Computational Modeling of Substituent Effects on Phenol Toxicity

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Received March 3, 2008

Standard computational models of cytotoxicity of substituted phenols relate the toxicity to a set of quatitative structure−activity relationship (QSAR) descriptors such as log P, pK_a, OH bond dissociation enthalpy (BDE), etc. Implicit in this approach is the idea that the phenoxyl radical is disruptive to the cell and factors increasing its production rate will enhance the toxicity. To improve the QSAR correlations, substituents are usually divided into electron-donating groups (EDG) and electron-withdrawing groups (EWG), which are treated separately and thought to follow different mechanisms of toxicity. In this paper, we focus on one important aspect of toxicity, the rate constant for production of phenoxyl radical. Activation energies are obtained for the reaction of X-phenol with peroxyl radical by using the Evans−Polanyi principle, giving rate constants as a function of ΔBDE values for both EDG and EWG sets. We show that (i) a plot of log k for phenoxyl formation vs ΔBDE shows a double set of straight lines with different slopes, justifying the usual EDG and EWG separation but without requiring any change in mechanism; (ii) the same method can be effectively used for different target radicals (e.g., *tert*-butoxyl) or different sets of parent compounds (e.g., substituted catechols), thus giving a useful general approach to analysis of toxicity data; (iii) regions of constant toxicity in all cases are predicted; and (iv) we argue that competing parallel mechanisms of toxicity are likely to be dominant for EWG-substituted phenols.

Introduction

The toxicity of phenols to cell cultures and other biological systems has been the subject of ongoing investigation, because of its relevance to human health. A variety of QSAR studies have been performed in an effort to establish a mechanism for the toxicity. In 1998, Selassie et al. (*1*) first divided the treatment of substituted phenols into sets containing electron-donating groups (EDG) and electron-withdrawing groups (EWG). They showed that the EDG set, which contained the more toxic phenols, correlated strongly with the electronic parameter σ^+ and weakly with log P, whereas the EWG set correlated only with log P. They attributed the toxicity of the EDG set to a phenoxyl radical-mediated process, while the EWG set was described as a nonspecific toxicity mediated by hydrophobicity. Another study by Selassie and co-workers (*2*) switched to the bond dissociation enthalpy (BDE) of the OH bond instead of σ^+ with improved correlation but the same conclusion. Additional work by Hansch and co-workers over the next few years (*3, 4*) also implicated phenoxyl radical processes for EDG. However, a QSAR study of polysubstituted phenols deviated from predicted behavior (*5*). Use of hepatic cells by O'Brien and co-workers (*6*) gave a different dependence of toxicity on BDE, but the dependence on BDE was very weak. Because these authors used only a 2 h exposure of the phenol to the hepatic cells, it is probable that they were testing nonspecific toxicity, which correlates with log P. Summarizing the literature, most of the QSAR work to date suggests that there is a change in mechanism that occurs near phenol itself, that is, at the boundary between EDG-phenols and EWG-phenols. The toxicity of the EDG set is thought to be mediated by the formation of phenoxyl radical, whereas the toxicity of the EWG set is apparently due to disruption of the cell membrane, which would correlate with lipophilicity (as measured by log P).

Because EDG-phenols can act as phenolic antioxidants, for example, by breaking the chain reaction of lipid peroxidation, the reaction of phenol + peroxyl radical has been well-studied. For example, Burton and co-workers (*7*) measured the bimolecular rate constants, k_2, for the reaction of methylperoxyl radical with phenolic compounds related to vitamin E. They obtained values for k_2 at 30 °C ranging from ca. 2×10^4 M^{-1} s^{-1} for 2,6-dimethylphenol up to 5×10^6 for compounds related to vitamin E. Because estrogens are phenols, their effectiveness as antioxidants has also been studied experimentally (*8–10*). Quantitative structure−activity relationship (QSAR) methods applied to various estrogen derivatives showed that they obeyed standard EDG trends described above (*11*).

