π-Acceptor Induced Reactions: Radicals vs. Ions in Thermally Induced Ether Cleavage Reactions[']

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Abstract. The reactions of benzyl ether (1a) and 4,4'-dicyanobenzyl ether (1b) with a wide range of π-acceptors in acetonitrile at 190°C have been studied. The π-acceptors were chosen in order to systematically vary the ΔG° for hydride or electron transfer from the ethers to the π-acceptors. The products of thermal activation of the bond cleavage reaction are the aldehyde and the alcohol derived from the starting ethers. A linear free energy correlation of the relative thermal reaction rates of 1a and 1b with the reduction potentials of the quinones was obtained. This relationship indicates that the rate of radical pair separation becomes increasingly important relative to the rate of the second electron transfer and subsequent product formation through the hydride transfer intermediate as the electron affinity of the quinone decreases.
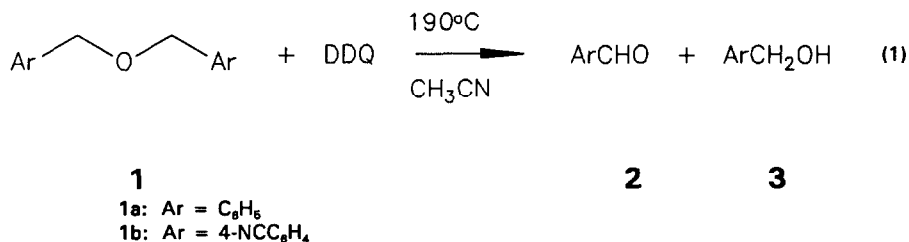
INTRODUCTION

The reactions of quinones in oxidation reactions[1] and dihydroquinones in reduction reactions[2] have attracted a great deal of attention in recent years because of the role of the redox reactions of these quinones in a variety of biochemical electron transport reactions including the conversion[3] of NADH to NAD^{+}, photosynthetic reactions,[4] and the reduction of cytochrome c.[5] A central question in the oxidation reactions by quinones has involved the timing of the transfer of the various parts of the hydride species to the quinone. In particular, this question concerns whether the transfer of hydride occurs in a single step,[6,7,8,9,10,11,12,13] or by an ECE mechanism consisting of discrete electron transfer and chemical steps.[14,15,16,17,18,19,20,21]

In connection with our studies related to cleaving bonds which may be found in the coal polymer, we have previously shown that quinones are capable of initiating various bond cleavage reactions. The reaction of benzyl ether (1a) or 4,4'-dicyanobenzyl ether (1b) with 2,3-dichloro-5,6-dicyanoquinone (DDQ) is shown in equation (1) and is representative of our work to date.[22,23,24] With this highly electron deficient quinone, the bond cleavage reaction of 1 occurs through a rate-determining hydride transfer to yield an aldehyde (2) and an alcohol (3). Interestingly, this reaction was shown to result in the formation of the same reactive intermediates from either thermal or photochemical excitation.[23]
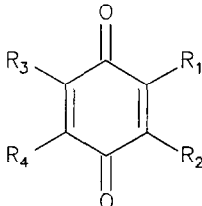
The hydride transfer mechanism advocated for eq (1) is only one mechanistic extreme in the more general ECE mechanism involving sequential electron transfer, chemical reaction, and electron transfer steps.[23] For a thermally initiated reaction, the mechanistic distinction between the ECE mechanism and a radical pathway or a hydride transfer arises from the point of entry onto the potential energy surface. Reactivity may arise from a radical cation-quinone radical anion ion pair (RCIP), a radical pair (*i.e.*, the radical-semiquinone radical pair, RP), or a carbocation-semiquinone anion ion pair (CCIP), depending on whether a single electron, a hydrogen atom, or a hydride has been transferred from the substrate to the quinone. Although we have described this reaction as occurring through an ECE reaction mechanism, the alternative views

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['] This manuscript is dedicated to Professor Gabor Fodor on the occasion of his 75th birthday.

of this reactivity originating in many laboratories suggests that definitive evidence requiring an ECE description of this particular reaction has not been provided to date.

$$Ar\diagup O \diagdown Ar \ + \ DDQ \ \xrightarrow[CH_3CN]{190^\circ C} \ ArCHO \ + \ ArCH_2OH \quad (1)$$

