J. Am. Chem. Soc. 1989, 111, 4594-4600

Dissociation of Substituted Anisoles: Substituent Effects on Bond Strengths

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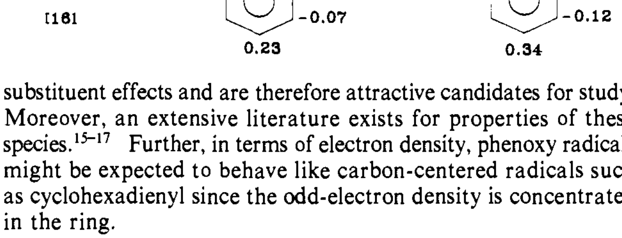
Abstract: Rates of O–methyl homolysis of 24 substituted anisoles were determined by the very-low-pressure pyrolysis technique. Assuming equal *A* factors for all reactions, all ortho substituents weakened the O–methyl bond, with effects ranging from −0.2 to −7.4 kcal. Para-substituent effects fell over the narrower range 1.2 to −2.9 kcal, while in the meta position effects were even smaller (1.1 to −1.0 kcal, including substituents previously studied). The *o*-NH_2 substituent had a dramatic effect, weakening the O–methyl bond by −7.4 kcal, similar to the previously studied *o*-OH group. Since para effects were ca. 5 kcal smaller, the most probable explanation for these ortho effects is a strong bond between an H atom on the substituent and the adjacent phenoxyl oxygen. The effect of *o*-hydroxymethyl was unexceptional and nearly the same as *o*-methyl (−2.6 kcal). Electron-withdrawing groups (CN, NO_2, and $COCH_3$) strengthened the O–methyl bond from the para position, while ortho substituents weakened it, presumably by release of steric repulsion in the molecule. The O–methyl bond weakening in 1-methoxynaphthalene was 5.9 kcal, which was 3.4 kcal more than for the 2-isomer. A 2.4-kcal bond weakening was caused by the *o*-vinyl substituent. The effects of F, Cl, and Br substituents were quite similar; ortho substituents weakened the bond by about 2 kcal, while para effects were approximately 1 kcal. There was some correlation between the measured differences in substituent effects on bond strengths (ΔBDE) and literature rates of H-abstraction from substituted phenols, but differences were also clear, presumably reflecting polar kinetic effects in the abstraction reactions. Overall, ΔBDE showed a fair, but clearly imperfect correlation with the σ^+ substituent constant ($r = 0.91$). Deviations were attributed to contributions to σ^+ from substituent bond dipole–charge interactions. A good correlation was also found between ΔBDE and ESR hyperfine coupling constants (hfcc) for ortho- and para-substituted phenoxy radicals.

I. Introduction

Substituents can affect reaction rates by altering bond strengths at the reaction site.[1-3] For H-abstraction from substituted toluenes (or phenols) by free radicals, for example, such effects are often presumed to be dominant.[4-6] However, nonthermodynamic ("polar") effects may also affect transition-state energies and thereby disrupt correlations between rates and thermodynamics. In fact, for certain classes of reactions, particularly those involving halogen atoms, it has been demonstrated that under some conditions "polar effects" in free radical reactions are dominant. This topic is under current debate.[7-12]

The separation of thermodynamic and polar effects on rates requires both thermodynamic and kinetic data. While extensive kinetic data on substituent effects exist, relevant thermodynamic data are scant. Most attempts to develop general correlations for free radical reactions have therefore depended on reactions presumed to be free from (or corrected for) polar kinetic effects or on physical properties thought to be closely related to bond strengths.[7-10] An exception is the determination of homolysis rates of benzyl mercurials by Agirbas and Jackson,[13] where rates should depend directly on bond strengths. However, synthetic difficulties have limited this method. Very recently, Mulder et al.[14] used a photoacoustic method to measure heat release associated with H-abstraction by *tert*-butoxy radicals from four para-substituted phenols (trifluoromethyl, chloro, *tert*-butyl, and methoxy).

Much of the recent discussion on substituent effects in free radicals has focused on benzyl radicals. However, these effects are generally small and therefore hard to measure to the desired degree of precision, making it difficult to critically compare results of the different methods. Phenoxy radicals, on the other hand, as demonstrated by Mahoney and DaRooge,[11] show much larger substituent effects and are therefore attractive candidates for study. Moreover, an extensive literature exists for properties of these species.[15-17] Further, in terms of electron density, phenoxy radicals might be expected to behave like carbon-centered radicals such as cyclohexadienyl since the odd-electron density is concentrated in the ring.



In the present work, we report substituent effects on phenoxy–methyl bond strengths for 10 substituents, a number of them in each of the available ring positions. Since a case can be made that substituent effects on O–CH_3 bond strengths in anisoles are similar to effects on O–H bond strengths in phenols, these results can be transferred to O–H bonds in substituted phenols. With this assumption, we compare bond strengths from the present work with other measures of substituent effects.

In these studies, dissociation rates of substituted anisoles were determined in the gas phase by a method of very-low-pressure

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pyrolysis (VLPP). This method provides a straightforward means for determining decomposition rates in the absence of bimolecular reactions.[19] It appears to be quite accurate; methyl substituent effects on benzylic bond strengths measured by VLPP[20] and derived from ion thermodynamic cycles by Beauchamp et al.[21] differed, on average, by only ±0.2 kcal.

Anisoles are especially suited for study by this method, since their low O–methyl bond strengths (ca. 64 kcal mol^{-1}) cause them to homolyze under relatively mild (for VLPP) conditions (900–1200 K). Moreover, in an earlier study,[22] we found the decomposition of substituted anisoles to proceed exclusively by simple homolysis, even in cases where alternative concerted paths seemed plausible.