A theoretical approach to understanding the toxicity of phenols is still at an early stage, but some steps have been made in that direction. The energy profile along the H-atom transfer (HAT) reaction path for phenol + peroxyl radical → phenoxyl radical + peroxide has been studied by several authors (*12–15*), mostly using the B3LYP density functional method. Klein and co-workers (*15*) discussed calculations relevant to whether the reaction path was HAT, or sequential proton loss electron-transfer (SPLET), and favored the latter in aqueous solution. Finally, for a series of substituted phenols, Singh et al. (*16*) showed that calculated BDEs gave a good correlation with experimental log k values. This implies that for this reaction the Evans−Polanyi principle (*17*) holds, that is, the activation energy E_a is proportional to the enthalpy change for the reaction.

In this paper, we examine the separation of phenol toxicity data into EDG and EWG sets. We analyze this separation in terms of the rate constant for formation of phenoxyl radical and try to obtain an expression for toxicity that covers the whole range of data. Unexpectedly, even if we restrict ourselves to a definition of toxicity that depends only on the rate of phenoxyl radical formation, there

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10.1021/tx800085a CCC: $40.75
Published on Web 05/31/2008

is nevertheless a natural separation into EDG and EWG sets caused by the different dependence of the activation energy for the two sets. The two regions can be fitted exactly by linear functions of the respective BDEs. The same approach is used to discuss toxicity for a series of substituted catechols (different parent molecule, same target radical) or by using *tert*-butoxyl radical (same phenol parent, different target radical).

Theoretical Methodology

The usual measure of toxicity is in terms of C_{50}, the concentration of compound that inhibits cell growth (or causes cell death) by 50%. QSAR correlations usually use the log of the inverse, that is, log $1/(C_{50})$, so larger values imply greater toxicity. For a parallel mechanism involving nonspecific and specific toxicity, then, we can write log $1/(C_{50}) = a \log P + b$ [concentration of phenoxyl radical]. Here, we are assuming that the phenoxyl radical mediates the observed specific toxicity and that hydrophobicity, as measured by log P, mediates the nonspecific toxicity. To agree with the separation into EDG and EWG groups, this could arise naturally if, for example, specific toxicity became dominant near phenol and continued to be dominant over the range of EDG.

Furthermore, we assume that the cell is subject to oxidative stress and that superoxide and lipid peroxyl radicals are being generated. Because the conjugate acid of $O_2^{\bullet -}$ is hydroperoxyl radical, $HO_2^{\bullet}$, and because the BDE of peroxides ROO−H does not change much as R is varied, we will use $HO_2^{\bullet}$ as our target radical. For HAT reactions, we can use gas-phase BDE data, which is appropriate for solvents of low dielectric constant or for reactions that occur inside the cell membrane. Because the low dielectric solvent does not stabilize ions, a neutral HAT reaction is the expected mechanism.

The bimolecular HAT reaction of interest is reaction 1:

$$X{-}ArOH + HO_2^{\bullet} \rightarrow X{-}ArO^{\bullet} + H_2O_2 \qquad (1)$$

where X refers to the substituent on the phenol ArOH. The rate of formation of phenoxyl radical, X−ArO$^{\bullet}$, is given by d[ArO$^{\bullet}$]/dt = k_2[X−ArOH][$HO_2^{\bullet}$], where k_2 is the bimolecular rate constant. Its magnitude does not exceed ca. 10^6 L/mol s for polysubstituted phenols (see below). The typical concentrations of $HO_2^{\bullet}$ would not exceed high nanomolars or possibly micromolars, because this is a transient species that disproportionates into H_2O_2 and O_2 (*18*). Assuming 1 μM for $HO_2^{\bullet}$ and a steady-state background concentration of X−ArOH equal to 10 μM, the rate of formation of phenoxyl radical from HAT would be 10^{-5} M s^{-1} or 10 μmol per L per s. This is the radical production rate against which any other mechanism can be compared. As phenoxyl radical is formed, it (or its metabolites) is scavenged by the cell. However, the faster the rate of formation of the phenoxyl radical is, the higher is the oxidative stress on the cell, hence the more toxic the phenol (*19, 20*).

