

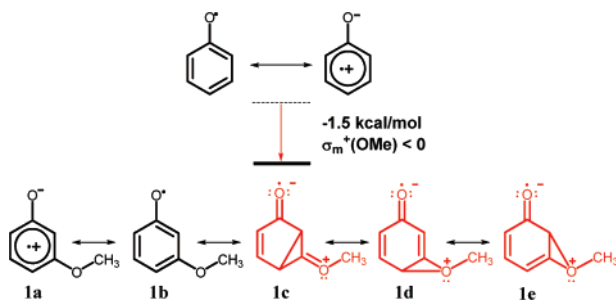
A Meta Effect in Nonphotochemical Processes: The Homolytic Chemistry of *m*-Methoxyphenol

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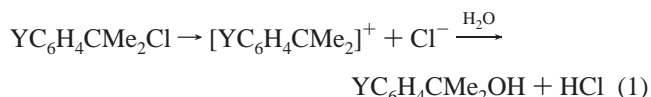


The *m*-methoxy group is normally electron-withdrawing (EW), $\sigma_m = +0.12$, $\sigma_m^+ = +0.05$. The strong EW activity of a phenoxyl radical's O[•] atom causes the *m*-methoxy group to become electron-donating (ED), $\sigma_m^+ = -0.14$. In valence bond terms, this can be ascribed to the nonclassical resonance structures **1c–e**. Although it has long been known that *m*-methoxy is ED in photoexcited states, it has now been found to be ED for homolytic O–H bond breaking in *ground-state* 3-methoxyphenol.

It is well-established that the methoxy group in ground-state aromatic molecules induces a substantial increase in electron density at the ortho and para positions (with which it is conjugated) and a small decrease in electron density at the meta position.¹ In contrast, in photoexcited aromatic molecules, the methoxy group increases electron density at the meta (and ortho) position, as was demonstrated in 1963 by Zimmerman et al.,² who observed that the photochemical solvolysis of benzyl acetate, for example, was enhanced by *m*-methoxy substitution.^{2a} This phenomenon was christened the “meta effect”. It was rationalized on the basis of calculated charge distributions in the singlet excited-states where methoxy (and other alkoxy) groups donate electron density to the meta (and ortho) positions

and thereby enhance heterolysis with formation of, for example, the *m*-methoxybenzyl cation.^{2,3} Other studies have produced many additional examples of enhanced photolyses by *m*-methoxy groups.^{4,5}

Zimmerman has emphasized that the meta effect is an *excited-state* phenomenon.^{2,3} However, the methoxy group is a highly unusual meta substituent because it appears to have a *variable* electronic effect on the reactions of *ground-state* molecules. Briefly, in 1958 Brown and Okamoto⁶ created a scale of electrophilic substituent constants, σ^+ , based upon the measured rate constants for the S_N1 solvolysis of 16 meta- and 21 para-substituted cumyl chlorides in 90% acetone/water at 25 °C, reaction 1.



Because “of the unimportance of resonance interactions at the *meta* position”⁷ (i.e., between meta substituents and the reaction center), kinetic data for meta-substituted compounds were correlated (eq 2) with Hammett $\sigma_m(\text{Y})$ constants. These were based on 3-YC₆H₄CO₂H ionization constants of “greatly variable quality”,⁶ and for this reason, the correlation was restricted to $\sigma_m(\text{Y})$ constants for which more reliable (± 0.02 units) thermodynamic dissociation constants in water were available (3-Y = MeO, Me, H, F, Cl, Br, I, O₂N).⁶

$$\log(k_1^{\text{Y}}/k_1^{\text{H}}) = \rho\sigma(\text{Y}) \quad (2)$$

Least-squares treatment of these eight “thermodynamic” points yielded the reaction constant, $\rho = -4.54$, which was combined with the rate data for the 21 para-substituted cumyl chlorides to obtain electrophilic substituent constants, $\sigma_p^+(\text{Y})$. These $\sigma_p^+(\text{Y})$ values were then shown to correlate rate data for nine other electrophilic substitution reactions from which additional $\sigma_p^+(\text{Y})$ values could be estimated.⁶

Despite Brown and Okamoto’s reservations about the quality of the ionization potentials for the other meta-substituted benzoic acids of interest to them, the rate constants for most of the remaining meta-substituted cumyl chlorides (3-Y = Et, *t*-Bu, Me₃Si, Ph, MeS, C(O)OEt, and CN) fell on or close to the eight-point line already defined. However, one of the supposedly “reliable” points, 3-MeO ($\sigma_m = +0.12$), was an outlier which caused Brown and Okamoto to *adjust* its electrophilic substituent constant, σ_m^+ , down to +0.047. Although this put the 3-MeO-substituted cumyl chloride on the defined line,⁸ this downward revision is insufficient for systems having even greater electron demand than the transition state for the cumyl chloride solvolyses. Specifically, and as detailed below, rate and thermo-

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[§] NRC Canada.