In these previous VLPP studies[22] we also reported that the *o*-hydroxy group caused a surprisingly large O-CH_3 bond weakening (7 kcal mol^{-1}) and, in agreement with the findings of Mahoney and DaRooge,[11] a large effect was also observed for the *p*-methoxy substituent (4 kcal mol^{-1}). However, measured relative bond strengths did not correlate with relative rates for H-abstraction from substituted phenols, suggestive of polar kinetic effects. These and other correlations are examined in more detail in the present work.

II. Experimental Section

General operating principles of the VLPP technique have been described by Golden et al.[19] Our set-up consists of a 75-cm^3 fused quartz reactor with an exit aperture area of 9.1 mm^2 and collision number of 1160.[23] Ethylbenzene and anisole decomposition were monitored periodically to check reproducibility. Percentage dissociation was reproducible to ±1%. Flow rates were regulated by controlling the temperature, hence vapor pressure of the reactants. To achieve measurable flow rates, some compounds were heated as high as 50 °C. To ensure a steady flow, the entire reactor inlet path was maintained at least 5° higher than the sample temperature.

An electron impact quadrupole mass spectrometer, tuned to 70-eV ionization energy, was used to monitor reactant decomposition. In some cases, reaction products were analyzed using another quadrupole mass spectrometer at 12–20 eV ionization energy. All chemicals were obtained from commercial sources and were used without further purification.

III. Semiempirical MO Calculations

To assist the interpretation of results, the semiempirical AM1 method was used to calculate heats of formation of a number of substituted anisoles and phenoxy radicals.[24] The method is claimed to adequately account for H-bonding and has been thoroughly compared to literature thermodynamic data.[25]

IV. Results

A. Product Analysis. In earlier studies of hydroxy- and methoxy-substituted anisoles, we reported that product analysis, including the direct detection of methyl radicals, indicated that the initial step in all decompositions was *O*–methyl bond homolysis.[22] Mass spectra of products in the present studies were equivalent to these earlier results. That is, mass spectral peaks corresponding to methyl radicals, phenols, and decomposition products (especially decarbonylation fragments) of substituted phenoxyl radicals were observed as the principal products in all reactions of anisoles.

B. Low-Pressure Rate Measurements. Experimental conditions were the same as employed in previous studies.[22] Rate measurements for several selected anisoles are shown in Figure 1. All other reactions generated curves parallel to these. It was a general finding that when flow rates were very high (ca. 10^{17} molecules s^{-1}) measured rates began to diminish at the highest extents of reaction, suggesting the re-formation of reactants by radical recombination. Flow rates were kept well below the inception of this behavior.

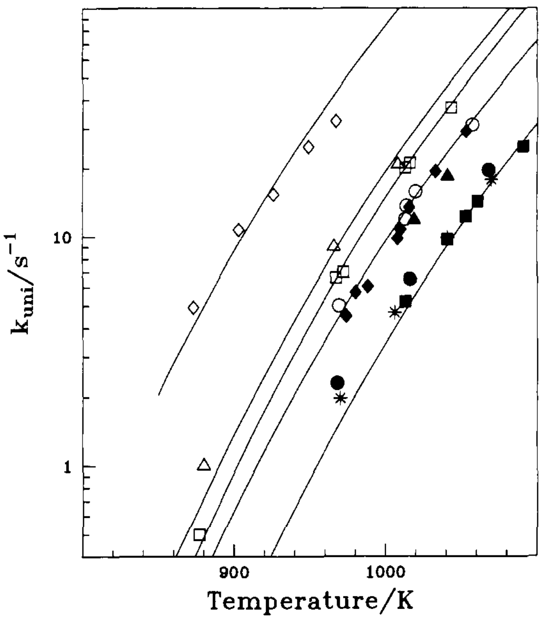

Figure 1. Rate constants measured from the thermal decomposition of several selected anisoles: (□) *p*-CH_3, (◇) *o*-NH_2, (△) *p*-NH_2, (○) *o*-F, (■) *m*-F, (◆) *m*-$COCH_3$, (▲) *p*-$COCH_3$, (●) *p*-NO_2, (*) *m*-CN; solid lines are RRKM fit to the data of *p*-CH_3, *o*-NH_2, *p*-NH_2, *o*-F, and *m*-F.

Unimolecular reaction rate constants, k_{uni}, under VLPP conditions were calculated from the equation:

$$k_{uni}/k_e = f/(1-f) = (I_0 - I)/I \qquad (1)$$

where, k_e, the escape rate constant is $3.965(T/M)^{0.5}$ s^{-1} for our 3-mm aperture reactor, M is the molecular weight (amu), T is the temperature (K), and f represents the fraction of reactant decomposed. The latter value is derived from mass spectrometer signal intensity of the parent molecular ion before reaction (I_0) and after reaction (I) at an ionization energy of 70 eV.

C. High-Pressure Rate Constants. For a meaningful comparison of rate constants for the different reactions, they must first be converted to their high-pressure (collision-frequency independent) values (k^∞). This was done with RRKM theory.[26] A vibrational model derived from an existing model for ethylbenzene[27] was used. An A factor of $10^{15.5}$ s^{-1} was assumed for all reactions, based on the reverse rate constant of $10^{9.5}$ s^{-1} and estimated reaction entropies.[28] VLPP experiments cannot yield independent values for A factors and activation energies;[27] hence one had to be fixed to obtain the other. Frequencies for each model were adjusted so that both heat capacities and entropies of reactants and products matched those of group additivity.[29] Activation energies were adjusted to match experimental rate constants.