A SPLET mechanism has been proposed recently by Litwinienko and Ingold (*21–24*) for reaction of substituted phenols with the DPPH radical. If the target radical is hydroperoxyl, then the reaction sequence is

$$X{-}ArOH + H_2O \rightarrow X{-}ArO^{-} + H_3O^{+} \qquad (2.1,\ \text{proton loss})$$

$$X{-}ArO^{-} + HO_2^{\bullet} \rightarrow X{-}ArO^{\bullet} + HO_2^{-} \qquad (2.2,\ \text{electron transfer})$$

The anion HO_2^{-} can then reform its conjugate acid so that the overall stoichiometry is identical to HAT. For SPLET, however, we require enthalpy changes for reactions in aqueous solution, since ions are present in both steps. A comparison of the two methods was given recently by Klein and Lukes (*15*). These authors favor an SPLET mechanism in water. However, they made no attempt to estimate the rate of phenoxyl radical formation for the two mechanisms, so we find their conclusion to be premature. Our own attempts to estimate phenoxyl formation rates by SPLET are discussed later.

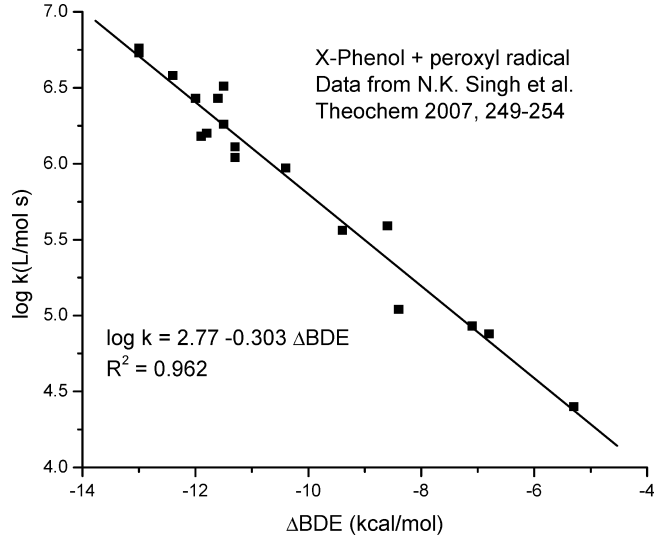

Figure 1. Fit of log k (Burton experimental data) vs Δ BDE (calculated gas-phase data from Singh).

Results and Discussion

Singh et al. (*16*) analyzed experimental data (*7*) for substituted phenols related to vitamin E. Using density functional theory (DFT), they calculated the gas-phase BDE for phenol and the BDE relative to phenol for all substituted phenols containing EDG, that is, where ΔBDE is negative. A plot of the Singh data for log k (experiment) vs ΔBDE (calculated) is shown in Figure 1. Note that the Singh calculated BDE values (ΔH_r, their notation) range only from −12.4 to −5.3 kcal/mol; that is, they all are in the range of electron-donating substituents relative to phenol. This is understandable since the data of ref *7* are relevant to antioxidants, where the objective is to lower the BDE relative to phenol. It would be desirable to extend this graph into the EWG range where log k = 2.77 and lower. However, there is no reason to expect that the theoretical treatment would be any less accurate in this region; the only real question is whether there would be a change of mechanism (see below). For the present purposes, we assume that the same mechanism holds and determine the consequences of this assumption.

Approximate values of ΔBDE values for substituted phenols are as follows: *o*,*o*-dimethyl, −4; *p*-OH, −6; *o*-OH, −9; and *o*,*o*-dimethyl, *p*-OH, −10; it is combinations of these EDG substituents that provided the experimental data for vitamin E derivatives in Figure 1. The data are well-fitted with the equation log k = 2.77 −0.303 ΔBDE (R^2 = 0.962). This correlation and the Arrhenius equation for k form the starting point for our theoretical treatment.