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dynamic data for *ground-state* reactions involving O–H bond homolyses in phenols require that the 3-MeO substituent is electron-donating (negative σ_m^+) rather than electron-withdrawing (positive σ_m^+).

In the early 1960s, rate constants for the homolytic abstraction of phenolic hydrogen atoms from substituted phenols by peroxy radicals at 65 °C¹¹ (reaction 3) and alkoxy radicals at 122 °C¹² were found to be well correlated by eq 2 using Brown's σ^+ constants.



The explanation for these two correlations with $\sigma^+(\text{Y})$ was later shown to be due to the thermochemistry. That is, the O–H bond dissociation enthalpies (BDEs) of meta- and para-substituted phenols are larger for electron-withdrawing (EW) substituents than for phenol and are smaller for electron-donating (ED) substituents than for phenol, yielding rates that are slower and faster, respectively, than the rate for phenol. Furthermore, differences between the O–H BDE of phenol and the O–H BDEs of meta- and para-substituted phenols give an excellent linear correlation with the σ^+ constants of the substituents,^{13,14} eq 4.^{13b}

$$\Delta\text{BDE} = [\text{BDE}(\text{C}_6\text{H}_5\text{O}-\text{H}) - \text{BDE}(\text{YC}_6\text{H}_4\text{O}-\text{H})]/\text{kcalmol}^{-1} = -7.1\sigma^+(\text{Y}) \quad (4)$$

This correlation with σ^+ , rather than σ^- derived from acidities of phenols, exists because the phenoxyl radical's O[•] moiety is strongly EW, as is the C⁺ atom of cumyl carbocations involved in deriving σ^+ values.¹⁵ Indeed, $\sigma_p = \sigma_p^+$ for O[•] has been estimated to be as large as +2.0.^{15,16} The most reliable method for determining differences in phenolic O–H BDEs is the EPR radical equilibrium technique developed by Pedulli and co-workers.¹⁴ For 3,5-dimethoxyphenol this procedure yielded^{14b} a $\Delta\text{BDE} = -1.6$ kcal/mol implying that the O–H bond in 3-methoxyphenol is *weaker* than that in phenol by ~ -0.8 kcal/mol. When combined with eq 4 this result yields $\sigma_m^+(\text{MeO})$

(8) Only two of the literature electrophilic substitution reactions considered by Brown and Okamoto⁶ included the 3-MeO substituent. For the protonolysis of aryltrimethylsilanes by sulfuric acid in acetic acid at 50 °C,⁹ the 3-MeO substituted reactant fitted the σ^+ correlation line with the "classic" $\sigma_m^+ = +0.047$.⁶ Partial rate factors for the bromination of mono-substituted benzenes in acetic acid at 25 °C¹⁰ required that $\sigma_m^+(\text{MeO}) = -0.054$.⁶

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(16) For comparison, $\sigma_p^+(\text{NO}_2) = +0.79$. However, a lower value for $\sigma_p^+(\text{O}^\bullet) = +0.73$ has also been suggested. Korth, H.-G. Private communication.

TABLE 1. Rate Constants^a ($\text{M}^{-1} \text{s}^{-1}$) for H-Atom Abstraction from Phenol and 3-Methoxyphenol by *dpph*[•], Cumyl-, and *t*-Butyloxy Radicals at 298 K in Various Solvents

solvent	PhOH		<i>m</i> -MeOPhOH			
	<i>dpph</i> [•]	CumO [•] × 10 ⁹	^t BuO [•] × 10 ⁷	<i>dpph</i> [•]	CumO [•] × 10 ⁹	^t BuO [•] × 10 ⁷
RH ^b	0.10	1.2		1.4	2.4	
W/A ^c	0.0115			0.037		
	0.0039 ^d			0.024 ^d		
	0.0030 ^e			0.017 ^e		
^t BuOH ^f			6			8

^a Experimental error, ±15%. ^b Cyclohexane (*dpph*[•]) and *n*-hexane (CumO[•]). ^c Acetone/water (9:1 v/v). ^d W/A in the presence of 0.083 M acetic acid. ^e W/A in the presence of 0.5 M acetic acid. ^f (Me₃CO)₂/Me₃COH (2:1 v/v).