1　　　　　　　　　　　　　　　**2**　　**3**

1a: Ar = C_6H_5
1b: Ar = 4-NCC_6H_4

In order to probe the existence of an ECE mechanism in this reaction, we desired to change the relative energetics of RP relative to CCIP. By making RP energetically favorable relative to CCIP, differing product ratios or relative reaction rates might be observable as the reaction mechanism changed from a regime dominated by hydride transfer to a regime dominated by radical pair reactivity as a molecular property of one of the reaction partners is changed systematically. In our systems, a systematic change in molecular property is readily accomplished through systematic changes in the structure of the quinones utilized to initiate the bond cleavage reaction. The quinones used in this study are shown in Scheme 1 together with their well-known one electron reversible reduction potentials. Although the reversible electrode potentials for the transfer of an electron to the substituted semiquinone radicals (and therefore, the energetics of hydride transfer) are not known explicitly in acetonitrile solution, a correlation of the energetics of this electron transfer process with the energetics of the E_r° values shown in Scheme 1 is reasonably expected.[20] Since the variation in one electron electrode potentials of these quinones extend over a 1.18 V range (≈ 27 kcal/mole), a large differential driving force may be expected in reactions employing these quinones.
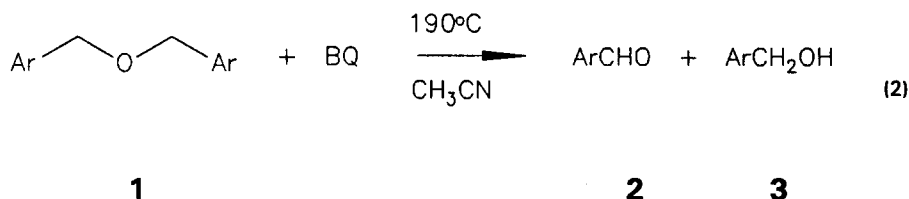
Quinone	R_1	R_2	R_3	R_4	$E_R^{\circ\ \bullet}$ (V vs SCE)[26]
DDQ	Cl	Cl	CN	CN	0.51
TCBQ	Cl	Cl	Cl	Cl	0.01
DCBQ	Cl	Cl	H	H	-0.18
BQ	H	H	H	H	-0.51
DMBQ	CH_3	H	CH_3	H	-0.67

Scheme 1

Our test for the existence of radicals in this reaction utilized benzyl ether (1a) and 4,4'-dicyanobenzyl ether (1b) as substrates. Cyano-substitution on the benzylic radical would stabilize the radical pair relative to the unsubstituted system. Therefore, if the rate of the second electron transfer is slowed relative to the rate of radical pair separation yielding radicals as the important reactive intermediates, then 1b should react at a faster rate than 1a. Conversely, if the carbocation ion pairs arising from hydride transfer are the most important intermediates, then cyano substitution should destabilize the carbocation relative to the unsubstituted carbocation. In this case, 1a should react faster than 1b. We report here our studies of the relative reactivities of these benzyl ethers as a function of quinone structure.

RESULTS

Bond Cleavage Reactions of Benzyl Ether and 4,4'-Dicyanobenzyl Ether; Product Identification: Our techniques for accomplishing thermal activation of chemical reactivity by π-acceptors have been previously described.[22-24] In brief, samples are dissolved in freshly distilled acetonitrile and placed into base washed tubes.[25] After several cycles of freeze-pump-thaw degassing, the tubes are sealed and placed in a thermostatted oil bath at the indicated temperature. Using this technique, we have found that the bond cleavage of benzyl ether (**1a**) and 4,4'-dicyanobenzyl ether (**1b**) can be induced by all of the π-acceptors shown in Scheme 1. Control experiments showed that no bond cleavage reactions occurred on the time scale of these experiments, unless the quinone was added to the reaction solution. The products of the DDQ induced reactions have been· previously determined.[23] In order to verify that the reactivity does not change as a function of the quinone structure, careful quantitative analyses of the reaction products were performed for the BQ initiated reactions of **1a** and **1b** (Table I). In addition to the reasonably good mass balance indicated in Table I, trace amounts ($\leq 3\%$) of bibenzyl or 4,4'-dicyanobibenzyl could be detected by GCMS analysis of the reaction mixture. These analyses were performed at low conversions in order to minimize the amount of secondary reactions and were unaffected by whether the analysis was performed by GC or HPLC. In all cases, the products can be quantitatively accounted for by compounds **2** and **3**. Residual water in the CH$_3$CN solution is responsible for the excess oxygen in **2** and **3** as we have already shown in the DDQ-induced bond cleavage reactions of **1**.[22] The residual water results from the fact that CH$_3$CN is well-known to be difficult to dry completely. The yields of **2** are larger than the yields of **3** and are larger than 100%, since **3** reacts faster than **1** under these reaction conditions.[23] The reactions of **1b** are similar to the reactions of **1a**. We conclude that the reaction pathway is independent of the quinone structure as the quinone is changed from the highly electron deficient DDQ to the moderately electron deficient BQ (Note eq (2)).

