $7.0 \pm 0.5$  at  $-33 \text{ }^\circ\text{C}$ . This temperature effect is considered below.

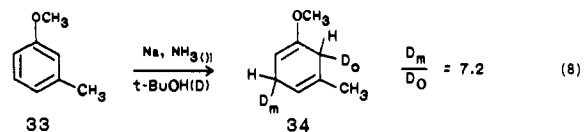
A second consideration was the acidity of the alcohols used in the Birch reduction. We wished to ascertain whether a variation of the acidity of the protonating alcohol would affect the regioselectivity in the reduction of anisole. Using methanol in place of the *tert*-butyl alcohol utilized in all of the results described above, we found a diminished meta to ortho deuterium introduction of  $4.0 \pm 0.01$  at  $-78 \text{ }^\circ\text{C}$ .

The third variable for consideration was the metal employed, and lithium was selected. The meta to ortho deuterium introduction, using lithium with the usual *tert*-butyl alcohol in the case of anisole, was observed to be  $4.1 \pm 0.4$ .

**Regioselectivity in the Reductions of 1,3-Dimethoxybenzene and 3-Methoxytoluene.** Having the regioselectivity in the anisole case in hand, we proceeded to examine the reduction of 1,3-dimethoxybenzene (**31**). Under the same conditions used for the Birch reduction of anisole, the reaction of methyl ether **31** proceeded to afford the single reduction product previously reported by Birch.<sup>20</sup> Deuterium NMR confirmed that only the methylene carbons bore deuterium. Again, the  $\text{Pr}(\text{FOD})_3$  shift reagent was required to permit peak separation. Confirmation of the peak assignments was derived, as before, from spin decoupling (see the Experimental Section). Deuterium NMR analysis afforded a meta to ortho deuterium ratio of  $7.9 \pm 0.3$ . This result is depicted in eq 7.



Thus far, only methoxy substituents had been considered. Therefore, the reduction of 3-methoxytoluene<sup>3a</sup> was investigated. With the same approach and precautions as described above, we obtained a meta to ortho deuterium ratio for the 3-methoxytoluene reduction of  $7.2 \pm 0.3$ . This result is given in eq 8.



**Exploration of the 2-Methoxynaphthalene Reduction.** One of the more frequently utilized Birch reductions of bicyclic aromatics is the reaction of 2-methoxynaphthalene (**35**), which has been

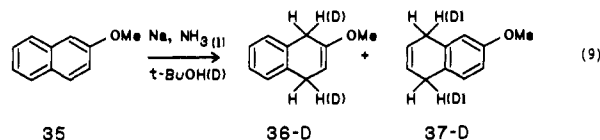
Table I. Relative Deuterium Introduction at the Naphthalene Sites<sup>a,b</sup>

	<i>t</i> -BuOH	MeOH
C1	0.31	0.31
C4	0.31	0.40
(C5 + C8)	0.38	0.30

<sup>a</sup> These values for each alcohol are normalized to unity. <sup>b</sup> The values are the product of the deuterium distribution in each given reduced compound multiplied by the relative amount of the compound.

reported to give rise to the conjugated dihydro tautomer of **36** reduced in the substituted<sup>21a</sup> ring and a doubly reduced product in which both rings were reduced.<sup>21b</sup>

Since this system had been studied synthetically, we wished to apply our general approach. However, we found that with a slight excess over 2 equiv of sodium and *tert*-butyl alcohol or methanol, two reduction products were obtained. One was 1,4-dihydro-2-methoxynaphthalene (**36**, the ring A reduction product) and the other was 1,4-dihydro-6-methoxynaphthalene (**37**, the ring B reduction product). Thus, our reaction differs from that reported in the literature.<sup>21</sup> In runs using *tert*-butyl alcohol, the ratio of ring A to ring B reduction products was 1.3:1.0, while with methanol, the ratio was 1.6:1.0 (see eq 9).



Proceeding to the deuteration runs, we again employed deuterium NMR analysis. However, despite the use of shift reagents, deuterium at C5 and C8 (using the original naphthalene atom numbering) could not be distinguished. In the case of the ring A reduction product, the distribution of deuterium at the two sites, C1 and C4, could be determined with the addition of  $\text{Pr}(\text{FOD})_3$ . The relative amounts of deuterium introduced in the four possible sites of the naphthalene anion are summarized in Table I.

**Check on the Reversibility of the Carbanion Protonation Step.** One point of importance was the concern that the Birch reduction products might exchange deuterium, with the result that the product deuterium distribution then would not be kinetically determined. For this reason, a series of control runs was carried out in which the undeuterated, unconjugated dienes—both actual Birch reduction products and the dimethylated analogs—were subjected to conditions simulating the basic environment of the Birch reductions. This employed *tert*-butoxide anion in deuterium-enriched *tert*-butyl alcohol in liquid ammonia along with dienes **12**, **26**, **28**, **30**, **36**, and **37**. With reaction times similar to those of the Birch reductions, no deuterium introduction was observed. This contrasts with the observation of Birch<sup>22</sup> in which deuterium exchange was observed at the C-2 methylene of 2,5-dihydroanisole under partially unspecified conditions.

## Interpretative Discussion

**The Anisole Birch Reduction Pathway: Validity of the Selectivity Premise.** We first consider the two alternative reaction mechanisms for the anisole reduction as outlined in Scheme I. Our study of the mechanism of the Birch reduction was predicated on the assumption that, in hydrogen vs deuterium protonation, the radical anion reacting in the first step would be considerably more selective than the carbanion protonating in the second step. The first requirement is an assessment of the validity of this assumption. As noted in the Results section, three relevant model carbanions were protonated, namely, that mimicking the second step of the Birch reduction of benzene itself (i.e., **25**), the carbanion **27** modeling the second step of the anisole reduction if the first step were to proceed via meta protonation (i.e., path M), and the

(19) (a) Rabideau, P. W.; Burkholder, E. G. *J. Org. Chem.* **1978**, *43*, 4283-4288. (b) Harvey, R. G.; Lindow, D. F.; Rabideau, P. W. *J. Am. Chem. Soc.* **1972**, *94*, 5412-5420.

(20) Birch, A. J. *J. Chem. Soc.* **1947**, 102-105.

(21) (a) Hüchel, W.; Vevera, E. *Chem. Ber.* **1956**, *89*, 2105-2114. It seems likely that a harsh workup was responsible for conjugation of the initially unconjugated 1,4-dihydro reduction product. (b) Birch, A. J.; Murray, A. R.; Smith, H. *J. Chem. Soc.* **1951**, 1945-1950.

(22) Birch, A. J.; Johnson, W. M. P. *Aust. J. Chem.* **1976**, *29*, 1631-1633.

**Table II.** Deuterium Incorporation in Carbanion Protonations and Birch Reduction of Anisole

example	deuterium incorporated <sup>a,b</sup>	
	carbanion runs all O or M	Birch reduction runs total
benzene	0.10 (m or o)	0.13
anisole, mech O	0.49 m	0.39 (0.05 o + 0.34 m)
anisole, mech M	0.21 o	0.39 (0.05 o + 0.34 m)

<sup>a</sup> These quantities represent absolute amounts of deuterium incorporated in the Birch reductions or the protonation of carbanions **25**, **27**, and **29** under the conditions described here. All amounts are normalized to 1% deuterium statistically available for protonation. <sup>b</sup> The error limits are estimated as  $\pm 10$  relative %.

carbanion **29** simulating path O where the first step is ortho protonation. In each case, as noted earlier, the carbanions generated differ for practical reasons from the precise structures of the Birch reduction in that they have dimethyl substitution. Comparison in each case of the total amount of deuterium introduced in the two steps of the Birch reduction with the amount of deuterium introduced in carbanion protonation (i.e., the second Birch step alone) leads to the conclusion that most of the deuterium is, indeed, introduced in the second Birch step (vide infra).

In the benzene reaction, almost as much deuterium is incorporated in the single, second step of the reaction as in the overall Birch reduction (see entry 1 in Table II). Thus, it can be inferred that in the case of benzene most of the deuterium is introduced in the carbanion protonation step, with very little being incorporated by protonation of the radical anion. Hence, the radical anion of benzene is indeed more selective than the corresponding carbanion.

For anisole, the situation proved more complex. The simulation of the second steps of the anisole reduction is given in entries 2 and 3 of Table II. We can deal most readily with this information by use of eqs 10 and 11, where  $D_1^m$  and  $D_1^o$  represent the amount of deuterium incorporated in radical anion protonation were path O or path M, respectively, operating completely.  $D_2^o$  and  $D_2^m$

$$D_o = (\text{extent mech O})D_1^o + (\text{extent mech M})D_2^o \quad (10)$$

$$D_m = (\text{extent mech M})D_1^m + (\text{extent mech O})D_2^m \quad (11)$$

represent similar quantities for the carbanion protonation were path M or path O, respectively, operating completely. Equation 10 gives the total amount of deuterium incorporated ortho in the anisole Birch reduction as deriving from two sources: (a) radical anion pickup in step one and (b) carbanion pickup in step two. The amount of deuterium incorporated in step one is the extent of path O multiplied by the amount,  $D_1^o$ , of deuterium introduction characteristic of this step. Similarly, the amount incorporated in step two is given by the extent of path M multiplied by the amount,  $D_2^o$ , of deuterium introduction characteristic of that step. Equation 11 has the same form and gives the amount of deuterium incorporated at the meta position in the anisole reduction.

For  $D_2^o$ , we can use the value 0.21 (note Table II) obtained from the simulation of carbanion protonation in mechanism M, recognizing the approximate nature of the dimethylated model. We also have our experimental measure of the total amount of deuterium introduced ortho in the overall Birch reduction of anisole, namely, 0.05 (note Table II again). Using the knowledge that the extents of the two mechanisms must total unity, we can write eq 12 giving the ratio of deuteration in step 1 relative to step 2 at the ortho position (note eq 12, which has two unknowns, (extent mech O) and  $D_1^o$ ). Using the known values of  $D_o$  (i.e.,

$$\frac{D_1^o}{D_2^o} = \frac{(D_o - D_2^o)/D_2^o + (\text{extent mech O})}{(\text{extent mech O})} \quad (12)$$

0.05) and  $D_2^o$  (i.e., 0.21), we can see that, independent of the value of (extent mech O),  $D_1^o/D_2^o$  is necessarily less than unity since the first numerator term is negative. This indicates that greater isotope selectivity results in the first, radical anion protonation step relative to the second, carbanion reaction process. Further,

since the numerator of eq 12 must be nonnegative, a minimum value of 0.76 is afforded for the term (extent mech O).