From the Arrhenius expression for the rate constant $k = A \exp(-E_a/RT)$, we obtain $\log k = \log A - E_a/(2.303RT) = \log A - 0.733E_a$, for E_a in units of kcal/mol at T = 298.15 K. We equated the theoretical and experimental expressions, $\log k = \log A - 0.733E_a = 2.77 - 0.303$ ΔBDE. Rearranging gives $E_a = 1.3644 \log A + 0.4134$ ΔBDE − 3.779. The Evans−Polanyi

Table 1. Activation Energy (E_a) and log k for EDG- and EWG-Phenol as a Function of ΔBDE[a]

ΔBDE (kcal/mol)		Ea (kcal/mol)	Log k (this work)	Log k (Singh)[a]
-24		0	8	
-20		0	8	
-16		0.5216	7.6177	
-12	EDG	2.1752	6.4057	6.45
-8		3.8288	5.1937	5.2
-4		5.4824	3.9817	4.1
0 (phenol)		7.136	2.7697	
+4		9.4824	1.0499	
+8	EWG	11.8288	-0.6699	
+12		14.1752	-2.3897	
+16		16.5216	-4.1095	

[a] Data are for k = A exp($-E_a/RT$), where T = 298.15 K and A = 1.0 × 10^8 L/mol s. [b] Data from ref *16*.

principle (*17*) is followed, which states that the activation energy E_a is linearly dependent on the enthalpy change for a series of reactions having the same type of transition state.

The A factor was determined by reproducing the magnitude of log k given by Singh for several points in ΔBDE over the range −5 to −12 kcal/mol. A good fit was found to the experimental log k vs ΔBDE plot using $A = 1.0 \times 10^8$ M^{-1} s^{-1}. Combining these results, for EDG-substituted phenols, we obtain

$$E_a = 7.136 + 0.4134\ \Delta\text{BDE (in kcal/mol)} \qquad (3)$$

Knowing E_a as a function of BDE and A, we generated artificial data values at regular intervals over a wide but plausible EDG range from −24 to 0 kcal/mol (Table 1). Here, the extreme negative end of the range (BDE = 64 kcal/mol) is easily reachable for a polysubstituted phenol; for example, 2,6-hydroxy-4-aminophenol is predicted to have a BDE of 64 kcal/mol (*25*), corresponding to ΔBDE = −24 kcal/mol. A plot of the simulated data from Table 1 for the EDG set shows that the activation energy $E_a > 0$ over the range 0 to −17.3 kcal/mol. The plot is linear over that range, with log k = 2.7697 − 0.303 ΔBDE.

From Table 1, the barrier height for phenol reacting with hydroperoxyl radical (for hydrogen peroxide BDE = 88 kcal/mol, so reaction is thermoneutral with phenol) drops from 7.1 kcal/mol in phenol to zero for ΔBDE = −17.3 kcal/mol, showing the profound reduction in barrier height for substituted phenols containing strong EDG. For ΔBDE values more negative than −17.3, the activation energy remains zero, so the limiting value is log k = constant = 8.0, Because we are assuming that toxicity is related to the rate of formation of phenoxyl radical, there must be a zone of constant toxicity for polysubstituted phenols with strong EDG. This is a testable hypothesis: A set of phenols could be constructed with BDE values below 71 kcal/mol, and there should be negligible variation in toxicity (assuming no change in mechanism).

How can we determine the activation energy dependence for phenols containing EWG? The reaction phenol + peroxyl → phenoxyl + peroxide is now endothermic, since ΔBDE is positive for EWG. The barrier height must be at least equal to the endothermicity and must join smoothly with the EDG set;

