glutamine residues. Measurements were carried out with a protein concentration of 3 mM at pH 5.5 and 313 K. During relaxation, the solvent resonance was saturated by low-power excitation. The GARP decoupling scheme[8] was employed during acquisition. Approximately 4 W decoupling power at 50.68 MHz resulted in a $\pi/2$ pulse length of 200 μs. The total acquisition time for the $^{15}\mathrm{NH}_2$-edited spectrum was 6 h, using an extended 64-step phase cycle.

Figure 2A shows the spectral region of the selected amide correlations. A reference spectrum of all backbone and side-chain amide resonances (Figure 2B) was recorded according to the procedures of Bax et al.[9] An expansion (Figure 2C) reveals all 11 of the expected NH_2 correlations. In the arginine side chain, the protons undergo rapid exchange at the chosen temperature;[10] therefore, they did not give rise to signals.

Of the few proton resonances in RNase T_1 not yet assigned,[11] the asparagine residues in positions 36, 43, 44, 98, and 99 are of particular interest as they are located close to the active site. Their NH_2 groups may be used as local spies for the investigation of base recognition and catalysis by means of NMR techniques. The addition of NOE or ROE transfer steps to the pulse sequence could eventually allow tracing of the connectivities to the carbon-bound protons of the amino acid side chains. The usefulness of this method for complete assignment of proton resonances in RNase T_1 is currently under investigation in our laboratory.

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Regioselectivity of the Birch Reduction

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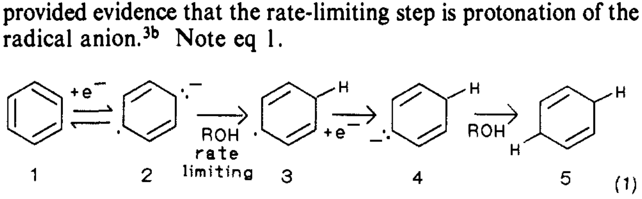
The Birch reduction[1] is one of the most fundamental reactions in organic chemistry. It is known[2] that the reaction proceeds via (a) radical anion formation, (b) protonation by an alcohol, (c) addition of a second electron, and (d) protonation of the resulting cyclohexadienyl carbanion. In 1959 Krapcho and Bothner-By[3a] provided evidence that the rate-limiting step is protonation of the radical anion.[3b] Note eq 1.

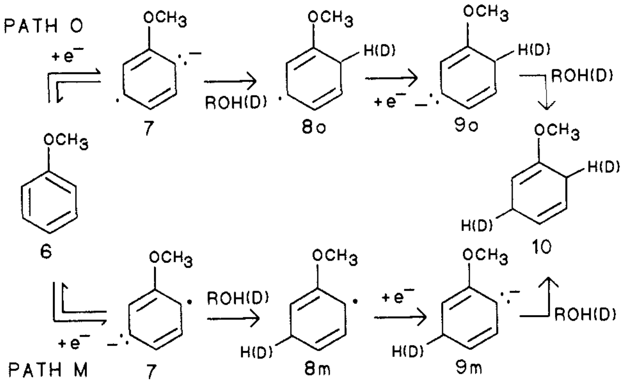


The regioselectivity follows the Birch rule that the 1,4-dihydrobenzene formed is the isomer having the maximum number of alkoxyl and/or alkyl groups on the residual double bonds. One rationale for this orientation was presented nearly three decades ago.[4] This suggested that there was preferential ortho protonation of the radical anion as the site of the highest electron density, based on Hückel calculations. Anisole is an example that has been the object of particular debate. Whether the initial protonation is ortho or meta has been subject to an unusual variation of viewpoints and speculation as summarized in Table I. In this communication, we report the first experimental test of the initial protonation site in the Birch reduction of anisole.

Table I. Literature Conclusions Regarding Regioselectivity of Protonation of the Radical Anion in the Birch Reduction of Anisole

suggested preference	basis	ref
meta	qual mechanistic	1959[2]
meta	qual mechanistic	1959[3]
ortho	Hückel QM	1961[4]
meta	qual mechanistic	1963[5]
none	ESR spin density	1966[6]
meta	SCF QM	1969[7]
ortho	SCF QM	1980[8]

Scheme I. Two Alternative Regioselectivities for the Reduction of Anisole



Our research began with and relies on the *premise that the isotope selectivity in a protium–deuterium medium will be greater for a radical anion such as 7 than a carbanion such as 9*. Since radical anions are known to be considerably less basic and reactive species than carbanions,[9] their protonation consequently will be less exothermic and more selective. Scheme I shows the two potential pathways for the reduction of anisole.

We studied the Birch reduction of anisole in a sodium–liquid ammonia–*tert*-butyl alcohol medium enriched in deuterium. Due to kinetic isotope effects of our original premise, we anticipated that the product site with less deuterium content would be the carbon protonated in the radical anion protonation step. Conversely, the site with greater deuterium should be the one protonated as a nonselective carbanion reacting in a less selective process.

The anisole reduction was run at −78 °C with sodium in liquid ammonia and *tert*-butyl alcohol containing ca. 2% deuterium. The ratio of *m*- to *o*-deuterium content in the 2,5-dihydroanisole product was determined by deuterium NMR analysis utilizing the $\mathrm{Pr(fod)_3}$ shift reagent to separate methylene absorption peaks.