The curvature of all temperature versus rate constant plots were well described by RRKM calculations (see Figure 1), indicating that the reactions are homogeneous and unimolecular. All activation energies for O–methyl bond dissociation of the substituted anisoles studied in this and previous VLPP studies are presented in Table I. Differences in activation energies were converted to bond dissociation energies relative to anisole (ΔBDE) which are

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Table I. O–Methyl Bond Energies (kcal mol^{-1}) for Unimolecular Decomposition of Substituted Anisoles[a]

	substituent position			
substituent	ortho	meta	para	other
NH_2	56.1	63.1	60.5	
OH[b]	56.3	63.8	61.0	
OCH_3[b]	59.3	62.4	59.5	
CH_3	60.9	63.0	61.6	
CH_2OH	61.0			
H[b]	63.5	63.5	63.5	
F	61.6	64.4	62.4	
penta-F				60.8
Cl[b]	61.3	63.7	62.4	
Br[b]	61.8			
$COCH_3$	62.0	63.7	64.1	
$CHCH_2$	61.0			
CN	63.4	64.6	63.8	
NO_2	62.1	63.0	64.6	
2,3-benzo				57.5
3,4-benzo				61.0

[a] Assuming an *A* factor of $10^{15.5}$ s^{-1} per methoxy group (see text). [b] From ref 22.

listed in Table II along with theoretical and other experimental determinations.

We estimate that errors in rate constants, measured at 50% decomposition, are approximately 10%. Extrapolation to high pressure will cause little relative error, even if *A* factors differed substantially. This might cause an additional 10% relative error. Thus, errors in relative high-pressure Gibbs energies for reaction are of the order of 0.4 kcal/mol. The deviation of points from the RRKM fit at the temperature extremes (Figure 1) are typical of VLPP measurements and are due to the inherently less accurate measurements made at very high and low extents of decomposition.

V. Discussion

In general, our results indicate that O–methyl bond strengths vary over a wide range, depending on both the position and nature of the substituent. In the ortho position, where all substituents weakened bonds, effects were the largest (–0.2 to –7.4 kcal). Para effects fell over a narrower range (+1.1 to –4.0 kcal), while meta effects were evenly distributed over a still narrower range (+1.1 to –1.0).

In the following discussion, effects of specific substituents are considered in the order (i) halogens, (ii) amino, (iii) methyl, (iv) electron-withdrawing substituents (cyano, aceto, nitro), and (v) conjugating groups (vinyl and benzo). This is followed by a brief discussion of earlier results for hydroxy and methoxy substituents and new results for the *o*-CH_2OH substituent. Then we examine the results as a whole, including comparisons with the previous ΔBDE values, substituent constants, ESR data, phenolic H-abstraction rates, AM1 (MNDO) calculations, and benzyl substituent effects.

In the following discussion we presume that substituent effects on the anisole O–CH_3 bond are the same as for the phenoxyl O–H bond. Any differences can be expressed in terms of differences in stabilities of the parent molecules. Specifically, this difference is equal to the enthalpy for the transfer of the substituent (X) from anisole to phenol:

$$PhOH + XPhOCH_3 \rightarrow XPhOH + PhOCH_3 \qquad (2)$$

In our previous study of anisole decomposition we presented both theoretical[15] and experimental[30] evidence to support the idea that the enthalpy of reaction 2 is very small.

A. Haloanisoles. Para substitution by either a fluorine or chlorine atom causes a 1 kcal mol^{-1} weakening of the O–methyl bond, while ortho substitution by these, and bromine as well, weakens the bond by about 2 kcal mol^{-1}. This modest ortho/para difference is presumably due to relaxation of repulsion in the ortho-substituted molecules. Meta substitution by fluorine strengthens the bond by nearly 1 kcal mol^{-1}, while chlorine at this position has virtually no effect. Substitution of five fluorine atoms weakens the O–methyl bond by 2.7 kcal mol^{-1}, nearly the same as would be predicted by additivity (3.1 kcal mol^{-1}).

B. Aminoanisoles. The amino group has nearly the same effect on bond strengths as previously found for the hydroxyl group. Ortho substitution causes a remarkable bond weakening of 7.4 kcal mol^{-1}, slightly larger than that found for the hydroxyl group.[22] Para substitution diminishes this bond strength by 2.9 kcal mol^{-1}, while meta substitution strengthens it by 0.4 kcal mol^{-1}.

C. Methylanisoles. Methyl substituents weaken the O–methyl bond in anisole at all positions, and 0.7 kcal mol^{-1} more in the ortho than in the para position. Qualitatively similar effects were found for C–methyl bonds in methyl-substituted ethylbenzenes,[20] although the magnitudes of the effects in *o*- and *p*-methylanisoles are about 1.5 kcal mol^{-1} larger.

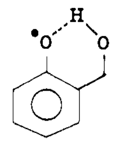
D. Cyano, Acetyl, and Nitro Substituents. These electron-withdrawing groups had relatively small effects on bond strengths. In contrast in the other substituents, in the para position the O–methyl bonds were strengthened, although the magnitude of this effect was greater than 1 kcal only for nitro. The largest meta effect of any substituent studied was observed for the cyano group, which strengthened the O–methyl bond by 1.1 kcal. Ortho substitution by these substituents caused modest bond weakening, this presumably due to a relaxation of repulsion in the molecule.

E. Vinylanisole and the Methoxynaphthalenes. In these molecules, the O–methyl bond is expected to be weakened by additional delocalization of the odd electron onto the "substituents". The methoxynaphthalenes are, in effect, benzo-substituted anisoles.

The decline in bond strength in the series anisole, 2-methoxynaphthalene, 1-methoxynaphthalene reflects the increase in relative resonance stabilization energies in the radicals.[31] As for the methyl substituent, the benzo group stabilized the phenoxy radical substantially more than it stabilized the benzyl radical[1] (an extra stabilization of 5.9 kcal mol^{-1} for 1-methoxynaphthalene versus 2.9 kcal mol^{-1} for 1-ethylnaphthalene). Bond weakening caused by the *o*-vinyl group presumably results from a combination of steric relief and additional conjugation in the radical.