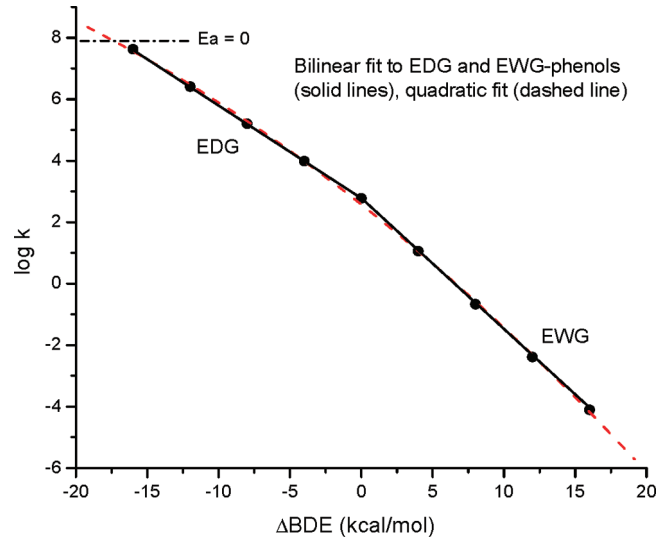

Figure 2. Bilinear fit to EDG- and EWG-substituted phenols (solid lines). Also shown is the second-degree polynomial fit over the same range (dashed line).

that is, the barrier is 7.136 kcal/mol for ΔBDE = 0 (phenol). The simplest approximation is to assume that the reverse reaction, which is now exothermic, has the same barrier height dependence and A factor as the forward reaction (see, however, ref *26*). So, now, we can construct a complete graph of log k vs BDE as follows: for 78 kcal/mol (ΔBDE = −10), the barrier is 7.13 − 4.13 = 3.00. The barrier height for 98 kcal/mol (ΔBDE = +10) will be 10 (the endothermicity) + 3.00 (residual barrier viewed from products toward reactants) = 13.00 kcal/mol. The general formula for E_a when ΔBDE > 0 is E_a = 7.136 − 0.4134 ΔBDE + ΔBDE = 7.136 + 0.5866 ΔBDE. This simple approximation, which should be accurate for symmetrical reactions of the type X−ROO$^\bullet$ + Y−ROOH → X−ROOH + Y−ROO$^\bullet$, where X and Y are different functional groups, allows completion of Table 1 for positive ΔBDE values, that is, the EWG set. Again, the EWG function is linear, with the same intercept but with a different slope from the EDG set, giving log k = 2.7697 − 0.430 ΔBDE. Combining both data sets onto the same figure results in a bilinear fit covering the entire range of data (Figure 2).

A typical QSAR analysis observing the change in slope near phenol would probably conclude that there was a change in reaction mechanism that was responsible. However, in the present example, the mechanism is identical; it is still the bimolecular HAT reaction of peroxyl radical with a substituted phenol. To further emphasize this point, it is also possible to fit the data over the range −16 to + 16 using a single function. Using a second degree polynomial, for example, gave log k = 2.5718 − 0.3665 ΔBDE − 0.0034(ΔBDE)^2 with R^2 = 0.9994 (Figure 2c), that is, almost an exact fit. In fact, it is the different dependence of the activation energy on BDE for EDG and EWG-phenols that caused the change in slope. Note that this does not rule out an actual change in mechanism when parallel (competing) mechanisms are possible (vide infra).

Rate constants for EDG range from 10^3 (phenol, BDE = 88) to ca. 10^7 (pyrogallol, BDE = 74). Rate constants are dropping very fast for EWG: by 92 kcal/mol (ΔBDE = +4), they are down to to 10^1 M^{-1} s^{-1}. A further increase in BDE, for example, to 100 kcal/mol, results in a rate constant below 10^{-2} M^{-1} s^{-1}, so HAT reaction with peroxyl should then have an overall rate that is 8 orders of magnitude less than that described earlier, that is, negligible. Therefore, when there is a parallel mechanism available to generate toxicity, it is reasonable that it will become