$$\text{Ar}\diagup\diagdown\text{O}\diagup\diagdown\text{Ar} \;+\; \text{BQ} \quad\xrightarrow[\text{CH}_3\text{CN}]{190^\circ\text{C}}\quad \text{ArCHO} \;+\; \text{ArCH}_2\text{OH} \tag{2}$$

1   **2**   **3**

Table I. Quantitative Analysis of **1a** and **1b** Bond Cleavage Reactions

Ethers	Temp. (°C)	Time (h)	π-Acceptor	Yield (mole%)	
				2	**3**
1a[a]	190	2	DDQ[c]	142	55
	190	24	BQ	136	72
1b[b]	190	4	DDQ[c]	139	55
	190	24	BQ	112	82

a) Method of Analysis GC; b) Method of Analysis HPLC; c) From Reference 23.

Absolute Reaction Rates: The absolute reaction rate for the DDQ-induced bond cleavage of 1a at 190°C was measured by determining the concentration of 1a as a function of time. As can be seen in Figure 1, the reaction rate falls off with time due to secondary reactions of DDQ and 3a. Thus, the reaction rate was determined only from the initial slope. In a similar fashion, the rate of the bond cleavage reaction of 1b initiated by DDQ was measured from the initial slope. Due to the slower reaction, the fall-off in reaction rate was not observed. These data are also shown in Figure 1. The rate constants measured from these data as well as estimates of the minimum reaction rate without added quinone are given in Table II. The bond cleavage reaction rates of 1a and 1b as initiated by BQ were determined from the data shown in Figure 2. These reactions are much slower than the corresponding reactions initiated by DDQ, in agreement with previously observed reactivity patterns of quinones.[27],[28] The rates of the DMBQ-induced reactions were of particular interest because of the reversal in relative reaction rates (*vide infra*). For this purpose, the data for absolute rate determinations are shown in Figure 3.

Table II. Absolute Rate Constants Measured in this Study[a]

Ether	Q	k_{obs} (M^{-1}s^{-1})
1a	DDQ	0.24
	BQ	5.8×10^{-6}
	DMBQ	2.3×10^{-4}
	[b]	$\leq 3.8 \times 10^{-6}$
1b	DDQ	8.3×10^{-3}
	BQ	4.2×10^{-6}
	DMBQ	2.8×10^{-4}
	[b]	$\leq 4.0 \times 10^{-6}$

a) Error limits are ±10%.
b) No quinone added.

Relative Thermal Reactivity of 1a and 1b: As a further check of the data obtained above, the relative thermal bond cleavage rates of 1a and 1b as a function of each quinone were measured by competition experiments in which equimolar ratios of 1a and 1b were reacted together in sealed tubes as previously described. The relative reaction rates were calculated by comparison of the amounts of each compound reacted. A minimum of three conversion amounts were examined for each quinone with excellent agreement of the relative rate ratios for each conversion amount. These data are gathered in Table III. Also gathered in Table III are data which can be calculated from the absolute rate data which was previously recorded in Table II. As can be seen from Table III, the relative rate ratios for the reactions of 1a and 1b are in excellent agreement with the relative rates determined by direct measurement. We conclude that the relative thermal reaction rates are independent of the method used for their determination.