Analogously, eq 11 can be rearranged to give

$$\frac{D_1^m}{D_2^m} = \frac{(D_m - D_2^m)/D_2^m + (\text{extent mech M})}{(\text{extent mech M})} \quad (13)$$

Here, again, the first numerator term is negative, and the amount of deuteration in step 1 is less than in step 2.

Hence, the experimental results for the benzene and anisole examples are quite in agreement with expectation relying on the considerably lesser basicity of radical anions relative to the related carbanions of the Birch reduction. Aside from our own results, the literature reports support this premise. In the case of anthracene, the basis is thermodynamic,<sup>14</sup> while in the case of naphthalene, rates of protonation in tetrahydrofuran were measured spectroscopically.<sup>15</sup> While the differences in basicity measured<sup>14</sup> were ca.  $10^4$ , the ratio of rates of protonation was reported as having a lower limit of 5.<sup>15</sup>

**The Anisole Birch Reduction Pathway: Mechanisms Operating.** With the original premise established, we now can proceed to contemplation of the two mechanisms under consideration. In the case of protonation of carbanion **29**, the dimethylated model meant to mimic the second intermediate (**11o**) in path O, more deuterium (0.49%; note Table II) was incorporated meta than in the overall Birch reduction of anisole at this site. However, we realize that deuterium introduced at the meta position in the Birch reduction itself derives potentially from both the initial radical anion protonation and the second step of carbanion protonation. To the extent that the dimethylated model **29** properly exhibits the same isotopic selectivity as the actual Birch reduction carbanion, this means that path O cannot operate exclusively. Similar reasoning can be employed in considering the protonation of the carbanion **27** designed to simulate the second species of path M. Here 0.21% of deuterium was captured by the carbanion **27** (again note Table II), while only 0.05% of ortho deuterium was found as a consequence of the two steps of the Birch reduction itself (Table II). This result signifies that path M cannot operate by itself. Again, this reasoning depends on the validity of the dimethyl-bearing model employed to simulate the Birch carbanion.

On the basis of this reasoning, one can draw some quantitative conclusions. With 0.49% deuterium introduced meta in the carbanion step of path O and 0.34% meta in the totality of the Birch reduction (note Table II), we find from eq 11 an upper limit of 69% participation of path O. In parallel fashion, from eq 10 with 0.21% deuterium introduced ortho in the carbanion step of path M and 0.05% total ortho in the Birch reduction, we arrive at an upper limit of 24% intervention of path M. With a 5% error, this would lead to the conclusion of a 3:1 ratio of operation of path O to path M. These results are close to the 0.76 limit for path O set above.

An alternative approach to evaluating the two mechanisms starts with the isotope effects on the four involved rate processes, that is, attack by protium and deuterium at the ortho and meta positions. Thus, we can begin with eqs 14a,b–17a,b. Here eq 14a

$$H_1^o + D_1^o = H_2^m + D_2^m \quad H_1^m + D_1^m = H_2^o + D_2^o \quad (14a,b)$$

$$R_o = H_1^o/D_1^o \quad R_m = H_1^m/D_1^m \quad (15a,b)$$

$$C_o = H_2^o/D_2^o \quad C_m = H_2^m/D_2^m \quad (16a,b)$$

$$D_o = D_1^o + D_2^o \quad D_m = D_1^m + D_2^m \quad (17a,b)$$

indicates that the sum of hydrogen and deuterium accumulated at the ortho position in step 1 equals the sum incorporated at the meta position in step 2 (note path O); likewise, eq 14b deals with the path M process. The isotope selectivities at each site are given in eqs 15a,b and 16a,b. The radical anion protonations have isotope selectivities denoted by  $R$ ; the carbanion protonation selectivities are denoted by  $C$ . It is critical to note that the  $C$  and  $R$  terms are not isotope effects, but rather the ratio of absolute incorporations under the given experimental concentrations. Equations 17a,b represent total deuterium at the ortho and meta

carbons acquired in both protonation steps. Equations 15a,b-17a,b were used to eliminate the  $H_1$ ,  $H_2$ , and  $D_2$  terms in eqs 14a and 14b, giving rise to eq 18, which gives the regioselectivity,  $W$ , in the radical anion protonation.<sup>23a</sup>

$$W = \frac{D_1^o}{D_1^m} = \frac{(C_m + 1)[(R_m + 1)D_m - (C_o + 1)D_o]}{(C_o + 1)[(R_o + 1)D_o - (C_m + 1)D_m]} \quad (18)$$

In our earlier efforts on the Birch regioselectivity, we needed to assume that the isotopic selectivity would be independent of ortho vs meta regioselectivity both in the radical anion protonation and also in the carbanion protonation step.<sup>2</sup> With the present independent determination of the reactivities of the carbanion of the second Birch reduction step, this assumption no longer is needed. Thus  $D_2^o$  and  $D_2^m$  (see Table II) allow, by difference, calculation of  $H_2^o$  and  $H_2^m$  and therefore of  $C_o$  and  $C_m$ . Using these values in eq 18 along with the values for  $D_o$  and  $D_m$  (see Table II again), we arrive at eq 19 for the regioselectivity of the radical anion protonation:

$$W = \frac{D_1^o}{D_1^m} = 0.43 \frac{(7R_m - 469)}{(R_o - 1427)} \quad (19)$$

With recognition that the denominator and numerator of eq 19 must have the same sign and that radical anion selectivity is greater than the observed carbanion selectivities (vide supra), we can conclude that the ortho isotope selectivity in radical anion protonation must be minimally 1427 with 1% deuterium present. This corresponds to an isotope effect of about 14. We realize that such large isotope effects are reasonable in view of the -78 °C temperature.<sup>24</sup> Further, as originally assumed, one does not anticipate that the ortho and meta isotope effects will differ greatly for protonation of the radical anion. Unless  $R_m$  is unrealistically smaller than  $R_o$ , one obtains an ortho:meta regioselectivity,  $W$ , of much greater than 1. This conclusion is related to the smaller expected differences in ortho vs meta radical anion electron density compared to that expected in the carbanion. Note the theoretical discussion section below.

It needs to be noted that the regioselectivity  $W$  given by the discussion above is the selectivity anticipated in a "deuterium world". In the ordinary Birch reduction in protium solvents, the regioselectivity will be given by

$$V = H_1^o/H_1^m = (R_o/R_m)W \quad (20)$$

For ortho protonation of the radical anion not to be greatly favored in a "protium world" would require  $R_o$  to be remarkably different from and less than  $R_m$ .

The theoretical basis of the regioselectivity in the anisole reduction is considered in connection with the quantum mechanical discussion section below.

**Regioselectivity in Other Monocyclic Birch Reductions.** The two other Birch reductions investigated, those of 1,3-dimethoxybenzene and 3-methoxytoluene, were found to afford excess deuterium at the carbon meta to the methoxy groups. In the case of 1,3-dimethoxybenzene there are three a priori possible sites of

initial protonation—ortho-ortho, meta-meta, and ortho-para. However, no products from protonation of the site ortho to one methoxy and para to the other are observed. Of the remaining two sites, the position meta to two methoxy groups is deuterated 7.9:1 relative to the site ortho to two methoxy groups. This signifies that, again, the radical anion prefers to protonate ortho to the maximum number of methoxy groups. In the case of 3-methoxytoluene, deuteration at the position meta to methoxy was preferred 7.2:1 over ortho. This leads again to a preference of ortho protonation of the radical anion.

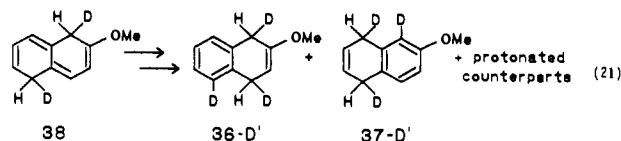
For these two examples, 1,3-dimethoxybenzene and 3-methoxytoluene, an approximate estimate of  $W$  derives from the assumption that isotope selectivity is relatively independent of the site involved. This leads eq 18 to one with only a single set of  $R$  and  $C$  values.<sup>23b</sup> With this assumption, the ortho over meta preference in protonation of the radical anions of the first step of the Birch reduction has a lower limit of 7.9 for 1,3-dimethoxybenzene and 7.2 for 3-methoxytoluene. The source of this regioselectivity is discussed below in connection with the theoretical analysis.

**Discussion of the Mechanism of the 2-Methoxynaphthalene Reduction.** Table I gives the experimental distribution of deuterium for both *tert*-butyl alcohol and methanol Birch reductions. Focusing attention on the methanol runs first, we note that the largest amount of deuterium is introduced at C-4 and the second largest amount at C-1. In the case of C-5 and C-8, as noted above, the extent of deuteration at these two sites could not be dissected experimentally, and as an approximation, we assume an equal division of the deuterium content between these two carbons.

The consequence of the heaviest deuteration at C-4 is that we may conclude that protonation of the radical anion in ring A preferentially is at C-1, ortho to the methoxy group. The same reasoning leads to the conclusion that the second most preferred site of protonation of the radical anion is C-4, meta to the methoxy group.

The ratio of reductions of the two rings favors the methoxy-bearing ring A relative to ring B by a factor of 1.6:1 in methanol, and this signifies that protonation at the two sites, C-1 and C-4, in ring A is favored over protonation at the two sites, C-5 and C-8, in ring B. This selectivity is somewhat less than that obtained purely for deuterium attack, where one obtains a ratio of 2.4:1 (see Table I).

A further point is that no aromatic deuterium was found in the reduction products. This permits the conclusion that protonation of the radical anion in one ring is followed by carbanion protonation only in the same ring. This is seen by consideration of one example, shown in eq 21, where the initial protonation is at C-1 and the second protonation is taken arbitrarily as at C-5. Tautomerization of either proton would result in some aromatic deuterium substitution. Potential reduction products 36-D' and 37-D' would result from this two-ring protonation.



Finally, we see no deuterium introduced at C-3. This establishes that neither radical anion protonation nor the carbanion reaction of the second step occurs at this position. That this is a site ortho to methoxy is noteworthy and requires subsequent discussion (vide infra).