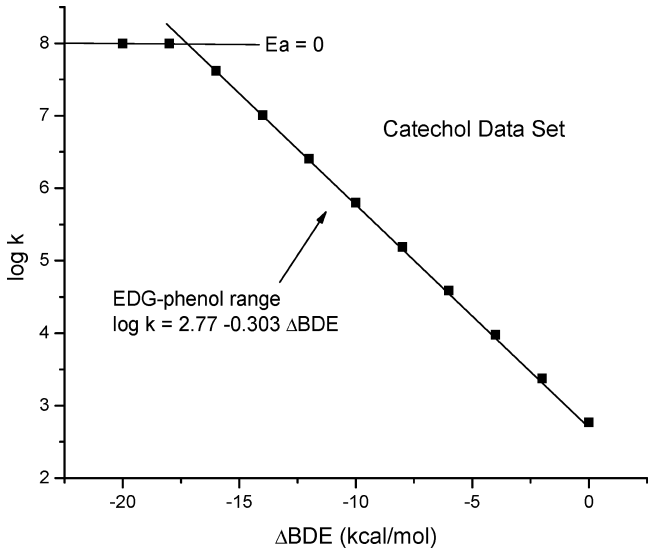

Figure 3. Log k vs ΔBDE for (hypothetical) substituted catechol data set.

significant somewhere close to the BDE region of phenol itself. This effect is amplified by the (almost 50%) steeper slope of log k vs ΔBDE.

Comparison of E_a to Literature Values. For phenol in a nonpolar solvent (e.g., styrene, above), the E_a is predicted to be 7.1 kcal/mol. The vitamin E model compound HPMC has ΔBDE = −12 kcal/mol, so Table 1 shows that E_a should be about 2.2 kcal/mol for HPMC + alkylperoxyl radical. According to Foti et al. (*26*), an E_a of 3 kcal/mol for peroxyl + phenol was obtained by laser flash photolysis at 298 K, so agreement with experiment is reasonable.

Changing the Substrate to Catechol. Polyphenols form an important class of antioxidants, but they also show cytotoxicity. O'Brien and co-workers have discussed the toxicity of substituted catechols using hepatic cells (*27*). In previous work, we calculated BDEs for a variety of substituted catechols (*28*). Using a DFT methodology that we termed medium-level model 2 (MLM2) (*29*), we obtained a BDE of 79 kcal/mol for catechol, so that a reaction of catechol with peroxyl is exothermic by this amount, that is, ΔBDE = −9 kcal/mol. Let us assume now that our data set for EDG and EWG-substtuted catechols has ΔBDE from −11 to + 9 kcal/mol relative to catechol or −20 to +0 relative to phenol.

Catechol has an internal hydrogen bond that complicates its reaction path with a peroxl radical. As a first approximation, we ignore the complication and treat catechol in the same way as we did phenol. Then, log A = 8 and E_a = 7.136 + 0.4134 ΔBDE where ΔBDE is relative to phenol. Over most of the range (0 to −17.3 kcal/mol), the data will follow the same linear function reported earlier for EDG-phenols, that is, log k = 2.77 −0.303 ΔBDE. Because the activation energy is zero at −17.3 kcal/mol and must remain zero for more negative values, there will again be a break in the slope at that point.

Figure 3 shows that reaction with peroxyl is already fast for catechol, with a rate constant ca. 10^5 M^{-1} s^{-1}. The figure also shows the break in slope reached below ΔBDE = −17.3 kcal/mol. Starting from a set of catechols, by analogy to phenol, toxicity will now depend on the rate of formation of the catechol. This break in slope is now more obvious than for the case of phenols, since for a substituted catechol data set the center of the range is already shifted lower than for phenols by 9 kcal/mol. This effect of limiting toxicity would be even more apparent for substituted pyrogallols, where the parent compound pyrogallol already has ΔBDE = −14 kcal/mol. A still more extreme example would be a series based on 2,4,6-trihydroxyphenol (ΔBDE = −20 kcal/mol), where the parent compound already lies in a region of constant toxicity.

Because log k is already ca. 3 for catechol containing a strong EWG, we predict that the phenoxyl radical toxicity mechanism will strongly dominate over the entire range of substituted catechols. In terms of observables, relative to phenol, the term in specific toxicity, ΔBDE, will be much larger than the term in log P. This prediction is testable, given a data set on substituted catechols reacting with peroxyl radicals (see ref *27*).