= -0.11 which means that the *m*-methoxy group is ED rather than EW (cf., Brown and Okamoto's $\sigma_m^+(\text{MeO}) = +0.047$). A variation in the sign of a substituent's electronic effect for ground-state species is sufficiently remarkable to be worth further study. To this end, we examined the kinetics of homolytic H-atom abstractions from the OH bonds of 3-methoxyphenol and phenol by free-radicals. If the O–H BDE in 3-methoxyphenol really is weaker than in phenol it should be the better H-atom donor. Initially this matter was explored in alkane solvents because these are neither hydrogen bond acceptors (HBAs) nor hydrogen bond donors (HBDs) and because they do not support phenol ionization.¹⁷ As the H-atom abstracting agents we chose both the relatively unreactive 2,2-diphenyl-1-picrylhydrazyl radical (*dpph*[•]) and the highly reactive cumyloxy radical (CumO[•]).¹⁹ Standard kinetic procedures were followed (see the Experimental Section). The measured rate constants, reported in Table 1, demonstrate that 3-methoxyphenol is more reactive than phenol toward both radicals, two results that are consistent with the O–H BDE being smaller for 3-methoxyphenol than for phenol. More importantly, a complete kinetic analysis of the reversible^{21a} reactions between *dpph*[•] and the phenols gave O–H BDEs of 86.7 and 85.7 kcal/mol for phenol and 3-methoxyphenol, respectively.^{21b} That is, the O–H BDE is 1.0 kcal/mol weaker in 3-methoxyphenol than in phenol, a difference in close agreement with the -0.8 kcal/mol that Pedulli's^{14b} observations imply, and yielding, via eq 4, $\sigma_m^+(\text{MeO}) = -0.14$.

Positive values for $\sigma_m^+(\text{MeO})$ were found by kinetic studies in 90% acetone/water⁶ and in acetic acid⁹ (and in some rather unreliable O–H BDE measurements in DMSO)²² while negative values were found by equilibrium measurements of O–H ΔBDEs in benzene,^{14b} and, in the present work, by kinetic studies in alkanes. This suggested to us that the *m*-methoxy

(17) The sequential proton loss electron transfer (SPLET) mechanism involves electron transfer from phenoxide to the radical.¹⁸

(18) (a) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, 68, 3433–3438. (b) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2004**, 69, 5888–5896. (c) Foti, M. C.; Daquino, C.; Geraci, C. *J. Org. Chem.* **2004**, 69, 2309–2314.

(19) Another difference between *dpph*[•] and CumO[•] is that the former has a relatively high electron affinity but the latter does not.^{18a} In principle, electron transfer from the phenol to the oxidizing agent followed by proton loss (a known reaction)²⁰ might be possible with *dpph*[•] (i. e., *dpph*[•] + ArOH → *dpph*⁻ + [ArOH]^{•+} → ArO[•] + H⁺), but it could not occur with CumO[•].

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group might be EW in polar solvents, including water,²³ but ED in nonpolar solvents. Such unexpected, Janus faced, behavior caused us to measure the rate constants for the reactions of phenol and 3-methoxyphenol with dpph^{\bullet} and an alkoxy radical ($\text{Me}_3\text{CO}^{\bullet}$) in polar solvents. In 90% acetone/water at 298 K, the rate constants for reaction of dpph^{\bullet} with phenol and 3-methoxyphenol were 1.15×10^{-2} and $3.70 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ (see Table 1), respectively. However, both reactions could contain a significant contribution to the rate from the SPLET mechanism.¹⁷ Indeed, upon the addition of acetic acid the rate constants decreased considerably (Table 1). Clearly, 3-methoxyphenol is a better H-atom donor than phenol in this polar medium which implies that the *meta*-methoxy group is electron-donating in polar solvents, just as it is in nonpolar solvents. The same conclusion was derived from the kinetics of H-abstraction by $\text{Me}_3\text{CO}^{\bullet}$ in $(\text{Me}_3\text{CO})_2/\text{Me}_3\text{COH}$ (2:1 v/v) at room temperature. Rate constants of 6×10^7 and $8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ were found for phenol and 3-methoxyphenol (Table 1), respectively, while in the presence of 0.5 – 0.7 M acetic acid these rate constants did not change significantly.