In the above discussion, we have utilized the methanol reduction conditions rather than those employing *tert*-butyl alcohol. There is some evidence that, in the case of polycyclic hydrocarbons (e.g., anthracene), the less acidic alcohols permit an alternative mechanism involving dianion formation followed by double protonation.<sup>25</sup> In the present case, if the same radical anion mechanism were being followed as with methanol, one would

(23) (a) Equation 18 provides a convenient analysis with the minimal number of unknown constants. However, one can treat the problem using normal isotope ratios. Thus we can take  $I_2^m = k_{211^m}/k_{210^m}$ ,  $I_2^o = k_{211^o}/k_{210^o}$ ,  $I_1^m = k_{111^m}/k_{110^m}$ , and  $I_1^o = k_{111^o}/k_{110^o}$  and write eq 18 as

$$W = \frac{(I_2^m[H]/[D] + 1)[(I_1^m[H]/[D] + 1)D_m - (I_2^o[H]/[D] + 1)D_o]}{(I_2^o[H]/[D] + 1)[(I_1^o[H]/[D] + 1)D_o - (I_2^m[H]/[D] + 1)D_m]} \quad (22)$$

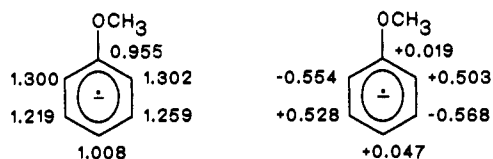
which explicitly incorporates the standard isotope effects (the  $I$ 's) for the two protonation steps but requires inclusion of hydrogen and deuterium concentrations. (b) This simplifies to a form similar to eq 19:

$$W = \frac{D_1^o}{D_1^m} = \frac{(R + 1)D_m - (C + 1)D_o}{(R + 1)D_o - (C + 1)D_m} \quad (23)$$

(24) (a) With simple Arrhenius reasoning, a room-temperature isotope effect of 7 corresponds to a factor of 20 at -77 °C. (b) Note: Wiberg, K. B. *Chem. Rev.* 1955, 55, 713-743.

(25) Rainis, A.; Tung, R.; Szwarc, M. *J. Am. Chem. Soc.* 1973, 95, 659-664.





Radical Anion  
 $\pi$ -Electron Densities

Frontier MO LCAO  
Coefficients

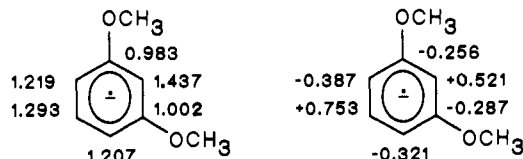
Figure 2. ROHF/6-31G//ROHF/STO-3G total electron densities and frontier MO coefficients for the anisole radical anion.

anticipate enhanced rather than the observed diminished site selectivity. Such an effect actually is seen in the anisole reduction (vide infra) with methanol.

**Variation of Alcohol, Metal, and Temperature.** We did explore to some extent the effect of these variables: (a) The enhanced regioselectivity of *tert*-butyl alcohol relative to methanol can be ascribed to a more selective protonation process occurring with a weaker protonating donor. (b) A second variable was the use of lithium<sup>26</sup> in the case of the anisole reduction. This seems likely to be a related factor, since lithium should afford solvent-separated ion pairs with greater facility.<sup>19a,27</sup> Unassociated radical anions should be more basic and thus exhibit lower selectivity, in accord with the findings of our study. (c) The last variable is temperature. The main point here is that, in the two examples investigated, namely, selectivity of the 4,4-dimethylcyclohexadienyl carbanion **25** and the Birch anisole reduction, a greater temperature effect on the selectivity was observed for the totality of the two steps of the Birch reduction compared with the single carbanion protonation step. This reflects the larger  $\Delta\Delta H^\ddagger$  of the radical anion protonation component, arising from the zero point energy contributions.

**Theoretical Considerations: The Radical Anion Protonation Step.** The Birch rule for regioselectivity states that the regioisomer formed in the reduction is that isomer having the maximum number of alkoxy and/or alkyl substituents on the residual double bonds. This empirical rule has proven invaluable. A mechanistic interpretation of this regioselectivity was first provided about three decades ago, when we suggested that there were two driving forces involved in the first step of radical anion protonation. One was protonation at the site of highest electron density in the radical anion.<sup>8a</sup> The second was formation of the most stable radical species upon this protonation.<sup>8b</sup> It was suggested, on the basis of theoretical considerations, that this initial protonation is ortho to these substituents. Our view initially was disputed<sup>3b,9,10,11</sup> and then accepted.<sup>12</sup> However, the differing viewpoints were based on a large variety of theoretical arguments of differing natures. The preceding portions of this article have presented experimental evidence demonstrating that the regioselectivity does, indeed, result from an initial ortho protonation. However, the theoretical basis for regioselectivity has remained unsettled.

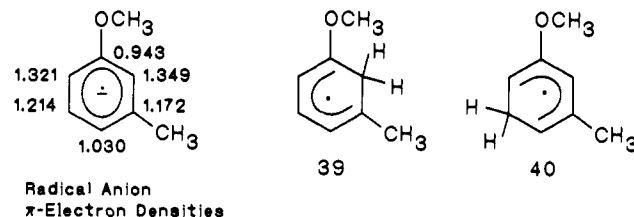
Our theoretical treatment in 1961–1963 was necessarily limited to Hückel level theory, while subsequent literature theory utilized more sophisticated approaches. With our experimental results now firm, we proceeded to utilize the GAUSSIAN92,<sup>28a</sup>



Radical Anion  
 $\pi$ -Electron Densities

Frontier MO LCAO  
Coefficients

Figure 3. ROHF/3-21G//ROHF/STO-3G total electron densities and frontier MO coefficients for the 1,3-dimethoxybenzene radical anion.



Radical Anion  
 $\pi$ -Electron Densities

Figure 4. UHF/3-21G methoxytoluene radical anion densities and alternative protonated species.

GAUSSIAN90,<sup>28b</sup> and GAMESS<sup>28b</sup> ab initio computations now currently available.

In the case of anisole, ROHF/6-31G computations with STO-3G geometry optimization showed the ortho site to be the most electron rich, with the meta position coming in second. The ipso and para positions were, by contrast, very low in electron density. These results are given in Figure 2. This seems to be a general feature of the mono- and polyalkoxylated benzenoids. One interesting facet is the electron density in the anisole radical anion frontier molecular orbital. These densities are included in Figure 2, and it is seen that it is the meta positions which are most electron rich, thus illustrating the danger of chemical predictions based on HOMO considerations alone.<sup>29</sup>

ROHF/3-21G//ROHF/STO-3G calculations on 1,3-dimethoxybenzene lead, again, to the prediction of much higher electron density at the site ortho to the two methoxy groups than at the meta one, which is higher than at the ipso sites and those which are simultaneously para and ortho. These densities, along with that for the highest occupied MO, are given in Figure 3. Experimentally, the predominant proton attack on the radical anion was seen to be ortho to the two methoxy groups in accord with the total electron density computations but, again, not correlating with the HOMO electron density.

Thus far, all of our examples have been understood on the basis of control of radical anion protonation by relative electron densities. However, the importance of stabilization of odd-electron density in the transition state for radical anion protonation was the second factor of importance considered in our initial efforts to understand the reaction regioselectivity.<sup>8b</sup> For the alkoxy aromatics considered thus far, the two effects are cooperative. Thus, for example, the radical produced by ortho protonation of the anisole radical anion is species **10o** (note Scheme 1), while the radical formed by meta proton attack is species **10m**. Simple resonance considerations argue that only in **10o** is there odd-electron stabilization by the methoxy group.<sup>8b</sup> In agreement with our early suggestion, geometry-optimized ab initio (UHF/3-21G) GAUSSIAN92 comparison of the radicals resulting from ortho vs meta protonation reveals that there is a 3.3 kcal/mol preference for ortho attack.<sup>13b</sup> It seems likely that three factors contribute to the ortho transition state being stabilized relative to the meta one, namely, having the greater electron density more readily localized in the ortho site, having greater odd-electron stabilization as the protonated radical anion develops, and maximizing the substitution, and thus  $\sigma$  stabilization, on the residual  $sp^2$ -hybridized carbons.<sup>30</sup> The two

(26) (a) It was first noted by Wilds and Nelson<sup>26b</sup> that improved yields could be obtained with lithium in place of sodium in the metal/ammonia reductions. (b) Wilds, A. L.; Nelson, N. A. *J. Am. Chem. Soc.* **1953**, *75*, 5360–5365.

(27) Rabideau, P. W.; Harvey, R. G. *Tetrahedron Lett.* **1970**, 4139–4142.

(28) (a) *Gaussian 92*, Revision A, Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1992. (b) *Gaussian 90*, Revision J, Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topial, S.; Pople, J. A. Gaussian Inc.: Pittsburgh, PA, 1990. (c) QPCE Program No. QG01, Quantum Chemistry Program Exchange, Indiana University. Schmidt, M. W.; Baldrige, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Gordon, M. S.; Nguyen, K. A.; Windus, T. L.; Elbert, S. T. *QPCE Bull.* **1990**, *10*, August.

(29) This is not to say that such considerations are not relevant in special cases. Perhaps the first example and discussion of such HOMO–LUMO control can be found in ref 8b.

(30) This effect, however, cannot be dominant, since in aromatic rings with electron-withdrawing groups the regioselectivity is reversed.

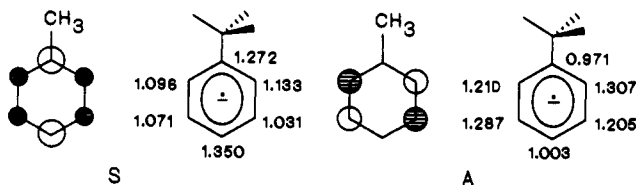


Figure 5. Two antibonding MOs and corresponding ROHF/3-21G//ROHF/STO-3G  $\pi$  densities for toluene radical anion.

radicals resulting from ortho and meta protonation of the anisole radical anion are shown with their relative energies:

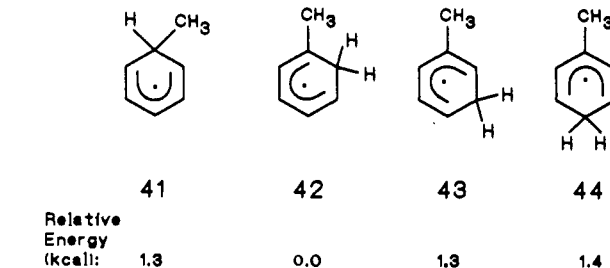
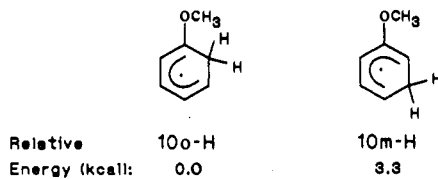


Figure 6. UHF/3-21G relative energies of protonated toluene radical anions.