Changing the Target Radical to *tert*-Butoxyl. Now suppose we change the target radical to *tert*-butoxyl instead of peroxyl and return to the set of substituted phenols. The reaction is X−phenol + *tert*-butoxyl$^\bullet$ → X−phenoxyl$^\bullet$ + *tert*-butanol. The BDE of *tert*-butanol is ca. 102 kcal/mol (*30*), and its log A factor for reaction with phenol is ca. 10.5 (*31*). Reaction with phenol is now exothermic by 102 − 88 = 14 kcal/mol. The activation energy for 298 K was given by these authors as 2.8 kcal/mol for the reaction with phenol. Thus, the reaction is very fast, with a low barrier and a very high A factor.

Now suppose we have a range of X−phenols whose BDE varies by ±10 kcal from phenol. All reactions with *tert*-butoxyl will be exothermic. Das et al. (*32*) determined bimolecular rate constants for substituted phenols and obtained $k = 3.3 \times 10^8$ for phenol, 3.2×10^9 for *p*-hydroxyphenol, and 1.6×10^9 M^{-1} s^{-1} for *p*-methoxyphenol. Because the latter two molecules are predicted to have the same BDE, we will average their values to obtain $k = 2.4 \times 10^9$. Then, if log A = 10.5, using log k = log A − 0.733E_a, we obtain E_a = 2.70 kcal/mol for phenol (ΔBDE = 0) and 1.53 kcal/mol for X = (*para*-OH, OMe) (ΔBDE = −6 kcal/mol). This gives a fit with E_a = 2.70 + 0.195 ΔBDE. We expect that, just as with catechol + peroxyl radical, reactions of X−phenol with *tert*-butoxyl will be strongly dominated by phenoxyl radical formation. This prediction is testable.

SPLET Mechanism. As discussed above, reaction of X−phenol + peroxyl radical slows down rapidly for BDE values >88 kcal/mol. At the same time, because of increasingly powerful EWG, the pK_a of the X−phenol drops. For example, the pK_a of phenol is 9.98, whereas 4-nitrophenol is 7.15 (*33*). Therefore, more anion is formed at pH 7. However, anion formation is the first step in the SPLET mechanism, that is, reaction 2.1. Therefore, the stronger the EWG is, the easier it is for the phenol to form its anion. This means that SPLET provides a natural mechanism to take over just where HAT fades in importance, but it is still a mechanism that depends on phenoxyl radical toxicity.

Using SPLET kinetics, the rate of production of phenoxyl radical is given by d[ArO$^\bullet$]/dt = k_2 [ArO$^-$][ROO$^\bullet$], where k_2 is the bimolecular rate constant for reaction between ArO$^-$ and ROO$^\bullet$, that is, reaction 2.2. Assuming as before that the concentration of peroxyl radical is 1 μM, the concentration of anion I is determined by the pH and the pK_a. Assume as above that the initial concentration of the parent phenol is 10 μM, the pH is 7 and the pK_a is also 7. In that case, the initial equilibrium gives [ArOH] = [ArO$^-$] = 5 μM. Electron transfer rate constants are usually greater than HAT rate constants, so assume $k_2 = 10^7$ M^{-1} s^{-1}. The rate of formation of phenoxyl radical in this case is $[10^7][5 \times 10^{-6}][10^{-6}] = 50$ μM per s. This is faster than the rate of generation of phenoxyl radical in this regime, so the switch to an SPLET mechanism is plausible for EWG. Note that this is still a phenoxyl radical mechanism for toxicity.