DISCUSSION

Energies of Potential Reactive Intermediates: In an earlier paper,[23] we have shown how it is possible to obtain a qualitative estimate of the radical pair energies (formed from transfer of a hydrogen atom from the ether to the π-acceptor) and the carbocation ion pair energies (formed from transfer of a hydride to the π-acceptor). A brief summary of the methodology follows. The energies of the RCIPs are derived from the one electron redox potentials of 1 (calculated from the oxidation potential of methylarenes as previously described[23]) and Q (the experimentally determined reduction potential of the quinones[26]). The energies of the radical intermediates of 1a and BQ are calculated from a thermodynamic cycle using standard $\Delta H_f°$ values and bond dissociation energies (BDE).[23] The RP energies of other quinones can be calculated relative to BQ from data given by Rich[29] and are seen to be relatively unaffected by the substituents on the quinone. The CCIP energies are calculated relative to the RP energies, assuming that the relative energetics of the second electron

Table III. Relative Reaction Rates (k_{1a}/k_{1b}) at 190°C

π-acceptor	k_{1a}/k_{1b}[a]	k_{1a}/k_{1b}[b]
DDQ	26.8	28.9
TCBQ	6.9	-
DCBQ	4.6	-
BQ	1.4	1.4
DMBQ	0.9	0.82

[a] Measured directly by the reaction of equimolar amounts of 1a and 1b.
[b] Calculated from the data presented in Table II.

transfer are identical to the relative energetics of the first electron transfer. We emphasize that these energies are only qualitative estimates due to the assumptions that were made to derive these numbers.[30] These energies are gathered in Table IV.

The reason for determining these qualitative energetics is to make predictions as to the most stable intermediate which may be observed under the reaction conditions. These estimates predict that the CCIP is more energetically favorable than RP in CH_3CN for BQ and those quinones which are more electron deficient than BQ. In contrast, the DMBQ RP and the CCIP are energetically similar within the limits of the assumptions used to derive these energies.

The relative energies of the cyano substituted intermediates are more difficult to determine precisely. However, if normal substituent parameters can be used to estimate the magnitude of the stabilization or destabilization of a certain substituent, then the effect of cyano on the energy of the 1b CCIP may be estimated to result in a minimum of 3.3 kcal/mole destabilization of the CCIP relative to the 1a CCIP for each quinone used in this study.[31] An energy stabilization of 0.8 kcal/mole for the RPs is estimated in a similar fashion using Creary's $\sigma^{\bullet}$ scale.[32] The important point for the analysis given below is that the energies of the 1b RPs should be somewhat lower in energy than the 1a RPs, while the 1b CCIPs should be somewhat greater in energy than the 1a CCIPs.

On the basis of energetics alone, we conclude that reactions initiated by single electron transfer (SET) to form the RCIP are unable to account for the observed reactivity. For example, the reaction of 1a initiated by BQ is predicted to be ca. 64 kcal/mole endothermic. The calculated energies of RP and CCIP are much lower than the RCIP energy for all acceptors. The lowest energy RCIP is that arising from DDQ which we have previously shown to undergo reaction through the CCIP.[23] Therefore, the bond cleavage reactions of 1 must proceed through entry onto the reaction coordinate at either RP or CCIP.

Relative Thermal Reaction Rates: As can be seen in Table III, the relative rate ratio for the reactions of 1a and 1b show a systematic variation relative to E_R° of the quinones. For DDQ which has an extremely low reduction potential, a high rate of reaction of 1a relative to 1b was obtained. This clearly indicates a strong preference for reaction through the CCIP (i.e., the hydride transfer pathway). In contrast, 1b reacts faster than 1a when the reaction is initiated by
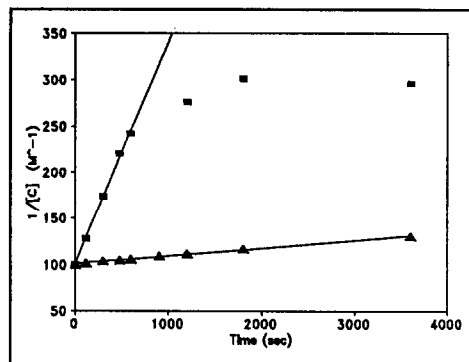

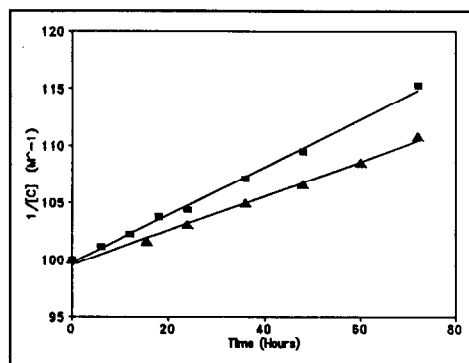Figure 1. Bond Cleavage Reaction Rates of 1a (■) and 1b (▲) Initiated by DDQ