The conclusion that the O–H BDE is weaker in 3-methoxyphenol than in phenol is supported by DFT calculations at the B3²⁴P86²⁵/6-311G(2d,2p)//B3P86/6-31G(d) level.^{26–28} For these systems, the differences in BDEs calculated using this level of theory should be just as reliable as the best experimental ΔBDE measurements. For phenol the calculations were straightforward, but for 3-methoxyphenol the calculations were complicated by the fact that this molecule has four stable structures (OH and OMe groups both pointing toward each other, both groups pointing away from each other, one group pointing toward and the other away) while its radical has two stable structures. A reliable O–H BDE for 3-methoxyphenol was obtained by a Boltzmann averaging of the energies of all the conformers (see the Supporting Information). The resultant O–H BDE was

(23) The Hammett $\sigma_m(\text{MeO})$ value of +0.12 is, of course, based on the ionization of benzoic acids in water.

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TABLE 2. Transition Energy (TE/eV) of the 3- $\text{YC}_6\text{H}_4\text{O}^{\bullet}$ First Excited State and Molecule Stabilization Energy (MSE), Radical Stabilization Energy (RSE), ΔBDE Values, and C–Y Rotation Barrier Differences, $\Delta E_{\text{rot}} = [E_{\text{rot}}(3\text{-YC}_6\text{H}_4\text{O}^{\bullet}) - E_{\text{rot}}(\text{C}_6\text{H}_5\text{Y})]$ (in kcal mol⁻¹)

Y	σ_m^{+a}	σ_p^{+a}	TE ^b	MSE	RSE	ΔBDE	ΔE_{rot}^d
NMe ₂		-1.70	1.07	0.38	1.27	-0.89	1.3
NH ₂	-0.16	-1.30	1.08	0.26	0.96	-0.71	1.1
MeO	+0.05	-0.78	1.03	0.19	1.47	-1.25	1.7 ^e
OH	-0.04	-0.92	1.11	0.15	0.60	-0.46	1.0
CH ₃	-0.07	-0.31	1.08	0.05	0.56	-0.51	0.2
H	0	0	1.05	0	0	0 ^c	
OCH ₂ F			1.10	0.02	-0.10	0.12	0.4 ^f
F	+0.35	-0.07	1.06	-0.04	-0.90	0.85	
Cl	+0.40	+0.11	1.05	-0.15	-1.18	1.03	

^a Values are from refs 6 and 29. ^b Calculated using time-dependent (U)B3²⁴LYP³⁰/6-311+G(2d,2p) level of theory. ^c Calculated phenol O–H BDE (kcal mol⁻¹) = 87.85, “best” experimental value = 86.7.³² ^d Calculated rotation barriers (kcal mol⁻¹) in the 3- $\text{YC}_6\text{H}_4\text{O}^{\bullet}$ radicals are as follows: Y = NMe₂ 6.0, NH₂ 6.9, OMe 5.1, OH 5.0, CH₃ 0.2, OCH₂F 2.25. ^e In this case, the rotation potential is highly asymmetric as a result of strong dipole interactions between MeO and O[•]. ^f The F atom of the 3-OCH₂F group interacts strongly with the aromatic hydrogen at the 4-position. This additional interaction, which is also present in the substituted benzene, increases the rotational barrier beyond that due to conjugation effects alone.

computed to be 1.25 kcal mol⁻¹ weaker in 3-methoxyphenol than that in phenol, a result slightly larger than the ~ -0.8 kcal mol⁻¹ estimated from Pedulli’s work and the -1.0 kcal/mol found from dpph^{\bullet} kinetics, vide supra, and which yields (eq 4), $\sigma_m^+(\text{MeO}) = -0.17$. Additional calculations on 3,5-dimethoxyphenol give the O–H BDE as 1.75 kcal/mol lower than phenol, in excellent agreement with Pedulli’s work. These findings nicely illustrate the ability of the first meta MeO group to attenuate the ED ability of a second MeO by ca. 40%. Details of the computational procedures, structures, and energetics are given in the Supporting Information.