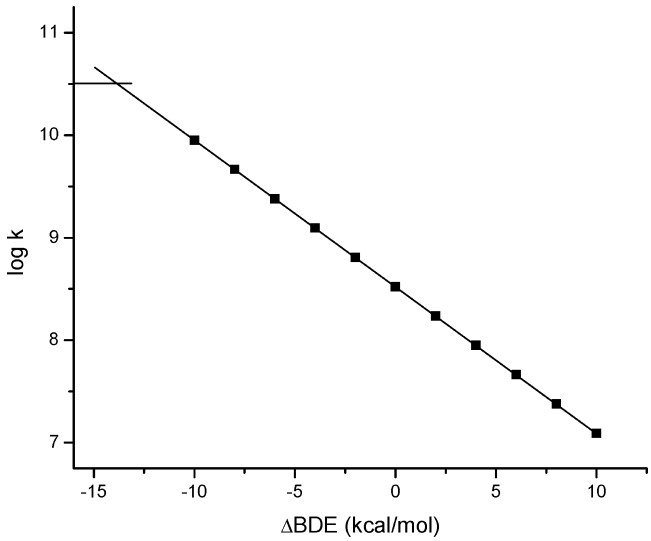

Figure 4. Plot of log *k* vs ΔBDE for *tert*-butoxyl + X−phenol.

However, the QSAR descriptors will be different, and the pK_a of the acid should be relevant.

Which mechanism will occur in a biological system, HAT or SPLET, and over what range of ΔBDE values? In fact, these reactions will occur in parallel, and it is a question of which one is dominant. It seems clear that as the radical reaction takes place in more lipophilic media (e.g., peroxyl radical reaction with vitamin E in the lipid bilayer of the cell) that HAT will predominate, but in aqueous media, this must be considered an open question. As stated above, pH is a factor, so one or the other mechanism could predominate in different cellular environments.

Baseline or Nonspecific Toxicity. Studies on substituted phenols by Selassie and co-workers (*1*–*5*) and O'Brien et al. (*6*) have consistently shown that toxicity of EWG-phenols correlates well with log *P* but not with BDE. This has been attributed to baseline or "nonspecific" toxicity, implying a switch in mechanism. Our understanding of this mechanism at the cellular level is that the phenols with the highest log *P* values may deposit into the cellular membrane bilayer and not be transported into the cell. At some point, this will interfere with cellular transport and toxicity will begin. This mechanism does not require a long incubation period, so it may be predominant in short exposure experiments. For example, O'Brien et al. (*6*) exposed hepatic cells to phenols for only 2 h and found a strong correlation with log *P* but only a weak correlation with BDE, even for EDG-phenols. We interpret this result to mean that exposure was too short to allow phenoxyl radical toxicity to get started, especially since it may be dependent on the formation of quinone metabolites (*28*). A rigorous study of this baseline toxicity would require a cellular analysis of transport through a membrane as a function of hydrophobicity. It is possible to do this, for example, by using a Virtual Cell (*34*) model, which includes transport through a membrane. However, it will also be of interest to do a deeper analysis of not only the split into EDG and EWG sets but also the behavior of hydrophobic vs hydrophilic functional groups within each data set. For this purpose, we can use log *P* as a descriptor. To the best of our knowledge, this type of analysis has not yet been done.

Conclusions

In this paper, we have shown how to predict the rate of formation of phenoxyl radical arising from the HAT reaction of X−phenol + peroxyl radical, where X is a substituent. Activation energies are related to experiment for EDG-phenols, and we used the Evans−Polanyi principle to construct activation energies for EWG-phenols. The two regions show different slopes of log *k* vs ΔBDE even though they arise from the same (HAT) mechanism. There is also a region of zero slope where the toxicity should be constant. The same approach was extended to the toxicity where the substituted parent phenol became a catechol or where the target radical was changed to *tert*-butoxyl, demonstrating the generality of the approach.

Analysis of the calculated rate constants shows that the EWG-phenols react more and more slowly as we make the transition from EDG to EWG-phenols. This opens the door to competing, parallel mechanisms. A SPLET mechanism is possible since the EWG-phenols have decreasing pK_a values as ΔBDE goes more and more positive. With some assumptions, reaction rates become plausible for SPLET in this region; however, this is still a mechanism that generates phenoxyl radicals.

An alternative mechanism, nonspecific toxicity, is briefly discussed. This mechanism can be significant depending on the conditions of the experiment. A more detailed investigation into mechanisms dependent on log *P* is in progress by the authors.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada and by the Canadian Breast Cancer Foundation.

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