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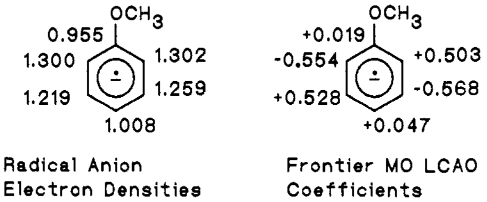

Figure 1. Total radical anion electron densities and frontier MO coefficients for the anisole radical anion.

The ratio of *m*- to *o*-deuterium content (i.e., $D_m:D_o$) was found to be 6.98 ± 0.67, thus establishing that the greater selectivity was at the ortho site. Hence we can conclude that the initial protonation in the Birch reduction of anisole occurs preferentially at the ortho carbon.

An alternative approach to this conclusion is algebraic. Equation 2a states that the sum of hydrogen and deuterium content accumulated in the ortho position in protonation step 1 (i.e., of radical anion **7**) is equal to the sum accumulated at the meta site in protonation step 2 (i.e., of carbanion **9o**); note path O in Scheme I. In parallel, eq 2b deals with the path M process

$$H_1^{o} + D_1^{o} = H_2^{m} + D_2^{m} \qquad H_1^{m} + D_1^{m} = H_2^{o} + D_2^{o} \qquad \text{(2a,b)}$$

in Scheme I. The isotope selectivities at each site in each step are given in the following four equations, where the *R* selectivities are those encountered in the radical anion protonation, and the *C* selectivities, in the final, cyclohexadienyl carbanion protonation:

$$R_o = H_1^{o}/D_1^{o} \qquad R_m = H_1^{m}/D_1^{m} \qquad \text{(3a,b)}$$

$$C_o = H_2^{o}/D_2^{o} \qquad C_m = H_2^{m}/D_2^{m} \qquad \text{(3c,d)}$$

These equations are utilized to eliminate the *H* terms in eqs 2a and 2b. Additionally, eq 4a and 4b give the total deuterium contents at the ortho and meta positions acquired in the two protonation steps. These are used to eliminate the terms D_2^{o} and

$$D_o = D_1^{o} + D_2^{o} \qquad D_m = D_1^{m} + D_2^{m} \qquad \text{(4a,b)}$$

D_2^{m} in eq 2a and 2b. This leads to eq 5, which gives the regioselectivity, *W*, in the initial radical anion protonation.

$$W = \frac{D_1^{o}}{D_1^{m}} = \frac{(C_m + 1)[(R_m + 1)D_m - (C_o + 1)D_o]}{(C_o + 1)[(R_o + 1)D_o - (C_m + 1)D_m]} \qquad (5)$$

One might anticipate that the deuterium versus hydrogen selectivity in the radical anion protonation would be relatively independent of position, and the same should be true for the carbanion protonation. With this assumption that $C_m = C_o = C$ and $R_m = R_o = R$, we obtain the simpler expression 6. Both expressions 5 and 6 prove useful in providing the desired ortho to meta regioselectivity, *W*, in the initial, radical anion protonation.

$$W = \frac{D_1^{o}}{D_1^{m}} = \frac{(R + 1)D_m - (C + 1)D_o}{(R + 1)D_o - (C + 1)D_m} \qquad (6)$$

With the experimental finding that $D_m > D_o$ (i.e., 6.98:1) and the original premise that $R > C$, we conclude from eq 6 that *W*, the ortho to meta radical anion protonation ratio, is greater than unity.

Further, eq 6 reveals that as the relative isotope selectivity of the radical anion protonation increases (i.e., $R \gg C$), the ortho to meta selectivity *W* of the radical anion protonation reaches a lower limit of 6.98 (i.e., D_m/D_o).

Interestingly, an ab initio ROHF/6-31G//STO-3G computation (note Figure 1) proved to be in qualitative agreement with the early Huckel calculations published[4a] in which we noted that the site ortho to the maximum number of alkoxy groups is most electron rich.[10] It is particularly noteworthy that the frontier MO has its highest density at the meta site and thus is not controlling protonation.

We are continuing our research on the regioselectivity of radical anion protonation in the Birch reduction with the aim of further dissecting the two protonation steps and assessing the validity of the original premise.

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Registry No. Anisole, 100-66-3; anisole radical anion, 34519-87-4.

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[10] Note also SCF computations in ref 8.

Photocycloaddition of Benzaldehyde to Cyclic Olefins: Electronic Control of Endo Stereoselectivity

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The Paternò–Büchi reaction[1] of aliphatic and aromatic carbonyl compounds with electron-rich alkenes has been shown to be an effective and versatile method for the generation of polyoxygenated and hydroxylated molecules (e.g., photo aldol reaction,[2] asymmetric induction[3]). In cases where the starting materials were acyclic olefins, only moderate regio- and stereoselectivity could be observed.[4] For reactions with electronically excited carbonyl compounds in their triplet states (aromatic ketones, aldehydes, esters), the exciplex model can be useful to explain low regiocontrol,[5] whereas the low stereoselectivity is due to bond rotation at the triplet biradical stage.[6] These triplet biradicals have been shown to be relevant intermediates in trapping experiments,[7] spectroscopy,[8] and independent generation.[9] Whereas the lifetime of these species is rather low (1–5 ns[8,10]) compared to that of their hydrocarbon analogues (50–200 ns[10]), bond rotation is fast enough to lead to stereorandomization. As we have previously shown,[11]

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