

# A QSPR Study of O–H Bond Dissociation Energy in Phenols

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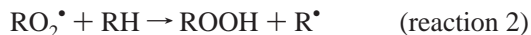
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A Quantitative Structure–Property Relationship (QSPR) is developed for the O–H bond dissociation energy (BDE) of a set of 78 phenols. The data set was composed of monosubstituted, disubstituted, and polysubstituted phenolic derivatives containing substituents with different steric and electronic effects in the *ortho*-, *meta*-, and *para*-positions of the aromatic ring. The proposed model, derived from multiple linear regression, contains seven descriptors calculated solely from the molecular structure of compounds. The average absolute relative errors are 1.37% ( $R^2 = 0.8978$ ; SD: 6.67) and 1.13% ( $R^2 = 0.9076$ ; SD: 4.26) for the working set (62 compounds) and the prediction set (16 compounds), respectively. These results are better than those obtained from DFT calculations, QSAR approach, and correlations with Hammett parameters.

## INTRODUCTION

Phenoxy radicals are important intermediates in many biological processes and have therefore been studied extensively.<sup>1</sup> In particular, their importance in relation to the antioxidant activity of phenols has led to an increased interest in these systems in recent years. The function of antioxidants is to intercept and react with free radicals at a faster rate than the substrate, and since free radicals are able to attack a variety of targets, including lipids, fats, and proteins, it is believed that they are implicated in a number of important degenerative diseases, including aging itself.<sup>2</sup> The role of the phenolic antioxidant, ArOH, is to trap the chain-carrying peroxy radicals, in accordance with reaction 1. This reaction is much faster than the attack of the peroxy radicals on the organic substrate (reaction 2)



To be effective, ArO<sup>•</sup> must be a relatively stable free radical so that it reacts slowly with the substrate RH but rapidly with RO<sub>2</sub><sup>•</sup>. Thus, a weak OH bond in ArOH will imply that reaction 1 will be thermodynamically more favorable, increasing the antioxidant efficiency of the compound. It is therefore not surprising that a large number of current studies are to be found using a diversity of modern experimental and computational tools that address the kinetic and the thermodynamic stabilities of the phenolic bond and how these stabilities are affected by the number, nature, and position of the substituents in the aromatic ring.

There are many reports in the literature on the determination of bond dissociation energies (BDE) of phenols. Those based on calorimetric, kinetic, and EPR methodologies have been reviewed.<sup>3</sup> Recently, values determined using two new

methods have been reported. One method is based on photoacoustic calorimetry;<sup>4</sup> the other makes use of thermodynamic cycles by combining the heat of heterolysis of a given species and the redox potentials of the resulting ions.<sup>5</sup> Other BDE values have been determined by studying the equilibration of couples of phenols and of the corresponding phenoxy radicals by means of EPR spectroscopy.<sup>6</sup> Equation 1, which relates BDE with acidities and the reduction potentials of the anions, has also been applied to phenol derivatives<sup>7</sup>

$$\text{BDE}_{\text{HA}} = 1.37\text{p}K_{\text{HA}} + 2.31E_{\text{ox}}(\text{A}^-) + C \quad (\text{equation 1})$$

The computational methods used to predict bond dissociation energies can be classified into two categories. The rigorous approaches involve quantum mechanical methods including density functional, ab initio, and semiempirical calculations. The other methods are more empirically based quantitative structure–activity relationship (QSAR) approaches. Some papers have been published on the calculation of O–H BDE of phenols by AM1 and DFT methods.<sup>8–10</sup> QSAR studies have shown that stabilization of the phenoxy radicals correlates with the energy of the highest occupied molecular orbital (HOMO) and the ionization potential.<sup>11</sup> In a recent review,<sup>12</sup> quantitative structure activity relationships have been established for both biological and nonbiological activities and properties of substituted phenols with electronic properties of the substituents. The parameters in the QSAR include Hammett  $\sigma$ ,  $\sigma^+$ , and  $\sigma^-$ , with  $\sigma^+$  being the most frequently used.<sup>8,13</sup> The calculation of  $\Delta\text{BDE}$  (relative to phenol) by a combination of quantum and statistical methods has been reported.<sup>14</sup> Despite all efforts, the present knowledge on the energetics of the phenolic bond is still unsatisfactory. Even for the simplest of those molecules—phenol itself—the published values for the O–H bonds' dissociation energy vary over a wide range ( $\sim 30$  kJ/mol).

The Quantitative Structure–Property Relationship approach (QSPR) has become very useful in the prediction and interpretation of several physical and chemical properties.