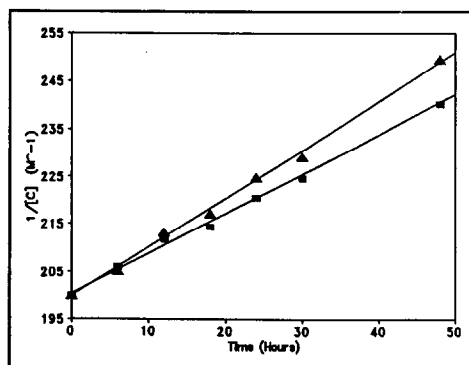Figure 2. Bond Cleavage Reaction Rates of 1a (■) and 1b (▲) Initiated by BQ

Figure 3. Bond Cleavage Reaction Rates of 1a (■) and 1b (▲) Initiated by DMBQ

DMBQ. In this case, the reaction pathway is predominately shifted to radical pair reactivity. In accord with this finding, trace amounts of bibenzyl and 4,4'-dicyanobibenzyl were found in the reaction mixtures initiated by BQ and DMBQ. The switch to radical reactivity is in exact agreement with our qualitative energetic picture, where the 1a/DMBQ CCIP is predicted to be energetically similar to the 1b/DMBQ radical pair energy. We find the agreement of the qualitative energetics and the observed kinetics to be surprisingly good and strongly supports our usage of these energetics to predict reactivity in these systems.

In Figure 4, the relative reaction rates of 1a and 1b are plotted as a function of the $E_R°$ of the quinones. The strong correlation of the relative reaction rates with the one electron reduction potential of the π-acceptor indicates that a linear free energy relationship of the relative

Table IV. Estimated Energies of 1a Geminate Pair Intermediates

Q	Energy (kcal/mole)		
	RCIP ($1a^{•+}/Q^{•-}$)	RP	CCIP
DMBQ	68	34	32
BQ	64	34	28
DCBQ	56	34	20
TCBQ	52	34	16
DDQ	39	34	7

reaction rates with the quinones exists. This does not imply reactivity through the CCIP, but is merely a reflection of the correlation of the hydride transfer energies with one electron reduction potentials of the quinone, since other molecular properties (e.g., QH⁻ energies) may correlate to this particular molecular property.[20] This correlation only applies to the relative reaction rates of 1a and 1b since the absolute reaction rates of 1a and 1b as given in Table II clearly show that the reactions initiated by BQ are a minimum value for the quinone induced reactions. The observation of a linear free energy relationship for the relative reaction rates and the reversal of absolute reactivity data supports our overall contention that the reaction will switch from an overall hydride transfer mechanism to a radical pair dominated mechanism when the relative energetics of the reaction become favorable.

A final point regarding our assertion that the reaction proceeds primarily through radical pair reactivity for DMBQ-initiated reactions concerns the identity of the product structures. Both 2 and 3 appear to arise from a full hydride transfer mechanism. For a reaction arising from the hydrogen radical abstraction from 1, 2 and a benzyl radical may be expected to arise from a thermally activated radical cleavage pathway.[33] As indicated above, ≤5% of the product (i.e., bibenzyl or 4,4'-dicyanobibenzyl) is observed to originate from products of the benzyl radical. A rate constant of ca. 10^5 s⁻¹ may be estimated for the production of benzyl radical from the activation parameters previously determined for this radical cleavage pathway. An alternative reaction of the initially formed radical is oxidation by a second molecule of quinone in the solution. The thermodynamics of this reaction may be estimated by consideration of the oxidation potential of the radical and the reduction potential of the quinone and is estimated to be +8.8 kcal/mole. Since this reaction is estimated to be endothermic for both BQ and DMBQ, the overall rate of oxidation of the radical by additional quinone must be ≥10^7 s⁻¹ based on a quinone concentration of 0.01 M and standard Eyring parameters. We conclude that the observation of products resulting from hydride transfer does NOT rule out reactions originating from radical species.

We believe that the linear free energy relationship obtained here will help to facilitate rational discussion of the ECE mechanism[14-21] vs hydride transfer mechanism[6-13] question in biological systems. We suggest that the differentiation of the radical and the hydride transfer mechanisms is simply a function of the relative reaction rates of cage separation of the radical pair and of the electron transfer event within the radical pair. Using this viewpoint, a detailed understanding of the relative importance of the ECE mechanism and the hydride transfer mechanism will require knowledge of the energetics of the radical pair and the ion pair AND will also require knowledge of the ability of the radical pair to separate.