F. Hydroxy-, Methoxy-, and Hydroxymethylanisoles. The results of our earlier studies of hydroxy and methoxy substituents are included in Table II. Bond weakening by *o*-hydroxy was extraordinary (7.1 kcal), accounting for the exception lability of guaiacol observed in the condensed phase by Vouri and Virk.[32,33] The *p*-hydroxy group, however, weakened the bond by only 2.5 kcal, with little effect caused by meta substitution. In the case of methoxy, both *o*- and *p*-methoxy groups weakened the O–methyl bond by 4 kcal.

Since the most probable explanation for the bond weakening caused by *o*-hydroxy and -amino substituents is a strong hydrogen bond in the radical, we determined the influence of another potential hydrogen-bonding substituent, the *o*-hydroxymethyl group. The H atom in the hydroxyl group in this substituent may form a hydrogen bond with the oxygen via a six-membered ring:



However, the observed bond weakening was only 2.4 kcal mol^{-1}, nearly the same as found for an *o*-methyl group (2.6 kcal mol^{-1}). Clearly, the large *o*-hydroxy effect is sensitive to the details of the hydroxyl–phenoxyl–oxygen interaction. The reason for the lack of effect for the hydroxyl-methyl substituent is, however, not clear. It might arise from an unfavorable geometry for hydrogen bonding or perhaps the inability to form an extended π system.

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Table II. Relative Bond Strengths of Substituted Anisoles

	substituent position[a]							
	ortho[b]		meta		para		other	
subst	expt	calc	expt	calc	expt	calc	expt	calc
NH_2	**-7.4**	-10.3	**-0.4**	0.8	**-2.9**	-7.2	-0.0	-0.0
OH[c]	-7.1	-6.0	0.3 2.6[d]	0.6	-2.5 -3.7[d]	-4.0		
OCH_3[c]	-4.2	-5.3	-1.0	0.1	-3.9 -4.3[e]	-4.1		
CH_3	-2.6	-1.6	-0.5	0.2	**-1.9** -1.8[e]	-1.4		
CH_2OH	**-2.4**	-1.0						
F	**-1.9**	-3.0	0.9	2.0	-1.1	-2.4		
penta-F[f]							-2.7	-4.0
Cl[c]	-2.2	-0.9		1.0		0.5		
Br[c]	**-1.7**	-0.6		0.7		0.9		
$COCH_3$	**-1.4**	0.0	**0.3**	0.6	**0.6**	1.9		
$CHCH_2$	**-2.4**	-2.8						
CN	**-0.2**	1.0	**1.1**	1.6	**0.3**	1.8		
NO_2	**-1.3**	2.6	**-0.5**	2.5	**1.2**	4.3		
2,3-benzo							**-5.9** -3.8[d]	-5.3
3,4-benzo							**-2.5** -1.8[e]	-0.4

[a] Values in boldface are from present study; relative to BDE(anisole). [b] BDE(expt) = 63.5 kcal mol^{-1}; calculated values by the MNDO(AM1) method: BDE(calc) = 66.3 kcal mol^{-1}. [c] Ref 22. [d] Via Brønsted relationship (ref 11). [e] From equilibrium constant (ref 11). [f] Refers to 1,2,3,4,5-pentafluoroanisole.

Table III. Methyl Substituent Effects on Benzylic and Phenoxylic Bond Strengths (kcal mol^{-1})

		ΔBDE		
parent	source	ortho	meta	para
anisole	present work	-2.6	-0.5	-1.9
ethylbenzene	VLPP[20]	-1.4	-0.3	-0.4
toluene[a]	Beauchamp[21]	-0.9	-0.4	-0.6

[a] Relative C–H bond strengths of isomeric xylenes.

G. Comparison with Previous Results. Mahoney and DaRooge have determined a series of substituent effects on O–H bond strengths in phenols.[11] Their values for the relative O–H bond strengths of substituted phenols are included along with our O–methyl bond strengths in Table II. Each of their values was obtained by one of two methods: (1) from an equilibrium constant derived from forward and reverse rate constants for H-transfer reactions; (2) from a H-abstraction rate constant and the Brønsted relationship (log $k \propto$ ΔBDE). As Table II indicates, the values for *p*-methyl-, 3,4-benzo-, and *p*-methoxyphenols obtained from equilibrium measurements agree well with our values for the anisoles (average deviation = 0.4 kcal). However, ΔBDEs for 2,3-benzo-, *m*-hydroxy-, and *p*-hydroxy-substituted phenols derived form the Brønsted relationship are substantially different (average deviation = 1.8 kcal). As discussed later, we feel that this difference is likely due to the failure of the Brønsted relation[22] in H-abstraction reactions.

H. AM1 Calculations. In Table IV are given calculated energies of substitution in anisole and phenoxy radicals relative to substitution in benzene. Resulting ΔBDEs values are included in Table II (each value is simply the difference in effects on the radical and molecule given in Table IV).

In both meta and para positions, substituent effects on the heats of formation of the molecules are quite small, generally less than 1 kcal mol^{-1}. In fact, in all cases where substantial ΔBDE values are predicted, the effect is due primarily to the effect of the substituent on the radical. Generally speaking, substituent effects in the molecule tend to enhance the net effects for para substituents, and diminish the net effects for meta substituents.

In qualitative agreement with experiment, in the para position, both electron-repelling and -conjugating substituents weaken the O–methyl bond while electron-withdrawing substituents strengthen it.