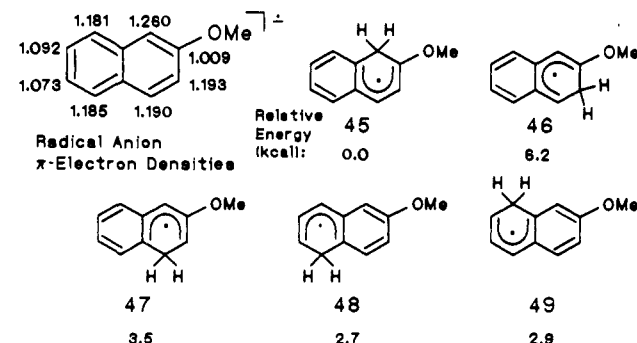


Figure 7. 2-Methoxynaphthalene radical anion ROHF/3-21G//ROHF/STO-3G densities and protonated radical anion MINDO/3 energies.

There is additional evidence in agreement with this view. In the Birch reduction of *m*-methoxytoluene, where protonation of the radical anion occurs ortho to the two substituents (vide supra), ab initio SCF calculations (UHF/3-21G) on the radical anion revealed that the site ortho to methoxy and methyl is highest in electron density, in agreement with radical anion protonation (note Figure 4). However, the carbon ortho to methoxy and para to methyl has electron density not much lower, and yet protonation at this site is not observed.

However, we note from the two structures that the radical generated by ortho protonation has odd-electron density at the methoxy- and methyl-bearing carbons and thus is subject to electronic stabilization, while the meta counterpart lacks similar delocalization. Note Figure 4 again. This differential stabilization in the radical formed must be partially present in the transition state for radical anion protonation.

Turning to the case of toluene where experimentally the first protonation is ortho and/or meta to methyl,<sup>6a</sup> we need to consider the same two contributing factors. Radical anion electron density is taken first. First we note that ESR evidence presented by Jones and Wood indicates the presence of two energetically close-lying states in an 80:20 ratio.<sup>31a</sup> One state of the radical anion has the odd electron in a molecular orbital antisymmetric (A) with respect to a perpendicular plane and is the favored one seen in the ESR for odd-electron occupation; the other state has the odd electron in a molecular orbital symmetric (S) with respect to a perpendicular plane. Jones and Wood found an energy difference of 2.75 kcal/mol between the two states using STO-3G computations on INDO-optimized geometries, with the lower energy state having the odd electron in an MO antisymmetric with respect to a perpendicular plane of symmetry. With INDO computations the energy orderings were reversed.<sup>31b</sup>

In our present study, we employed ROHF/3-21G//ROHF/STO-3G computations and found a small energy difference of 0.5 kcal/mol between the two states, with the lower energy state having the antisymmetric MO populated. The two MOs and the total electron densities of the radical anions with these MOs are given in Figure 5. While the electron density in the higher energy radical anion (S) had the highest electron densities at the para and ipso positions, the lower energy (A) state has its highest electron densities at the ortho and meta positions. These results differ from those of Birch and Radom,<sup>12</sup> who had used only STO-3G computations on a benzenoid geometry. In assuming that the symmetric (S) species was dominant, these workers noted a discrepancy with ESR results. In any event, unless the upper S state species has a significantly higher rate of reaction, one would anticipate predominantly ortho protonation of the A state on the basis of electron densities alone.

Table III. Protonation of the Toluene Radical Anion: Relative Energy vs Distance

$E(\text{para}) - E(\text{ortho})$ (kcal/mol)	distance <sup>a</sup> (Å)			
	1.2	1.4	1.6	1.8
	1.3	1.3	1.1	0.7

<sup>a</sup> Defined as fixed distance in angstroms between incoming proton and reacting carbon.

However, in addition to electron densities of the radical anions, the second factor we have argued to be involved is stabilization of the odd-electron density in the transition state for radical anion protonation. This might be treated in two ways. First one might just use the relative stabilities of the protonated radical anions as a guide to the relative transition-state energies. Second, one might approximate the transition states by bringing a proton toward the radical anion. For the former, we employed UHF/3-21G geometry optimized ab initio computations which reveal the radical formed by ortho protonation to be more stable by 1.3 kcal/mol than that for the three remaining sites, as outlined in Figure 6. Corresponding computations using a lower basis set and without geometry optimization afforded larger differences but still favored the ortho-protonated radical anion.<sup>13a</sup>

Both our computations and those of the literature agree in suggesting the curious phenomenon that methyl substitution on the central position of a cyclohexadienyl radical has little stabilizing effect, while substitution at the end of the conjugated radical  $\pi$  system is stabilizing.

As the second approach to considering odd-electron stabilizing effects, we considered the relative energies of two approaches of a proton to the toluene radical anion. In this we used UHF/3-21G//ROHF/STO-3G calculations with geometry optimization, except that the six-membered ring was kept planar by fixing the ring dihedral angles and each distance between the incoming proton and the carbon being protonated. These results are given in Table III. For all distances of approach studied, the ortho-protonating species was preferred over the para.

With these results, we can conclude that the two effects of preferences for protonation at (a) the site of highest electron density and (b) the site maximizing odd-electron delocalization are contributing factors operating in the same direction. In any case, some combination of the two leads to prediction of our experimental results.

(31) (a) Ihrig, A. M.; Jones, P. R.; Jung, I. N.; Lloyd, R. V.; Marshall, J. L.; Wood, D. E. *J. Am. Chem. Soc.* 1975, 97, 4477-4482. (b) INDO energy calculations by these authors yielded an 8 kcal/mol preference for the S state.<sup>31a</sup>



**2-Methoxynaphthalene Reduction.** In this case, both radical anion electron density and odd-electron stabilization factors lead to the observed preferential protonation ortho at C-1 of 2-methoxynaphthalene. Here ROHF/3-21G//ROHF/STO-3G computations with geometry optimization were used to obtain the radical anion electron densities, while MINDO/3<sup>32</sup> SCF calculations, again with geometry optimization, were employed to gauge the relative energies of the protonated radical anions. These results are summarized in Figure 7.

In comparison with experimental observation we used the methanol runs, since the *tert*-butyl alcohol Birch reductions in this case seemed possibly to involve a dianion mechanism. For the methanol experiments, the theoretical computations outlined in Figure 6 seem to be in nice agreement with the observation of a preferential protonation at C-1; the calculations showed lesser but similar calculated densities at C-3, C-4, C-5, and C-8. We note that, although experiment dealt only with the total protonation at C-5 and C-8, the theoretically similar densities at C-5 and C-8 are in accord with the earlier discussion of the experimental results.

Interestingly, while the radical anion densities do not disallow C-3 protonation, the odd-electron stabilization factor predicts the observed lack of protonation at C-3 of 2-methoxynaphthalene. In this context, it seems likely that literature observation of the conjugated Birch reduction product<sup>21a</sup> resulted from base- or acid-catalyzed conjugation of the kinetic product **36**, possibly during workup.

**The Second Step of the Birch Reduction.** Invariably, under standard Birch conditions using an alcohol for protonation, it is the unconjugated cyclic diene which is kinetically produced.<sup>33</sup> The source of this regioselectivity requires consideration. Simple Hückel theory predicts that a pentadienyl anion has its negative charge equally distributed among the three alternating carbons, i.e., C-1, C-3, and C-5. This is not in agreement with the universal observation that such conjugated systems invariably protonate with kinetic preference for the central atom.<sup>8b,34</sup> In our very early efforts,<sup>8a,35</sup> we used the Mulliken-Wheland-Mann modification<sup>36</sup> of Hückel calculations, in which the resonance integral for an iteration is taken as a function of the bond order obtained from the previous iteration; the variation of the Coulomb integral was not included. With this approach it was shown that, with increasing iterations, the bond orders 1-2 and 4-5 initially were greater and increased relative to 2-3 and 3-4 with the consequence of concentration of electron density on the central carbon atom.

With more modern computational methodology available, the same phenomenon was of interest. Thus, the cyclohexadienyl anion involved in the Birch reduction of benzene was investigated using RHF/3-21G both with STO-3G geometry optimization and also with a fixed, equi-bond-length counterpart. In both cases, electron density was highest at the center of the conjugated system. The effect was only slightly more pronounced with geometry optimization (1.467 at C-3, compared to 0.940 at C-2 and 1.300 at C-1). We can conclude that the central electron density enhancement derives primarily from the larger 1-2 and 4-5 bond orders resulting in even Hückel calculations and that the shortening of these bonds in geometry optimization is a consequence rather than a main cause of the effect. The off-diagonal elements of the Fock matrix between two basis orbitals become more negative in SCF computations when the bond order between these orbitals increases. The  $\pi$  bond orders 1-2 and 4-5 were higher initially and converged with higher values (0.811) relative to 2-3 and 3-4

(0.392). Shorter distances of 1.34 Å for the terminal "pentadienyl" bonds relative to those involved in bonding to the central carbon (1.41 Å) were obtained. The central carbon charge concentration may additionally derive from an electrostatic effect due to the  $sp^2$ - $sp^3$  bonds at the termini of the pentadienyl carbanionic system.

**Generalization of the Mechanistic Method.** The general problem here was determining the sequence of events in a mechanism of multiple sequential steps and multiple sites of transformation by a single reagent. However, the method of differential isotope effects may be utilized for other reaction mechanisms involving two sequential intermediates differing markedly in reactivity and undergoing attack by the same external species. The less reactive species should identify itself by exhibiting the lower isotope effect.

**Conclusion.** The overall regioselectivity of the Birch reduction has been clear for a considerable period. However, the regiochemistry of the individual steps of the mechanism has been elusive, and the present study has provided the details of these steps by means of a conceptually new approach in which two consecutively formed species of differing reactivity exhibit differing isotope effects.