m-Methoxy is an EW group in heterolytic reactions, benzoic acid ionization, $\sigma_m(\text{MeO}) = +0.12$; cumyl chloride solvolysis,⁶ $\sigma_m^+(\text{MeO}) = +0.047$; and the protonolysis of aryltrimethylsilanes,^{8,9} $\sigma_m^+(\text{MeO}) = +0.047$, but it is an ED in homolytic reactions (OH BDEs in phenols) both by experiment, $\sigma_m^+(\text{MeO}) = -0.11$ ^{14b} and -0.14 ,³³ and by computation, $\sigma_m^+(\text{MeO}) = -0.17$.³³ The rate constants for abstraction of the phenolic H-atoms are also consistent with an electron-donating *m*-methoxy.^{33,34} This Janus-faced “switch” in the electronic properties of the *m*-methoxy group is not a consequence of changes in solvent polarity. The possibility that the “*meta*-effect” in 3-methoxyphenoxy radical is the result of some admixture of an excited-state into the ground-state was rejected based on the results of calculations on 3-Y-phenoxy radicals. These reveal that all of the phenoxy radicals examined possess low-lying excited states of similar energy; see Table 2.^{35,37}

For a ground state with sufficiently strong electron demand we can see no reason why the *m*-methoxy group should not

(33) This work.

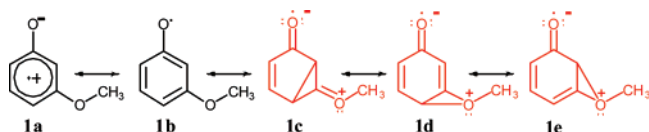
(34) See also: Hogg, J. S.; Lohmann, D. H.; Russell, K. E. *Can. J. Chem.* **1961**, *39*, 1588–1594.

(35) For 3-methoxyphenoxy, the lowest energy transition to have been observed is ca 2 eV (46 kcal mol⁻¹).³⁶ Our computations reveal that there is also an $n \rightarrow \pi^*$ transition at lower energy (1.03 eV, see Table 2).

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(37) Following the suggestion of a reviewer, we performed complete active space SCF calculations on the *m*-OCH₂FPhOH/*m*-OCH₂FPhO[•] and the *m*-MeOPhOH/*m*-MeOPhO[•] pairs. The results indicate that excited states contribute approximately equally to the ground state wave functions of both radicals, relative to their respective parent molecules.

become an electron donor. In valence bond (VB) terms, 3-methoxyphenoxy (**1b**) can also be represented by the structures **1c–e**, where **1c** is essentially the same as Zimmerman's VB representation of the (excited-state) *m*-methoxy effect.^{2,38} In fact, O[•] is more strongly electron withdrawing ($\rho^+ = -7.1$ kcal/mol, eq 4) than the incipient positive charge on the cumyl cations formed in Brown and Okamoto's cumyl chloride solvolyses ($\rho^+ = -4.54 \equiv 6.2$ kcal/mol free energy).⁴⁰ This may sound surprising but it is a consequence of there being incomplete charge development in the transition state for this S_N1 reaction in the aqueous acetone solvent employed. Calculations⁴⁰ indicate that ρ^+ would increase to 16.3 kcal/mol for the same S_N1 heterolyses in the gas phase where full charges are present on the cumyl cation and chloride anion in the transition state.



There are two obvious consequences if **1c–e** play any role in the structure and energetics of the 3-methoxyphenoxy radical. First, the barrier to rotation of the methoxyl group in the radical should be greater than in the starting phenol (and anisole). Second, the meta effect on phenoxy radicals should not be limited to the OMe group, it should extend to other meta substituents that possess lone pairs of electrons such as HO, NH₂, and NMe₂ and should even extend to a *m*-methyl substituent via a hyperconjugative interaction. Both of these predicted consequences are realized in the results of our calculations of Y–C rotation barriers in 3-YC₆H₄O[•] radicals and O–H Δ BDEs; see Table 2. These O–H Δ BDEs have also been partitioned^{13c} into the contributions made by the molecule and radical stabilization energies, MSEs and RSEs.