For ortho substituents, effects are generally significant in both the molecule and radical. However, for the two exceptional substituents, hydroxy and amino, the substituent effect in the radical is dominant. Both OH and OCH_3 were predicted to have similar net effects, but for *o*-methoxy the major contribution is

Table IV. Calculated (AM1) Differences in Energies of Substitution in Anisoles (mol) and Phenoxy Radicals (rad), Relative to Substitution in Benzene

	substituent position							
	ortho		meta		para		other	
subst	mol	rad	mol	rad	mol	rad	mol	rad
NH_2	0.7	-9.6	-0.3	0.5	0.7	-6.5		
OH	0.1	-5.9	-0.4	0.2	0.6	-3.4		
OCH_3	3.4	-1.9	-0.4	-0.3	0.6	-3.5		
CH_3	0.8	-0.8	-0.1	0.1	-0.1	-1.5		
CH_2OH	0.6	-0.4						
F	2.7	-0.3	0.3	2.3	0.4	-2.0		
penta-F							7.5	3.5
Cl	4.2	3.3	0.4	1.4	0.0	0.5		
Br	4.0	3.4	0.4	1.1	-0.1	0.8		
$COCH_3$	1.6	1.6	0.4	1.0	-0.8	1.1		
$CHCH_2$	2.2	-0.6						
CN	1.4	2.5	0.5	2.1	-0.5	1.3		
NO_2	2.9	5.5	1.1	3.6	-1.0	3.3		
2,3-benzo							0.6	-4.7
3,4-benzo							-0.4	-0.8

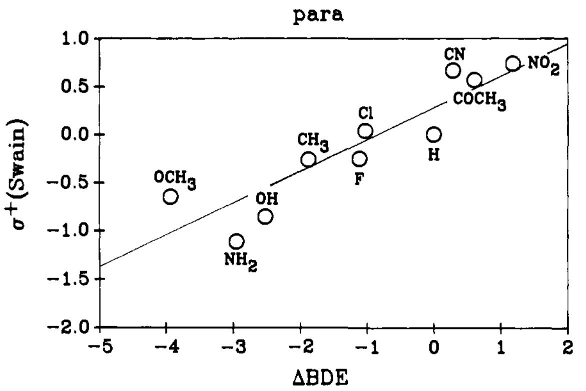


Figure 2. Substituent constant σ^+ vs ΔBDE.

predicted to result from relief of strain in the molecule. An experimental measurement of the heat of formation of this *o*-methoxyanisole, however, shows no measurable destabilization.[22] We believe that the calculation fails for this case.

The average deviation of experimental and AM1 ΔBDE values is 1.5 kcal, a reasonable value.[24] However, this was sufficiently large to obscure some of the most interesting findings. For instance, contrary to experiment, calculations predicted that OH and OCH$_3$ would have similar effects, that NH$_2$ would have a significantly larger effect than OH, and that para electron-accepting substituents (especially nitro) would have significantly larger relative effects than observed.

I. Substituent Constants and ΔBDE. In this section we examine the relation between ΔBDE and two substituent constants, σ^+ (from solvolysis of cumyl chlorides in 90% acetone[34]) and σ_R (Taft's resonance term[35]).

Values for the σ^+ substituent constant are widely used to correlate the effect of substituents on rates of (ionic) electrophilic reactions. However, σ^+ is also strongly correlated with rate constants for H-abstraction from phenols by polar radicals.[17,36] The physical basis of this correlation with noncharged species is not obvious. Conceivably, σ^+ might be strongly correlated with ΔBDE, in which case, at least for phenoxy radical reactions, σ^+ works simply because it provides a coarse, indirect measure of ΔBDE.

To examine this idea, ΔBDE is plotted against σ^+ in Figure 2. While the two variables are clearly correlated ($r = 0.91$), there are sizable deviations. The large deviations are well outside the range of experimental error. The correlation coefficient of Mulder et al.[14] between ΔBDE and σ^+ was significantly higher ($r = 0.98$), but only four substituents were examined. ΔBDE is a major, but not the sole contributor to σ^+. Separate contributions to σ^+ can arise from interactions of net charge with the substituent. In fact, differences in trends of ΔBDE and σ^+ can be rationalized if this extra stabilization of charge is due to a charge–dipole interaction. Specifically, the larger deviations in ΔBDE versus σ^+ trends seem to correlate with trends in the effective dipole moment of the substituent.

Consider, for instance, methoxy and hydroxy substituents. While their σ^+ values are nearly the same, *p*-methoxy has a significantly greater bond-weakening effect than does *p*-hydroxy. It seems plausible that the higher bond dipole of OH increases the ability of this substituent to stabilize positive charge, compensating for its inherently weaker resonance contribution to σ^+.

The relatively small magnitude of the bond-strengthening effects of the electron-withdrawing groups in comparison to larger differences in σ^+ values can also be rationalized in this manner. That is, dipole–charge interactions in the cations cause a destabilization that has no parallel in the uncharged radicals.

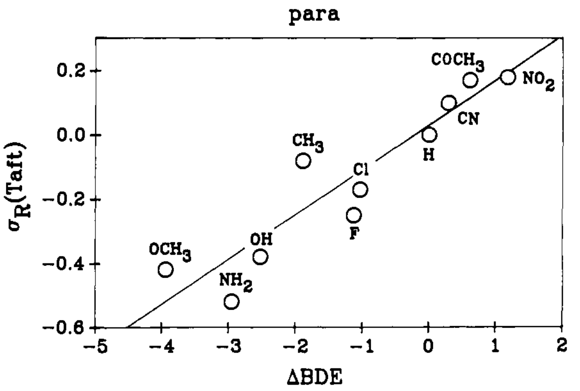


Figure 3. Taft's resonance term for substituent constants, σ_R,[35] vs ΔBDE.