### Experimental Section

**General Procedures.** Melting points were determined on a Mel-Temp heating block and are reported uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN). All reactions were performed under an atmosphere of dry nitrogen. Anhydrous sodium sulfate was used as the drying agent. Column chromatography was performed on silica gel (J. T. Baker Inc., 60-200 mesh). High-pressure liquid chromatography (HPLC) was performed on a liquid chromatograph employing an LDC 254-nm detector and an LDC 6000-psi minipump. Analyses were performed with a 0.38 × 50 cm polished stainless steel column packed with 10- $\mu$ m porous silica beads.<sup>37</sup> Neutral workup refers to quenching the reaction with water followed by ether or pentane extraction, washing the organic layer with water, drying, filtering, and concentrating in vacuo. Basic-acidic workup used sequential base and acid washes after ether extraction.

*tert*-Butyl alcohol was distilled from calcium hydride. Liquid ammonia was distilled from sodium. Dimethoxyethane (DME) was purified by successive distillation, under a nitrogen atmosphere, from calcium hydride, lithium aluminum hydride, and sodium benzophenone ketyl. Hexane used for HPLC was washed with 1:1 nitric acid and sulfuric acid, water, saturated aqueous sodium bicarbonate, and brine, dried over calcium chloride, passed through alumina, and distilled from calcium hydride.

Deuterium NMR analyses were performed on an AM 500-MHz Bruker instrument. Methylene identification in Birch-reduced dienes was achieved by lanthanide-induced shifts in the <sup>1</sup>H NMR spectrum with added tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium (Eu(FOD)<sub>3</sub>) or tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)praseodymium (Pr(FOD)<sub>3</sub>). For the determination of relative deuterium content at methylene carbons, Pr(FOD)<sub>3</sub> (0.60 equiv) was added to resolve methylene resonances in the <sup>2</sup>D NMR. For determination of absolute % D, two standardization methods were used: (1) 3,3-dimethyl-2,2-diphenylcyclopropanecarboxaldehyde-*d*<sub>1</sub><sup>38</sup> was added, or (2) the natural abundance of deuterium in the NMR solvent was utilized. A relaxation delay of 2-3 s was used in absolute % D determinations. Experimentally determined values are reported as the mean of the specified number of experimental runs, followed by the standard deviation of the data set.

**General Procedure for Birch Reduction of Monocyclic Benzenes.** A modification of the method of Birch<sup>39</sup> was used. A solution of 0.481 mL (0.330 g, 4.40 mmol) of *tert*-butyl alcohol-*O-d*<sub>1</sub> (91.9% D by <sup>2</sup>D NMR) and 2.00 mmol of the aromatic substrate was allowed to equilibrate in 4.0 mL of anhydrous ammonia and 0.40 mL of anhydrous ether for 30 min at -78 °C. Sodium metal (96.7 mg, 4.20 mmol) was added in small pieces over a period of 20 min. Ammonium chloride (0.30 g, 5.6 mmol) was added to quench alkoxides, followed by the cautious addition of 5.0 mL of water and neutral workup<sup>40</sup> with ether. 2,5-Dihydrobenzenes were analyzed by <sup>2</sup>D NMR without further purification. Reductions using methanol-*O-d*<sub>1</sub> (99.5% D) as the proton source, reductions using lithium,

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(33) In the absence of added alcohol, amide-catalyzed conjugation of the initial product is generally followed by further reduction. However, the present discussion concerns kinetic product formation.

(34) (a) In addition to the Birch reduction, one common example is the kinetic preference in protonation of dienolates, derived from enones, where the unconjugated enone is formed preferentially.<sup>8b,34b</sup> (b) Paufler, R. M. Ph.D. Thesis, Northwestern University, Evanston, IL, 1960.

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and reductions at  $-33\text{ }^{\circ}\text{C}$  were performed in a similar fashion.

**Birch Reduction of Anisole (8).** Reduction afforded only 2,5-dihydroanisole (**12**);<sup>32</sup> spectral data were identical to those previously recorded.<sup>41</sup> The C-2 and C-5 methylenes of **12** were identified in the  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ) spectrum as follows: the addition of 0.27 equiv of  $\text{Pr}(\text{FOD})_3$  caused the methylene at  $\delta$  2.76–2.66 (2 H) to move upfield by  $\delta$  0.11, whereas the addition of 0.48 equiv of  $\text{Eu}(\text{FOD})_3$  caused a downfield shift of  $\delta$  0.14 of the same methylene. Furthermore, irradiation of the methylene at  $\delta$  2.87–2.76 (2 H) caused decoupling of the high-field,  $\alpha$ -vinyl ( $\delta$  4.63, 1 H) triplet to a singlet.  $^2\text{D}$  NMR revealed that deuterium had been incorporated only at the methylene positions.

For reduction runs at  $-78\text{ }^{\circ}\text{C}$  with sodium and *tert*-butyl alcohol-*O-d*<sub>1</sub>,  $^2\text{D}$  NMR indicated the amount of deuterium incorporated in **12** to be  $0.39 \pm 0.03\%$  and the ratio of deuterium at C-5 to that at C-2 to be  $7.0 \pm 0.7$  (average of four determinations).

For reduction runs at  $-78\text{ }^{\circ}\text{C}$  with lithium and *tert*-butyl alcohol-*O-d*<sub>1</sub>,  $^2\text{D}$  NMR indicated the amount of deuterium incorporated in **12** to be  $0.44 \pm 0.07\%$  and the ratio of deuterium at C-5 to that at C-2 to be  $4.1 \pm 0.4$  (average of three determinations).

For reduction runs at  $-78\text{ }^{\circ}\text{C}$  with sodium and methanol-*O-d*<sub>1</sub>,  $^2\text{D}$  NMR indicated the amount of deuterium incorporated in **12** to be  $0.87 \pm 0.03\%$  and the ratio of deuterium at C-5 to that at C-2 to be  $4.0 \pm 0.01$  (average of three determinations).

For reductions runs at  $-33\text{ }^{\circ}\text{C}$  with sodium and *tert*-butyl alcohol-*O-d*<sub>1</sub>,  $^2\text{D}$  NMR indicated the amount of deuterium incorporated in **12** to be  $0.46 \pm 0.01\%$  and the ratio of deuterium at C-5 to that at C-2 to be  $3.8 \pm 0.2$  (average of two determinations).

**Birch Reduction of 1,3-Dimethoxybenzene (31).** Reduction at  $-78\text{ }^{\circ}\text{C}$  with sodium and *tert*-butyl alcohol-*O-d*<sub>1</sub> afforded only 1,5-dimethoxy-1,4-cyclohexadiene (**32**);<sup>20</sup> the spectral data were identical to those previously recorded.<sup>42</sup> The C-3 and C-6 methylenes of **32** were identified in the  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ) spectrum as follows: the addition of 0.35 equiv of  $\text{Pr}(\text{FOD})_3$  resolved the multiplet at  $\delta$  2.90–2.73 (4 H) into two multiplets,  $\delta$  2.89–2.76 (2 H) and  $\delta$  2.70–2.58 (2 H). Irradiation of the methylene at  $\delta$  2.89–2.76 caused decoupling of the high-field,  $\alpha$ -vinyl triplet ( $\delta$  4.66, 1 H) to a singlet.

$^2\text{D}$  NMR indicated that deuterium had been incorporated only at the methylene positions in **32** and that the ratio of deuterium at C-3 to that at C-6 in **32** was  $7.9 \pm 0.3$  (average of four determinations).

**Birch Reduction of 3-Methoxytoluene (33).** Reduction at  $-78\text{ }^{\circ}\text{C}$  with sodium and *tert*-butyl alcohol-*O-d*<sub>1</sub> afforded only 1-methoxy-5-methyl-1,4-cyclohexadiene (**34**);<sup>3a</sup> the spectral data were identical to those previously recorded.<sup>41</sup> The C-3 and C-6 methylenes of **34** were identified in the  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ) spectrum as follows: the addition of 0.35 equiv of  $\text{Pr}(\text{FOD})_3$  caused an upfield shift of the multiplet at  $\delta$  2.64–2.60 (2 H) of  $\delta$  0.08. Furthermore, irradiation of the methylene at  $\delta$  2.88–2.74 (2 H) caused decoupling of the high-field,  $\alpha$ -vinyl triplet ( $\delta$  4.64, 1 H) to a singlet.

$^2\text{D}$  NMR indicated that deuterium had been incorporated only at the methylene positions and that the ratio of deuterium at C-3 to that at C-6 in **34** was  $7.2 \pm 0.3$  (average of four determinations).

**Birch Reduction of 2-Methoxynaphthalene (35).** A mixture of 0.505 mL (0.398 g, 5.31 mmol) of *tert*-butyl alcohol-*O-d*<sub>1</sub> (90.7% D by  $^2\text{D}$  NMR) and 0.401 g (2.54 mmol) of 2-methoxynaphthalene was allowed to equilibrate in 20.0 mL of anhydrous ammonia and 2.0 mL of ether for 30 min at  $-78\text{ }^{\circ}\text{C}$ . Sodium metal (115 mg, 5.02 mmol) was added in small pieces over a period of 10 min. Ammonium chloride (0.30 g, 5.6 mmol) was added to quench alkoxides, followed by immediate addition to 50 mL of 1:1 saturated sodium bicarbonate/benzene. The layers were separated, and the organic phase was dried over sodium sulfate at  $-14\text{ }^{\circ}\text{C}$ . Filtration and cold concentration in vacuo yielded 0.383 g of a clear colorless oil, which solidified upon standing.  $^1\text{H}$  NMR indicated this to be a 1.2:1.3:1.0 mixture of 2-methoxynaphthalene (**35**)/1,4-dihydro-2-methoxynaphthalene (**36-D**)/1,4-dihydro-6-methoxynaphthalene (**37-D**). A portion of the mixture (102 mg) was subjected to HPLC eluted with 2% triethylamine and 3% ether in hexane to afford the following: peak 1,  $t_R = 16.3$  min, 34.2 mg (31.6%) of 1,4-dihydro-2-methoxynaphthalene, bp  $109\text{ }^{\circ}\text{C}$  (1 mmHg) (lit.<sup>43</sup> bp  $110\text{ }^{\circ}\text{C}$  (1 mmHg)); peak 2,  $t_R = 18.8$  min, 21.1 mg (19.5%) of 1,4-dihydro-6-methoxynaphthalene, bp  $90\text{--}94\text{ }^{\circ}\text{C}$  (0.5 mmHg) (lit.<sup>44</sup> bp  $90\text{--}95\text{ }^{\circ}\text{C}$  (0.5 mmHg)); peak 3,  $t_R = 25.4$  min, 30.1 mg of 2-methoxynaphthalene. Spectral data were identical to those previously recorded for 1,4-dihydro-2-methoxynaphthalene<sup>45</sup> and 1,4-dihydro-6-methoxynaphthalene.<sup>44</sup>