The studies reported in this paper have been carried out at a relatively high temperature. The high temperature condition favors both the cage separation of the radicals and the equilibration of the radical pair/ion pair through electron transfer, allowing for a clearer interpretation of experimental results. In contrast, biological systems, where reactions take place at lower temperatures, and potentially within the confines of enzymatic cavities, may operate with different limitations. Experiments in our laboratory using photochemical excitation of the quinones to generate these reactive intermediates in close proximity to each other support the view that temperature plays a critical role in establishing the reaction products by changing the mechanism. We conclude that the high temperature conditions and the systematic variation of molecular properties described here may serve as a limiting situation to assist in the elucidation of the ECE vs hydride transfer mechanism debate.

Figure 4. Relative Rates of 1a and 1b as a Function of Quinone $E_R°$

Summary: Changes in the reduction potential of the quinone structure can change the reaction mode from predominant reaction through a hydride transfer mechanism to a radical initiated mechanism. The change in reaction mechanism will occur near to the point at which the redox couple for the second electron transfer becomes thermoneutral. High temperatures may accelerate the rate of cage separation relative to electron transfer, resulting in an increased tendency for radical reactivity.
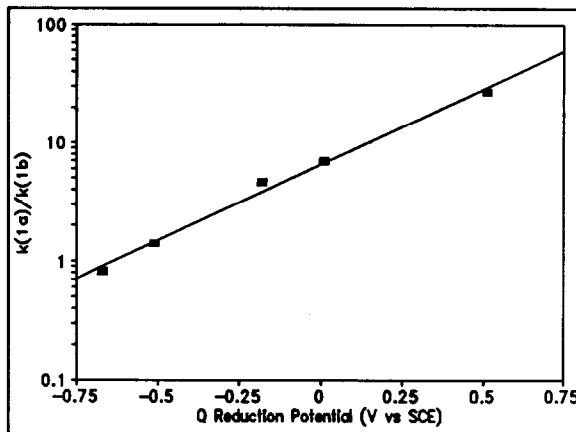
ACKNOWLEDGEMENT

EXPERIMENTAL SECTION

Melting points were determined on a Laboratory Devices Mel-temp apparatus and are uncorrected. Both ^1H and ^{13}C NMR spectra (δ (ppm) and J (Hz)) were measured in the indicated solvent with TMS as an internal standard on a Varian EM-360 or a JEOL GX-270 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 1310 IR spectrophotometer. GLC analyses were conducted on a Hewlett-Packard Model 5890A GC equipped with a 10 m 5% phenylmethylsilicone or a Carbowax 20M Megabore Column. Integration of the signals was performed by a Hewlett-Packard Model 3390A digital integrator. GC-MS data were measured with a Finnigan Model 4021 quadrapole mass spectrometer equipped with a Model 9610 data reduction system for comparison of mass spectra to those of authentic samples. HPLC analyses were performed on a Waters Associates Protein Peptides I system capable of gradient elution and using uv detection at 254 nm. Acetonitrile was predried over CaH_2, and then distilled from CaH_2 shortly before use. 1a was purchased from Aldrich and purified by vacuum distillation prior to use. 1b was synthesized by literature methods.[34] Reaction solutions were prepared by adding the compounds, internal standard, and CH_3CN to base-washed pyrex tubes, degassing using three freeze-pump-thaw cycles, and sealing under vacuum. These sealed tubes were heated at 190°C for the designated time. Analytical methods for 1a were developed for GC analysis using phenyl benzoate, hexyl cyanide, or octyl cyanide as internal standards. 1b was analyzed by HPLC analysis using phenyl benzoate as an internal standard. Relative reaction rates where both 1a and 1b were dissolved in the same solution utilized GC or HPLC as appropriate.

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30. Three major assumptions have been made to derive these energies. First, the energies for all semiquinone radicals are approximately equal, leading to equal radical pair energies for all π-acceptors. Second, the $\Delta\Delta G^\circ$ for the second electron transfer has the same magnitude as the $\Delta\Delta G^\circ$ for the first electron transfer for each quinone. Finally, the energy for the carbocation has been derived from estimates of the oxidation potential of appropriate model systems.

31. This value is based on the ρ value of -2.25 determined previously for benzyl phenyl ether derivatives with DDQ (Reference 24) and $\sigma+ =0.70$, which leads to $\Delta\Delta G_{190} =3.3$ kcal/mole.

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