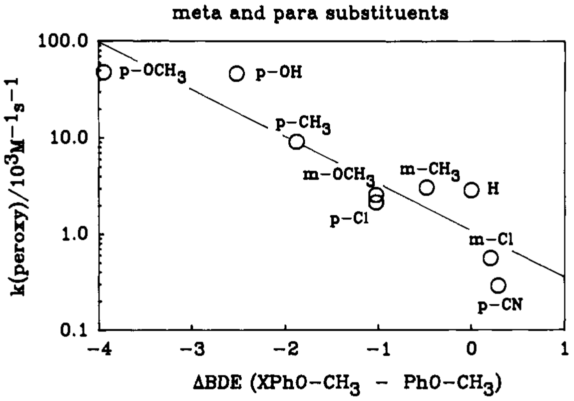
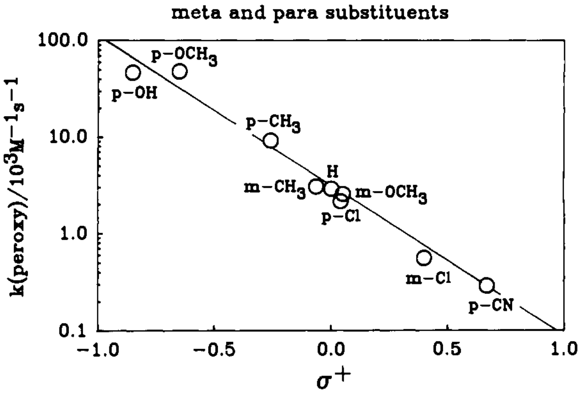


Figure 4. Rate constant, k_{abs}/M^{-1} s^{-1}, for the phenolic H-abstraction reaction by peroxy radical of a number of phenols (Howard and Ingold[17]) vs ΔBDE of the corresponding anisoles.



(Rate data from Ingold and Howard, 1963)

Figure 5. Rate constant, k_{abs}/M^{-1} s^{-1}, for the phenolic H-abstraction reaction by peroxy radicals for a number of phenols (Howard and Ingold[17]) vs the electrophilic substituent constant σ^+.

In the approach of Taft and co-workers,[35] net substituent effects are separated into several terms. The one most pertinent to the present studies is σ_R, a term designed to represent substituent effects on resonance energy. In Figure 3, ΔBDE is plotted against σ_R. Overall, the correlation constant is 0.92, virtually the same as for the σ^+/ΔBDE comparison. This is not surprising since σ^+ and σ_R are themselves strongly correlated ($r = 0.96$ for the substituents examined in this work). However, if the methyl and methoxy substituents are ignored, we obtain a remarkable correlation of ΔBDE and σ_R of 0.99. Unfortunately no other single term in Taft's scheme can account for the apparently exceptional behavior of both methyl and methoxy.

J. Phenolic H-Abstraction Rates in Relation to ΔBDE. Extensive kinetic studies of the effect of substituents on rates of H-transfer to oxygen-centered radicals have been reported by Ingold,[17] Simonyi,[36] and their co-workers. Excellent linear correlations between log k_{abs} and σ^+ for para substituents have been

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(34) Okamoto, Y.; Brown, H. C. *J. Org. Chem.* **1957**, *22*, 485.

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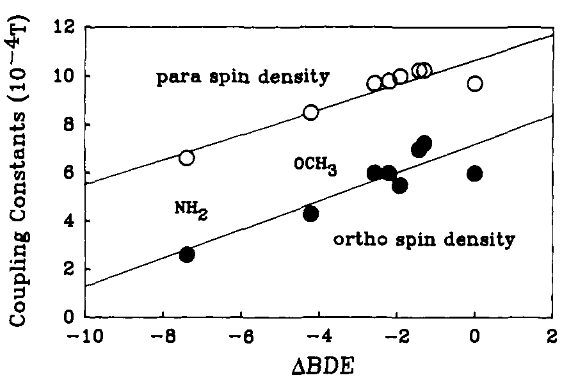
(36) Simonyi, M.; Fitos, I.; Kardos, J.; Kovacs, I.; Lukovits, I.; Pospisil, J. *J. Chem. Soc. Faraday Trans.* **1977**, *73*, 1286.



(ESR data from Dixon et al. 1975)

Figure 6. Ortho and para H hyperfine coupling constants for ortho-substituted phenoxy radicals[16] vs ΔBDE for the corresponding substituted anisoles.

reported by both groups. In Figures 4 and 5 Ingold's rates are plotted versus both ΔBDE and σ^+. Reaction rates correlate distinctly better with σ^+ ($r = 0.99$) than with ΔBDE ($r = 0.92$), immediately suggesting that polar kinetic effects are operative in these reactions.

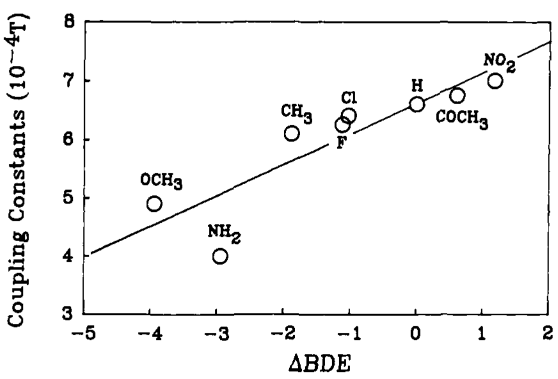
For ortho substituents, there seems to be little correlation between H-abstraction rates and ΔBDE. Simonyi and co-workers[36] have determined the H-transfer rates by polyvinyl acetate radicals from *o*-, and *p*-hydroxyphenols to be approximately equal. Franz and co-workers have found H-abstraction by the 2-allyl benzyl radical from *p*-hydroxyphenol to be slightly faster than from *o*-hydroxyphenol.[37] Yet, our results indicate that the O–H bond the ortho isomer is 5 kcal weaker than the para isomer. Apparently, the full stabilization effect of the *o*-hydroxy group is not developed in the transition state for abstraction.