**Table IV.** Kinetic Order Determination of Anisole Reduction

time (s)	c ([anisole], M)	$1/c^2, \text{M}^{-2}$	$1/c^3, \text{M}^{-3}$
0	0.411	5.93	14.44
33	0.322	9.64	29.95
116	0.243	16.99	41.35
601	0.126	62.98	499.8

The C-2 and C-5 methylenes of 1,4-dihydro-2-methoxynaphthalene were identified in the  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ) spectrum as follows: the addition of 0.30 equiv of  $\text{Pr}(\text{FOD})_3$  caused the methylene at  $\delta$  3.52–3.46 (2 H) to move upfield by  $\delta$  0.03, whereas the addition of 0.29 equiv of  $\text{Eu}(\text{FOD})_3$  caused a downfield shift of  $\delta$  0.05 of the same methylene. Furthermore, irradiation of the methylene at  $\delta$  2.52–2.46 (2 H) caused decoupling of the high-field,  $\alpha$ -vinyl ( $\delta$  4.82, 1 H) triplet to a singlet.  $^2\text{D}$  NMR indicated that deuterium had been incorporated only at the methylene positions, that the ratio of deuterium incorporation in **36-D** to that in **37-D** was  $1.22 \pm 0.30$ , and that the ratio of deuterium at C-4 to that at C-1 in **36-D** was  $1.03 \pm 0.05$  (average of two determinations).

Reductions using methanol-*O-d*<sub>1</sub> (99.5% D) were performed in a similar fashion. In the case of methanol-*O-d*<sub>1</sub> as the proton source,  $^1\text{H}$  NMR indicated the product to be a 2.2:1.6:1.0 mixture of 2-methoxynaphthalene/1,4-dihydro-2-methoxynaphthalene/1,4-dihydro-6-methoxynaphthalene.  $^2\text{D}$  NMR indicated that the ratio of deuterium incorporation in **36-D** to that in **37-D** was  $1.30 \pm 0.05$  and that the ratio of deuterium at C-4 to that at C-1 in **36-D** was  $1.30 \pm 0.01$  (average of two determinations).

**Kinetic Order Determination for Birch Reduction of Anisole (8).** The method of Krapcho and Bothner-By was utilized.<sup>6a</sup> Sodium (0.446 g, 19.3 mmol) was dissolved in 18 mL of anhydrous ammonia and 2.0 mL of ether at  $-78\text{ }^{\circ}\text{C}$  in a three-necked flask with a stopcock fused to its bottom. A solution of 1.02 g (9.43 mmol) of anisole and 1.95 mL (1.54 g, 20.7 mmol) of *tert*-butyl alcohol was added over 8 s. Aliquots (ca. 1 mL) were drained at intervals (ca. 1 min apart) into a 1:1 mixture of ether/water containing 1 mmol of sodium benzoate, followed by neutral workup<sup>40</sup> with ether. Aliquots were analyzed by  $^1\text{H}$  NMR utilizing a relaxation delay of 5 s. The extent of reduction was determined by NMR integration of the  $\delta$  7.00–6.85 aromatic region of anisole (**8**) and the  $\delta$  2.90–2.60 allylic region of 2,5-dihydroanisole (**12**). Table IV shows typical concentration and time data. A correlation coefficient of  $r = 0.99995$  was obtained for the third-order plot of  $1/c^2$  vs time, whereas  $r = 0.99132$  for the fourth-order plot of  $1/c^3$  vs time.

**3-Methoxy-6,6-dimethyl-1,4-cyclohexadiene (14).**<sup>46</sup> To a suspension of 0.391 g (16.3 mmol) of sodium hydride in 10.0 mL of DME at  $0\text{ }^{\circ}\text{C}$  was added 1.45 g (11.7 mmol) of 3-hydroxy-6,6-dimethyl-1,4-cyclohexadiene<sup>47</sup> in 10.0 mL of DME. The mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 1.7 h. Then 2.02 mL (4.61 g, 32.4 mmol) of methyl iodide was added over 3 min, and the mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 1 h. Neutral workup<sup>40</sup> with pentane followed by trap-to-trap distillation at 21 to  $-78\text{ }^{\circ}\text{C}$  at 2.5–3.0 mmHg afforded 1.31 g (81.1%) of 3-methoxy-6,6-dimethyl-1,4-cyclohexadiene (**14**) as a clear colorless oil, bp  $28\text{ }^{\circ}\text{C}$  dec. Spectral data were identical to those previously recorded for **14**.<sup>46</sup>

**2-Methoxy-4,4-dimethylcyclohexa-2,5-dienone (16).** A mixture of 1.10 g (7.11 mmol) of 2-methoxy-4,4-dimethylcyclohex-2-enone,<sup>48</sup> 1.90 g (8.38 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 38.9 mg (0.205 mmol) of *p*-toluenesulfonic acid monohydrate, and 71.3 mg (0.401 mmol) of lithium tosylate was refluxed in 22 mL of anhydrous benzene. The mixture was taken up in 25 mL of ether and subjected to basic-acidic workup,<sup>40</sup> followed by saturated sodium bicarbonate and brine wash. The ether layer was then dried over sodium sulfate and concentrated in vacuo to yield a brown oil, which was distilled to afford 0.415 g (38.4%) of 2-methoxy-4,4-dimethylcyclohexa-2,5-dienone (**16**) as a clear yellow oil, bp  $44\text{--}48\text{ }^{\circ}\text{C}$  (0.15 mmHg). The spectral data were the following: IR ( $\text{CHCl}_3$ ) 2937, 2250, 1664, 1640, 1124, 1212  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  6.85 (dd,  $J = 10.1, 2.7$  Hz, 1 H, (C=O)-CH=CH), 6.24 (d,  $J = 10.1$  Hz, 1 H, (C=O)CH=), 5.76 (d,  $J = 2.7$  Hz, 1 H, C(OCH<sub>3</sub>)=CH), 3.57 (s, 3 H, OCH<sub>3</sub>), 1.31 (s, 6 H, gem-CH<sub>3</sub>); MS  $m/e$  152.0838 (calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub>;  $m/e$  152.0839).

**3-Hydroxy-2-methoxy-6,6-dimethyl-1,4-cyclohexadiene (17).** To 7.22 g (47.5 mmol) of 3-methoxy-4,4-dimethylcyclohexa-2,5-dienone (**16**) in 150 mL of anhydrous benzene at ca.  $6\text{ }^{\circ}\text{C}$  was added 47.5 mL (47.5 mmol) of a 1.0 M solution of diisobutylaluminum hydride in hexane over

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**Table V.** Chemical Shifts of Protons in 3-Methoxy-4,4-dimethylcyclohex-2-enone (**21**) as a Function of Eu(FOD)<sub>3</sub> Concentration<sup>a</sup>

proton	mole fraction of Eu(FOD) <sub>3</sub> <sup>b</sup>						
	0.00	0.077	0.172	0.267	0.364	0.473	0.576
vinyl	5.26	6.18	7.27	8.33	9.39	10.51	11.49
methoxy	3.68	3.82	3.99	4.15	4.31	4.48	4.62
$\alpha$ -methylene	2.41	3.35	4.47	5.57	6.69	7.88	8.94
$\beta$ -methylene	1.83	2.14	2.51	2.88	3.25	3.64	4.00
<i>gem</i> -dimethyl	1.20	1.39	1.61	1.83	2.05	2.29	2.50

<sup>a</sup>Shifts are in ppm downfield from TMS. <sup>b</sup>Relative to substrate.

3 min. The mixture was stirred for 5 min at 0–5 °C and then quenched by rapid addition to 300 mL of 10% sodium hydroxide. Separation of layers, extraction of the aqueous layer with 2 × 250 mL of ether, washing the combined organics with 500 mL of brine, drying over sodium sulfate, and concentration in vacuo yielded 7.85 g of a clear colorless oil. Distillation afforded 6.77 g of a clear colorless oil (bp 49–56 °C (0.45 mmHg)), which solidified upon standing. This solid was recrystallized from pentane to produce 4.94 g (67.6%) of 3-hydroxy-2-methoxy-6,6-dimethyl-1,4-cyclohexadiene (**17**) as white needles, mp 45.6–46.7 °C. Spectral data were the following: IR (CHCl<sub>3</sub>) 3588, 3013, 2961, 2935, 1685, 1648, 1467, 1229, 1148 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  5.72 (m, 2 H, CH=CH), 4.67 (d, *J* = 1.4 Hz, 1 H, C(OCH<sub>3</sub>)=CH), 4.54 (dd, *J* = 4.9, 3.1 Hz, CH(OH)), 3.60 (s, 3 H, OCH<sub>3</sub>), 2.14 (d, *J* = 4.9 Hz, 1 H, CH(OH)), 1.14 (s, 3 H, *gem*-CH<sub>3</sub>), 1.09 (s, 3 H, *gem*-CH<sub>3</sub>); MS *m/e* 154.0992 (calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub> *m/e* 154.0994). Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>: C, 70.10; H, 9.15. Found: C, 70.02; H, 9.20.

**2,3-Dimethoxy-6,6-dimethyl-1,4-cyclohexadiene (18).** To a slurry of 0.427 g (10.7 mmol active reagent) of sodium hydride as a 60% dispersion in mineral oil in 20 mL of anhydrous DME at 0 °C was added 1.00 g (6.51 mmol) of 3-hydroxy-2-methoxy-6,6-dimethyl-1,4-cyclohexadiene (**17**) in 20 mL of anhydrous DME. The mixture was stirred at 0 °C for 1 h. Then 1.14 mL (2.60 g, 18.3 mmol) of methyl iodide was added over 1 min, and the mixture was stirred at 0 °C for 25 min. Neutral workup<sup>40</sup> with pentane afforded 1.19 g of a clear yellow oil, which was distilled to yield 0.904 g (82.6%) of 2,3-dimethoxy-6,6-dimethyl-1,4-cyclohexadiene (**18**) as a clear colorless oil, bp 37–38 °C (0.4 mmHg). Spectral data were the following: IR (CHCl<sub>3</sub>) 2963, 2928, 1680, 1642, 1472, 1359, 1167, 993, 956 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  5.85 (dt, *J* = 10.0, 1.5 Hz, 1 H, C(CH<sub>3</sub>)<sub>2</sub>CH=CH), 5.59 (dd, *J* = 10.0, 3.7 Hz, 1 H, C(CH<sub>3</sub>)<sub>2</sub>CH=CH), 4.82 (d, *J* = 1.5 Hz, 1 H, C(OCH<sub>3</sub>)=CH), 4.66 (dd, *J* = 3.7, 1.5 Hz, 1 H, C(OCH<sub>3</sub>)H), 3.60 (s, 3 H, CH=C(OCH<sub>3</sub>)), 3.20 (s, 3 H, CH(OCH<sub>3</sub>)), 1.14 (s, 3 H, *gem*-CH<sub>3</sub>), 1.10 (s, 3 H, *gem*-CH<sub>3</sub>); MS *m/e* 168.1153 (calcd for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub> *m/e* 168.1151). Anal. Calcd for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.72.