The results in Table 2 show that ED Y-substituents do have small stabilizing effects on the parent 3-Y-phenols (positive MSE), but they have a considerably larger stabilizing effect on the 3-Y-phenoxy radicals (positive RSE). The net effect of these stabilizing interactions is to produce a significant lowering of the O–H BDEs in these compounds. The nonclassical resonance-stabilization afforded in 3-YC₆H₄O[•] by ED Y substituents is also reflected in the calculated increases in C–Y rotation barriers in 3-YC₆H₄O[•] compared to the barriers in the corresponding monosubstituted benzenes, C₆H₅Y (ΔE_{rot}). Quite large ΔE_{rot} values are found when the leading atom of Y has a lone-pair of electrons (conjugation) but the value is smaller when, as for 3-methylphenoxy, only hyperconjugation can contribute to ΔE_{rot} . However, it should be noted that the presence of a lone-pair on the leading atom of Y is not sufficient to ensure a meta

(38) Although a ground-state VB representation of the claimed^{10a} (and confirmed^{10d}) indirectly measured accelerating effect of *m*-methoxy on the noncatalyzed bromination of anisole similar to **1c** was proposed,³⁹ it was quickly dismissed^{7,10d} because:⁷ “In the reactions where a direct experimental method is available, the (*meta*) methoxy group deactivates the ring” and therefore “The conclusion that there is an activating influence by the *m*-methoxy group should be treated with considerable reservation.”

(39) de la Mare, P. B. D.; Ridd, J. H. *Aromatic Substitution, Nitration and Halogenation*; Butterworths: London, UK, 1959; p 141.

(40) DiLabio, G. A.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 1620–1624.

effect since the O–H BDE in 3-CH₂FOC₆H₄OH is slightly higher than that in phenol. Perhaps the most surprising result in Table 2 is that the magnitudes of the nonclassical meta resonance effect for the substituents do not parallel their classical resonance effects as exemplified by their $\sigma_p^+(Y)$ {or $\sigma_m^+(Y)$ } values.

In conclusion, the meta effect is *not* restricted to excited states. It should also be observed in ground states for methoxyl and the other groups considered in this paper whenever there is strong electron demand in a reaction, or in a molecule, or radical (or, as recently noted, cation).⁵ The magnitude of this meta effect, i.e., the value of $\Delta\sigma_m(Y) = \sigma_m(Y) - \sigma_m^+(Y)$, will increase as the electron demand at the 1-position increases which, unfortunately, means that $\sigma_m^+(Y)$ values will not be single-valued for Y = MeO, HO, H₂N, etc.,⁴¹ nor is it single-valued when other substituents are present on the ring.

As a corollary to meta effects observed with ED substituents when the 1-position is strongly EW, a related meta effect should occur with EW substituents when the 1-position is strongly ED. To our knowledge such an (inverted) meta effect has not been reported.

Experimental Section

Di-*tert*-butyl peroxide and 3-methoxyphenol were passed through alumina and silica gel, respectively, prior to the kinetic experiments. The other reagents were used as received.

Reactions with dpph[•]. Phenol or 3-methoxyphenol (1 – 50 mM) was reacted with dpph[•] (ca. 0.05 – 0.1 mM) at 298 K. Glacial acetic acid was used in a few experiments to a final concentration of 0.08–0.5 M. The reaction was followed at 512 nm, and the rate constants were obtained either from initial rates or from decay curves analyzed with pseudo-first-order kinetics.

Laser Flash Photolysis. Solutions of dicumyl peroxide (1 M in *n*-hexane) or (Me₃CO)₂/Me₃COH (2:1 v/v) in the presence of 1–15 mM phenol or 3-methoxyphenol were deoxygenated and photolyzed at 355 nm with a Nd:YAG laser (pulse width 6 ns; 9–15 mJ/pulse) at room temperature. In a few cases, glacial acetic acid was added to a final concentration of 0.5–0.7 M. The decay of cumyloxy was monitored at 480 nm, and with Me₃CO[•], growth of the aryloxy radicals was monitored at 390 nm (phenol) and 410 nm (3-methoxyphenol). Rate constants were calculated from plots of k_{obs} vs [ArOH].

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Supporting Information Available: Coordinates and energies for the optimized structures listed in Table 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(41) This raises an old debate as to whether electrophilic substituent constants could be single-valued as is required for any Hammett treatment; see refs 6, 7, 10, and 39.