K. ESR Spin Density and ΔBDE. Since the above calculations suggest that ΔBDE values for para substituents are due primarily to differences in the stability of the radicals, one might expect a correlation between ESR spectral parameters of para-substituted phenoxyl radicals and ΔBDE. To compare ΔBDE and ESR measurements we extend a line of reasoning developed by Arnold and co-workers for substituted benzyl radicals.[7] They used proton hyperfine coupling constants (hfcc, or, loosely, odd-electron densities) at the benzylic carbon as a measure of the net stabilizing effect of the substituent. The greater the stabilization by a substituent, they reasoned, the more it would withdraw electron density from the remainder of radical, hence the lower would be the electron density at the benzylic position. The opposite effect would result from a destabilizing substituent.

Since electron densities cannot be readily measured at the oxygen atom in a phenoxyl radical, to apply Arnold's ideas we use hfcc values from conjugated ring positions. Dixon and co-workers carried out an extensive series of studies providing these data.[16] Hfcc values for ring protons were highly sensitive to the substituent, in sharp contrast to benzylic radicals where the effects on ring protons were barely measurable.[7]

Plots of ΔBDE versus Dixon's hfcc values for phenoxy radicals measured by Dixon and co-workers are given for ortho and para substituents in Figures 6 and 7. For ortho substituents, hfcc values at each of the two different conjugated positions are used. For para substituents, values at only one was measurable. Perhaps surprisingly, the correlation was at least as good for ortho substituents as for para substituents. Substituent effects on the stability of the ortho-substituted molecules are therefore either substantially smaller than predicted by AM1 or are strongly correlated with effects on the radical. Both ΔBDE and hfcc effects for meta substituents were too small to make a meaningful comparison of these properties.

A closer inspection of the ESR spin densities, however, calls into question the simple physical picture that we suggested above for phenoxyl. Dixon and co-workers found that substituent-induced changes in spin density at positions conjugated to the substituent were almost exactly compensated by opposite changes in the neighboring nonconjugated positions. Hence, the substituent affected the degree of alternation of hfcc values rather than simply their absolute values, thereby obscuring the physical connection between hfcc and substituent stabilization energies for phenoxyl radicals.



(ESR data from Dixon et al. 1975)

Figure 7. Ortho H hyperfine coupling constant for para-substituted phenoxy radicals[16] vs ΔBDE for the corresponding substituted anisoles.

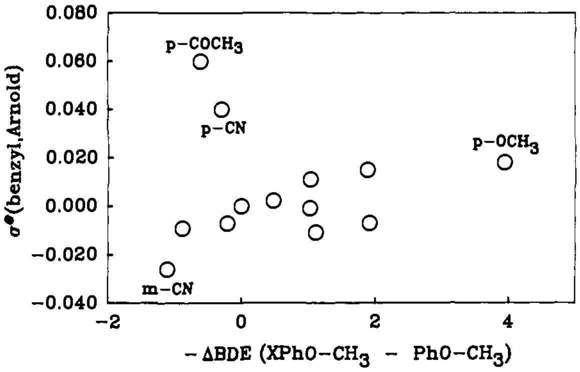


Figure 8. ESR-derived benzyl substituent parameter $\sigma^{\bullet 7}$ vs ΔBDE of anisoles.

L. Benzyl versus Phenoxyl. Although direct measurements of ΔBDE for substituted benzyl radicals are few and effects are not large, it is generally accepted that these, like other carbon-centered radicals, do not follow trends in σ^+. The critical difference is that both electron-withdrawing ($\sigma^+ > 0$) and electron-donating groups ($\sigma^+ < 0$) at para positions stabilize carbon-centered radicals, whereas in phenoxy the latter substituents stabilize the radical and the former have the opposite effect. In the benzyl radical, ESR data are used by Arnold[7] to argue that the cyano group has a significant stabilizing effect in the para position and a distinct destabilizing effect in the meta position. In phenoxyl, we observe destabilization from both positions. Differences between substituted methyl radicals and phenoxyl are even clearer; both amino and cyano groups have large stabilizing effects on the methyl radical.[38,39]

In Figure 8, we plot ΔBDE versus Arnold's benzyl substituent constants. There is no noticeable correlation. A comparable lack of correlation exists between ΔBDE and other published measures of carbon-centered free radical substituent constants.[7a,40,41] The simple idea, stated in the Introduction, that phenoxyl radicals might behave like C-centered radicals because the odd-electron density is concentrated on carbon atoms is invalid. We are not able to offer a simple physical explanation for this difference. This lack of correspondence between phenoxy and benzyl radicals

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(38) Colussi, A. J.; Benson, S. W. *Int. J. Chem. Kinet.* **1977**, *9*, 307.

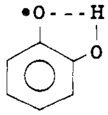
(39) King, K. D.; Goddard, R. D. *Int. J. Chem. Kinet.* **1975**, *7*, 83.

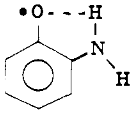
(40) Fisher, T. H.; Meierhoefer, A. W. *J. Org. Chem.* **1978**, *43*, 224.

(41) Duncturk, S.; Jackson, R. A.; Townson, H.; Agirbas, H.; Billingham, N. C.; March, G. *J. Chem. Soc., Perkin Trans.* **1981**, *2*, 1121.

illustrated in Figure 7, we feel, bodes poorly for the development of a simple universal scale of free radical substituent effects.

M. On the Origin of the Large *o*-Amino and *o*-Hydroxyl Effects. The most probable explanation for the large ortho effect of both hydroxyl and amino is the presence of a strong bond between the H atom on the substituent and the phenoxyl oxygen in the radical.





The present experiments measure, in effect, the change in Gibbs energy caused by the substituent. Since any H-bonding in the radical would reduce the reaction entropy (and therefore *A* factor for dissociation), the actual bonding enthalpy should be even larger than the reported ΔBDE. Assuming that this bonding increases the barrier of rotation from 0 to ca. 8 kcal mol^{-1}, and then using Pitzer's tables,[42] we estimate that an additional 3 kcal mol^{-1} should be added to the reaction enthalpy from this effect. Thus, the H-bonding energy in the *o*-hydroxyphenoxy and *o*-aminophenoxy radicals is estimated to be ca. 10 kcal mol^{-1} greater than in the parent molecules. These are very strong hydrogen bonds.