**3-Methoxy-4,4-dimethylcyclohex-2-enone (21).** A solution of 20.9 g (0.149 mol) of 4,4-dimethyl-1,3-cyclohexanedione<sup>49</sup> and 1.75 g (9.21 mmol) of *p*-toluenesulfonic acid monohydrate was refluxed in 280 mL of methanol for 1.5 h. The methanol was removed by concentration in vacuo, and the residue was distilled (bp 58–66 °C (0.3–0.5 mmHg)) to yield 19.4 g (84.4%) of a clear colorless oil. <sup>1</sup>H NMR revealed this to be a 3.4:1.0 mixture of 3-methoxy-6,6-dimethylcyclohex-2-enone (**20**)/3-methoxy-4,4-dimethylcyclohex-2-enone (**21**). Fractional distillation of 65.6 g of the mixture through a 105 × 1.5 cm thermostated metal helices column afforded 42.3 g of 100% isomerically pure (as determined by <sup>1</sup>H NMR) 3-methoxy-6,6-dimethylcyclohex-2-enone, bp 45.1–46.1 °C (0.08 mmHg), and 12.6 g of 99.1% isomerically pure (as determined by <sup>1</sup>H NMR) 3-methoxy-4,4-dimethylcyclohex-2-enone (**21**), bp 46.8–48.9 °C (0.08 mmHg).

Spectral data for 3-methoxy-6,6-dimethylcyclohex-2-enone were the following: IR (neat) 2962, 2940, 2866, 1656, 1613, 1454, 1377, 1248, 1195, 1174, 1041, 997, 982, 870, 842 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  5.27 (s, 1 H, vinyl), 3.68 (s, 3 H, OCH<sub>3</sub>), 2.43 (t, *J* = 6.0 Hz, 2 H, C(OCH<sub>3</sub>)CH<sub>2</sub>), 1.81 (t, *J* = 6.0 Hz, 2 H, C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>), 1.12 (s, 6 H, C(CH<sub>3</sub>)<sub>2</sub>); MS *m/e* 154.0990 (calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub> *m/e* 154.0994). Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>: C, 70.10; H, 9.15. Found: C, 70.22; H, 9.41. Spectral data for 3-methoxy-4,4-dimethylcyclohex-2-enone were the following: IR (neat) 2972, 2939, 2871, 1655, 1594, 1485, 1462, 1362, 1222, 1203, 1167, 1038, 1000, 988, 832 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  5.26 (s, 1 H, vinyl), 3.68 (s, 3 H, OCH<sub>3</sub>), 2.41 (t, *J* = 6.6 Hz, 2 H, C(OCH<sub>3</sub>)CH<sub>2</sub>), 1.83 (t, *J* = 6.6 Hz, 2 H, C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>), 1.20 (s, 6 H, C(CH<sub>3</sub>)<sub>2</sub>); MS *m/e* 154.0987 (calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub> *m/e* 154.0994). Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>: C, 70.10; H, 9.15. Found: C, 70.38; H, 9.25.

The assignment of regiochemistry was accomplished in a <sup>1</sup>H NMR shift reagent study of each isomer in CDCl<sub>3</sub> with tris(6,6,7,7,8,8-

**Table VI.** Chemical Shifts of Protons in 3-Methoxy-6,6-dimethylcyclohex-2-enone (**20**) as a Function of Eu(FOD)<sub>3</sub> Concentration<sup>a</sup>

proton	mole fraction of Eu(FOD) <sub>3</sub> <sup>b</sup>						
	0.00	0.13	0.236	0.354	0.444	0.569	0.671
vinyl	5.27	7.09	8.31	9.54	10.76	11.81	12.60
methoxy	3.68	3.84	3.94	4.04	4.13	4.21	4.25
C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	2.43	3.04	3.46	3.90	4.36	4.80	5.15
C(CH <sub>3</sub> ) <sub>2</sub> CH=CH	1.81	2.43	2.87	3.33	3.82	4.28	4.66
<i>gem</i> -dimethyl	1.12	2.08	2.76	3.49	4.26	4.99	5.59

<sup>a</sup>Shifts are in ppm downfield from TMS. <sup>b</sup>Relative to substrate.**Table VII.** Observed Slopes for Lanthanide-Induced Shifts for 3-Methoxy-4,4-dimethylcyclohex-2-enone (**21**) and 3-Methoxy-6,6-dimethylcyclohex-2-enone (**20**)

proton ( <b>20</b> )	slope <sup>a</sup>	proton ( <b>21</b> )	slope <sup>a</sup>
vinyl	10.93	vinyl	10.85
methoxy	0.853	methoxy	1.64
C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	4.05	$\alpha$ -methylene	11.37
C(CH <sub>3</sub> ) <sub>2</sub> CH=CH	4.25	$\beta$ -methylene	3.78
<i>gem</i> -dimethyl	6.68	<i>gem</i> -dimethyl	2.26

<sup>a</sup>Slope from plot of chemical shift vs Eu(FOD)<sub>3</sub> concentration.

heptafluoro-2,2-dimethyl-3,5-octanedionato)europium (Eu(FOD)<sub>3</sub>). For 3-methoxy-6,6-dimethylcyclohex-2-enone, a 0.166 M solution of substrate was used. For 3-methoxy-4,4-dimethylcyclohex-2-enone, a 0.175 M solution of substrate was used. The chemical shifts for each isomer as a function of mole fraction of added Eu(FOD)<sub>3</sub> are tabulated in Tables V and VI. Table VII shows observed slopes, obtained from graphs of chemical shift vs mole fraction of Eu(FOD)<sub>3</sub>, for the lanthanide-induced shifts.

Large shifts were seen for the vinyl and *gem*-dimethyl protons of 3-methoxy-6,6-dimethylcyclohex-2-enone and for the vinyl and  $\alpha$ -methylene protons of the 3-methoxy-6,6-dimethylcyclohex-2-enone, allowing assignment of regiochemistry.

**3-Methoxy-4,4-dimethylcyclohexa-2,5-dienone (22).** A mixture of 2.84 g (18.5 mmol) of 3-methoxy-4,4-dimethylcyclohex-2-enone (**21**), 5.05 g (22.3 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and 0.669 mg (3.52 mmol) of *p*-toluenesulfonic acid monohydrate was refluxed in 50 mL of anhydrous benzene for 16 h. An additional 3.24 g (14.3 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was added, and the mixture was refluxed for 47 h. The mixture was taken up in 50 mL of ether and subjected to basic-acidic workup,<sup>40</sup> followed by saturated sodium bicarbonate and brine wash. The ether layer was then dried over sodium sulfate and concentrated in vacuo to yield 2.29 g of a brown oil. Distillation afforded 1.46 g (51.4%) of 3-methoxy-4,4-dimethylcyclohexa-2,5-dienone (**22**) as a clear colorless oil, bp 67–70 °C (0.65–0.70 mmHg). The spectral data were the following: IR (CHCl<sub>3</sub>) 2975, 2942, 2246, 1658, 1590, 1225 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  6.56 (d, *J* = 9.9 Hz, 1 H, C(CH<sub>3</sub>)<sub>2</sub>CH=CH), 6.11 (dd, *J* = 9.9, 1.6 Hz, 1 H, C(CH<sub>3</sub>)<sub>2</sub>CH=CH), 5.54 (d, *J* = 1.6 Hz, 1 H, C(OCH<sub>3</sub>)CH=), 3.74 (s, 3 H, OCH<sub>3</sub>), 1.29 (s, 6 H, *gem*-CH<sub>3</sub>); MS *m/e* 152.0990 (calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub> *m/e* 152.0839).

**3-Methoxy-4,4-dimethylcyclohexa-2,5-dienone Tosylhydrazone (23).** In 18 mL of methanol were refluxed 2.26 g (14.9 mmol) of 3-methoxy-4,4-dimethylcyclohexa-2,5-dienone (**22**), 2.79 g (15.0 mmol) of tosylhydrazine, and 132 mg (0.692 mmol) of *p*-toluenesulfonic acid monohydrate for 13 h. Concentration in vacuo yielded ca. 5 g of a clear orange oil, which was chromatographed on two 4.2 × 9.0 cm silica gel columns that had been slurry packed with 5% methanol in hexane; elution with 300 mL of 10% ether in chloroform gave 1.82 g of an orange oil. Recrystallization from ethanol yielded 1.28 g (26.8%) of 3-methoxy-4,4-dimethylcyclohexa-2,5-dienone tosylhydrazone (**23**) as colorless needles, mp 171.9–173.3 °C. The spectral data were the following: IR (CHCl<sub>3</sub>) 3225, 3028, 2972, 1660, 1598, 1322, 1222, 1163 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  7.88 (d, *J* = 8.6 Hz, 2 H, arom), 7.31 (d, *J* = 8.6 Hz, 2 H, arom), 6.06 (dd, *J* = 9.7, 1.9 Hz, 1 H, C(CH<sub>3</sub>)<sub>2</sub>CH=CH), 5.92 (d, *J* = 9.7 Hz, 1 H, C(CH<sub>3</sub>)<sub>2</sub>CH=), 5.47 (d, *J* = 1.9 Hz, 1 H, C(OCH<sub>3</sub>)=CH), 3.73 (s, 3 H, OCH<sub>3</sub>), 2.42 (s, 3 H, arom CH<sub>3</sub>), 1.19 (s, 6 H, *gem*-CH<sub>3</sub>); MS *m/e* 320.1215 (calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S *m/e* 320.1196). Anal. Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S: C, 59.98; H, 6.29. Found: C, 59.77; H, 6.28.

**1,3-Dimethoxy-6,6-dimethyl-1,4-cyclohexadiene (24).** To 1.23 g (3.84 mmol) of 3-methoxy-4,4-dimethylcyclohexa-2,5-dienone tosylhydrazone (**23**) was added 0.270 g of sodium methoxide in 9.3 mL of methanol at 0 °C. The mixture was stirred at 0 °C for 2 h and then irradiated with a 75-W heat lamp for 2 days. Neutral workup<sup>40</sup> with pentane yielded

0.577 g of a yellow oil, which was distilled to yield 0.403 g (62.5%) of 1,3-dimethoxy-6,6-dimethyl-1,4-cyclohexadiene (**24**) as a clear colorless oil, bp 29–31 °C (0.75 mmHg). The spectral data were the following: IR (CHCl<sub>3</sub>) 2967, 2938, 1681, 1658, 1471, 1358, 1214, 901 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 5.73–5.64 (m, 2 H, CH=CH), 4.66, 4.65 (2 s, 2 H, vinyl, methine), 3.59 (s, 3 H, CH=C(OCH<sub>3</sub>)), 3.23 (s, 3 H, CH(OCH<sub>3</sub>)), 1.19 (s, 3 H, *gem*-CH<sub>3</sub>), 1.14 (s, 3 H, *gem*-CH<sub>3</sub>); MS *m/e* 168.1152 (calcd for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub> *m/e* 168.1151). Anal. Calcd for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>: C, 71.39; H, 9.59. Found: C, 71.79; H, 9.59.

**Reductive Cleavage of 3-Methoxy-6,6-dimethyl-1,4-cyclohexadiene (14) in Sodium/Liquid Ammonia.** A solution of 404 mg (2.93 mmol) of 3-methoxy-6,6-dimethyl-1,4-cyclohexadiene and 0.606 mL (480 mg, 6.38 mmol) of *tert*-butyl alcohol-*O-d*<sub>1</sub> (90.7% D by <sup>2</sup>D NMR analysis) was allowed to equilibrate in 5.0 mL of anhydrous ammonia and 0.50 mL of anhydrous ether for 30 min at -78 °C. Sodium metal (146 mg, 6.35 mmol) was added in small pieces over a period of 17 min. Ammonium chloride (0.46 g, 8.5 mmol) was added to quench alkoxides, followed by the cautious addition of 15 mL of water. Neutral workup<sup>40</sup> with pentane and careful distillation (*T* < 36 °C) of pentane yielded 3,3-dimethyl-1,4-cyclohexadiene (**26**) as a pale yellow solution in pentane. Generally this material was not purified further before <sup>2</sup>D NMR analysis, but could be by trap-to-trap distillation from room temperature to -78 °C to yield 0.275 g (87.0%) of 3,3-dimethyl-1,4-cyclohexadiene (**26**) as a clear colorless oil, bp 111.5 °C (lit.<sup>18</sup> bp 110–113 °C).

<sup>2</sup>D NMR analysis indicated that deuterium had been incorporated only at the methylene position and that the amount of deuterium incorporation in **26** was 0.10 ± 0.01% (average of three runs). For reduction runs at -33 °C, <sup>2</sup>D NMR analysis indicated that the amount of deuterium incorporation in **26** was 0.14 ± 0.01% (average of two runs).

**Birch Reduction of Benzene.** Reduction at -78 °C with sodium and *tert*-butyl alcohol-*O-d*<sub>1</sub> afforded only 1,4-cyclohexadiene;<sup>50</sup> spectral data were identical to those previously recorded.<sup>51</sup> <sup>2</sup>D NMR indicated that deuterium had been incorporated only at the methylene positions and that the amount of deuterium incorporated in 1,4-dihydrobenzene was 0.13 ± 0.00% (average of two runs).

**Reductive Cleavage of 2,3-Dimethoxy-6,6-dimethyl-1,4-cyclohexadiene (18) in Sodium/Liquid Ammonia.** A solution of 0.498 g (2.96 mmol) of 2,3-dimethoxy-6,6-dimethyl-1,4-cyclohexadiene and 0.697 mL (0.550 g, 7.33 mmol) of *tert*-butyl alcohol-*O-d*<sub>1</sub> (90.7% D by <sup>2</sup>D NMR analysis) was allowed to equilibrate in 5.0 mL of anhydrous ammonia and 0.50 mL of anhydrous ether for 20 min at -78 °C. Sodium metal (164 mg, 7.13 mmol) was added in small pieces over a period of 15 min. Ammonium chloride (0.43 g, 8.1 mmol) was added to quench alkoxides, followed by the cautious addition of 5.0 mL of water. Neutral workup<sup>40</sup> with pentane and careful distillation (*T* < 36 °C) of pentane yielded 1-methoxy-3,3-dimethyl-1,4-cyclohexadiene as a pale yellow solution in pentane, which was generally analyzed by <sup>2</sup>D NMR without further purification. However, pure material could be obtained by distillation to yield 0.250 g (61.3%) of 1-methoxy-3,3-dimethyl-1,4-cyclohexadiene (**28**) as a clear colorless oil, bp 35–40 °C (11 mmHg). Spectral data were the following: IR (neat) 3022, 2952, 2899, 1689, 1685, 1467, 1377, 1226, 1147, 1031 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 5.60–5.44 (m, 2 H, CH=CH), 4.49 (s, 1 H, C(OCH<sub>3</sub>)=CH), 3.54 (s, 3 H, OCH<sub>3</sub>), 2.66 (bs, 2 H, CH<sub>2</sub>), 1.08 (s, 6 H, *gem*-CH<sub>3</sub>); MS *m/e* 138.1042 (calcd for C<sub>9</sub>H<sub>14</sub>O *m/e* 138.1046). Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O: C, 78.21; H, 10.21. Found: C, 77.99; H, 10.15.

<sup>2</sup>D NMR analysis indicated that deuterium had been incorporated only at the methylene position and that the amount of deuterium incorporation in **28** was 0.21 ± 0.01% (average of two runs).

**Reductive Cleavage of 1,3-Dimethoxy-6,6-dimethyl-1,4-cyclohexadiene (24) in Sodium/Liquid Ammonia.** A solution of 281 mg (1.67 mmol) of 1,3-dimethoxy-6,6-dimethyl-1,4-cyclohexadiene and 0.346 mL (273 mg, 3.90 mmol) of *tert*-butyl alcohol-*O-d*<sub>1</sub> (90.7% D by <sup>2</sup>D NMR analysis) was allowed to equilibrate in 4.0 mL of anhydrous ammonia and 0.40 mL of anhydrous ether for 30 min at -78 °C. Sodium metal (81.1 mg, 3.53 mmol) was added in small pieces over a period of 8 min. Ammonium chloride (0.25 g, 4.7 mmol) was added to quench alkoxides, followed by the cautious addition of 10 mL of water. Neutral workup<sup>40</sup> with pentane and careful distillation (*T* < 36 °C) of pentane yielded 0.275 g of 1-methoxy-6,6-dimethyl-1,4-cyclohexadiene as a clear yellow oil, which was generally analyzed by <sup>2</sup>D NMR without further purification. However, pure material could be obtained by trap-to-trap distillation from room temperature to -78 °C at 5 mmHg to afford 106 mg (46.1%) of 1-methoxy-6,6-dimethyl-1,4-cyclohexadiene (**30**) as a clear colorless oil, bp 20–22 °C dec (11 mmHg). Spectral data were the following: IR (neat) 2962, 2944, 2902, 2829, 1685, 1648, 1472, 1356, 1208, 1164, 722 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 5.68–5.38 (m, 2 H, CH=CH), 4.54 (t, *J* = 3.2 Hz, 1 H, C(OCH<sub>3</sub>)=CH), 3.52 (s, 3 H, OCH<sub>3</sub>), 2.79–2.75 (m, 2 H, CH<sub>2</sub>), 1.14 (s, 6 H, *gem*-CH<sub>3</sub>); MS *m/e* 138.1042 (calcd for C<sub>9</sub>H<sub>14</sub>O *m/e* 138.1045). Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O: C, 78.21; H, 10.21. Found: C, 78.49; H, 10.09.

<sup>2</sup>D NMR analysis indicated that deuterium had been incorporated only at the methylene position and that the amount of deuterium incorporation in **30** was 0.49 ± 0.05% (average of three runs).

**General Procedure for Allylic Deuterium Exchange Studies on Undeuterated Dienes.** To 1 mmol of undeuterated diene in 2.0 mL of anhydrous ammonia and 0.20 mL of anhydrous ether at -78 °C was added 0.283 g (2.52 mmol) of potassium *tert*-butoxide and 0.114 mL (90.0 mg, 1.20 mmol) of *tert*-butyl alcohol-*O-d*<sub>1</sub> (90.7% D by <sup>2</sup>D NMR). The mixture was stirred at -78 °C for 2 h. Water (10 mL) was then added, followed by neutral extraction<sup>40</sup> with ether or pentane. Removal of solvent yielded diene, which was analyzed by <sup>2</sup>D NMR without further purification.

For all dienes tested (2,5-dihydroanisole (**12-H**), 1,4-dihydro-2-methoxynaphthalene (**36**), 1,4-dihydro-2-methoxynaphthalene (**37**), 3,3-dimethyl-1,4-cyclohexadiene (**26**), 1-methoxy-3,3-dimethyl-1,4-cyclohexadiene (**28**), and 1-methoxy-6,6-dimethyl-1,4-cyclohexadiene (**30**)) no deuterium incorporation was detected by <sup>2</sup>D NMR.

**Quantum Mechanics Calculations.** The quantum mechanics calculations were performed using the GAUSSIAN92,<sup>28a</sup> GAUSSIAN90,<sup>28b</sup> or GAMESS<sup>28c</sup> programs with geometry optimization unless otherwise specified. Initial geometries were obtained with the MOPAC<sup>52</sup> package using the MNDO<sup>53</sup> or MINDO/3<sup>52</sup> approximation. For the 2-methoxynaphthalene radical calculations, MINDO/3 was used. For the two states of the toluene radical anion, initial geometries were the INDO-optimized geometries reported in the literature.<sup>31a</sup> For calculations on the toluene radical anion-water and toluene radical anion-proton approach complexes, the toluene ring carbon framework was restricted to a planar conformation.

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