VI. Summary

We have determined the effects of a number of substituents on the O–CH_3 bond in anisoles. The range of ΔBDE (kcal mol^{-1}) from this and previous studies for ortho substituents was −0.2 to −7.4, for para 1.2 to −3.9, and for meta 1.2 to −1.1. In the ortho and para positions, electron-donating substituents ($\sigma^+ < 0$) significantly weakened bonds; electron-accepting groups ($\sigma^+ > 0$) had significantly less effect but strengthened bonds somewhat when in the para position. Meta substituents showed no clear systematic trends.

An exceptionally large bond weakening was observed for the *o*-NH_2 substituent, quite similar to the value for the *o*-OH group reported recently. It is tentatively proposed that this effect is due to an unexpectedly strong H bond in the radical. We calculate that such a bond is ca. 10 kcal mol^{-1} stronger than in the molecule.

Phenolic H-abstraction rates for para substituents show some correlation with ΔBDE, but are correlated much better by σ^+ substituent constants. This is interpreted as consequence of significant polar kinetic effects in the H-abstraction reactions.

ΔBDE values for both ortho and para substituents are well correlated by ESR hyperfine coupling constants of substituted phenoxy radicals. However, unlike seemingly related effects observed for substituted benzyl radicals, stabilizing substituents decrease the apparent alternation of hfcc's (spin density) in the radical rather than simply withdrawing density from the other sites.

ΔBDE correlates poorly with existing measures of substituent effects for carbon-centered radicals. This is somewhat surprising since in terms of odd-electron density, phenoxy radicals are essentially carbon centered radicals.

Acknowledgment. This work was supported by a grant from the Gas Research Institute.

Registry No. *o*-NH_2PhOCH_3, 90-04-0; *o*-$HOPhOCH_3$, 90-05-1; *o*-$CH_3OPhOCH_3$, 91-16-7; *o*-CH_3PhOCH_3, 578-58-5; *o*-$HOCH_2PhOCH_3$, 612-16-8; $PhOCH_3$, 100-66-3; *o*-$FPhOCH_3$, 321-28-8; $(F)_5PhOCH_3$, 389-40-2; *o*-$ClPhOCH_3$, 766-51-8; *o*-$BrPhOCH_3$, 578-57-4; *o*-$CH_3COPhOCH_3$, 579-74-8; *o*-$H_2C{=}CHPhOCH_3$, 612-15-7; *o*-$CNPhOCH_3$, 6609-56-9; *o*-$O_2NPhOCH_3$, 91-23-6; *m*-NH_2PhOCH_3, 536-90-3; *m*-$HOPhOCH_3$, 150-19-6; *m*-$CH_3OPhOCH_3$, 151-10-0; *m*-CH_3PhOCH_3, 100-84-5; *m*-$FPhOCH_3$, 456-49-5; *m*-$ClPhOCH_3$, 2845-89-8; *m*-$CH_3COPhOCH_3$, 586-37-8; *m*-$CNPhOCH_3$, 1527-89-5; *m*-$O_2NPhOCH_3$, 555-03-3; *p*-NH_2PhOCH_3, 104-94-9; *p*-$HOPhOCH_3$, 150-76-5; *p*-$CH_3OPhOCH_3$, 150-78-7; *p*-CH_3PhOCH_3, 104-93-8; *p*-$FPhOCH_3$, 459-60-9; *p*-$ClPhOCH_3$, 623-12-1; *p*-$CH_3COPhOCH_3$, 100-06-1; *p*-$CNPhOCH_3$, 874-90-8; *p*-$O_2NPhOCH_3$, 100-17-4; 1-methyoxynaphthalene, 2216-69-5; 2-methoxynaphthalene, 93-04-9.

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Real-Time Reaction Monitoring by Continuous-Introduction Ion-Spray Tandem Mass Spectrometry

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Contribution from Drug Testing and Toxicology, New York State College of Veterinary Medicine, Cornell University, 925 Warren Drive, Ithaca, New York 14850, and SCIEX, 55 Glencameron Road, Thornhill, Ontario, Canada L3T 1P2. *Received November 18, 1988*

Abstract: A temperature-controlled reaction vessel was closely coupled to the ion-spray LC/MS interface on an atmospheric pressure ionization, triple quadrupole mass spectrometer and used to study mechanistic and kinetic aspects of reactions taking place in solution. Free access to the reaction vessel and temperature control as well as minimal sample consumption make continuous-introduction ion-spray mass spectrometry a useful approach for real-time measurement of reactions. The reaction medium, reactants, and products were transferred to the ion source of the mass spectrometer from the reaction vessel in less than 1 s. A variety of model reactions have been investigated to demonstrate the feasibility and potential for continuous-introduction ion-spray mass spectrometry for real-time reaction monitoring. The half-life for the solvolysis of methandrostenolone sulfate in aqueous medium and the Michaelis–Menten constant of the enzymatic hydrolysis of *O*-nitrophenyl β-D-galactopyranoside by lactase were determined. The enzymatic hydrolysis of dynorphin 1–8 by α-chymotrypsin and leucine aminopeptidase and the reduction of the disulfide bridge in oxytocin with β-mercaptoethanol were obtained on-line to emphasize the technique's capability for peptide sequencing and structural elucidation.

The study of reaction mechanisms and kinetics is fundamentally important for characterizing synthetic pathways of chemical reactions and for understanding biochemical processes occurring in life science. Nearly all known analytical techniques have been used to follow reaction mechanisms and kinetics.[1] The objectives and challenges imposed by the complexity and speed of the reaction under investigation require instrumentation possessing the necessary selectivity and sensitivity to follow the reaction to completion.

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