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The basis of such relationships is the assumption that the variation of behavior of the compounds, as expressed by any measured physical or chemical properties, can be correlated with changes in molecular features of the compounds termed descriptors. While the traditional approach often needs some intuitive vision to derive the relevant mathematical relationship, QSPR methods are based on statistically determined linear or nonlinear functional forms that relate the property of interest with descriptors.<sup>15</sup> Descriptors are numerical values used to describe different characteristics about a certain structure in order to yield information about the property being studied. QSPR studies have been successfully applied to the correlation of many and diverse physicochemical properties of chemical compounds. Recently, Katritzky et al. have reviewed the applications of the QSPR approach to technologically relevant physical properties.<sup>16,17</sup> Reaction rates<sup>18,19</sup> of several chemical processes and NMR chemical shifts<sup>20,21</sup> have also been analyzed by QSPR.

The bond dissociation energy can be an appropriate property to be studied by QSPR methodology. Because its numerical value depends on the molecular structure, the compounds studied have similar structural characteristics and the calculated descriptors reflect their changes. Nevertheless, to the best of our knowledge there is no calculation of bond energies by the QSPR approach. In this paper, we apply the QSPR methodology to the calculation of the O–H bond dissociation energy of phenols. We use one set of 78 phenols. This set includes, besides the phenol itself, 77 substituted derivatives. Of these 44 are monosubstituted and the others 22 are polysubstituted. They all contain many kinds of substituents with different electronic and steric effects, occupying the *ortho*-, *meta*-, and *para*- positions of the aromatic ring. Moreover, 40 of them have at least one substituent in *ortho*-position. The corresponding values of the O–H BDE have been taken from the critical review published by Simoes et al.<sup>22</sup>

## DATA AND COMPUTATIONAL METHODS

**Data Set.** The values of bond dissociation energy of the phenols studied have been taken from the review published by R. M. Borges dos Santos and J. A. Martinho Simoes.<sup>22</sup> This review presents a critical assessment of the available experimental information of the thermochemistry of the O–H bond in phenol and substituted derivatives. These authors have collected all the available experimental data for the thermochemistry of the phenolic O–H bond and have also included, for the sake of completeness, the results of several theoretical studies. It was observed that gas phase and solution data are often similar within ~5 kJ/mol. This is a difference which is lower than the usual uncertainties affecting both experimental and computational results; therefore, these authors concluded that most of the experimental values, which have been derived from solution studies, can also apply to the gas phase. The analysis of all the available data led them to propose a set of recommended values for the O–H bond dissociation energies. However, the authors recognize that their proposal may be controversial, particularly when large discrepancies exist between data of the same compound obtained from different experimental and theoretical methods.

Table 1 contains the bond dissociation energy for the data set, in kJ/mol; the average error of these values is ~10 kJ/mol (~3%). The data set contains 78 compounds. Besides the phenol, there are 77 substituted phenols, 44 of which are monosubstituted, 11 disubstituted, 18 trisubstituted, 2 tetrasubstituted, and the other 2 pentasubstituted. They contain 25 kinds of substituents with different electronic and steric effects. Some of these substituents are electron-donating such as Me, *t*-Bu, NH<sub>2</sub>, NMe<sub>2</sub>, OMe, while others are electron-withdrawing, such as F, Cl, Br, I, NO<sub>2</sub>, CF<sub>3</sub>, COR, SO<sub>2</sub>Me. These substituents occupy the *ortho*-, *meta*-, and *para*- positions of the aromatic ring; 40 of the phenols studied have at least one substituent in the *ortho*-position. Some of them are very bulky, especially, *t*-Bu, and can produce important interactions with the OH moiety in the *ortho* position.

The bond dissociation energy ranged from 321.3 to 397.3 kJ/mol, with a mean value of 362.3 kJ/mol. This data set was split randomly into a 62 member working set (wkgset) and an external prediction set (pset) of 16 compounds.

**Structural Descriptors.** The generation of the descriptors and the multilinear regression analysis was performed with the CODESSA and SPSS programs,<sup>23</sup> respectively. The structures of the compounds were drawn with HyperChem Lite (Hypercube, Inc.) and exported in a file format suitable for MOPAC. The geometry optimization was performed with the semiempirical quantum method AM1<sup>24</sup> using the MOPAC 6.0 program.<sup>25</sup> All the geometries have been fully optimized without symmetry restrictions. In all cases frequency calculations have been performed in order to ensure that all the calculated geometries correspond to true minima. The MOPAC output files were used by the CODESSA program to calculate about 600 descriptors. CODESSA computes five classes of descriptors: constitutional (number of various types of atoms and bonds, number of rings, molecular weight, etc.); topological (Wiener index, Randic indices, Kier-Hall shape indices, etc.); geometrical (moments of inertia, molecular volume, molecular surface area, etc.); electrostatic (minimum and maximum partial charges, polarity parameter, charged partial surface area descriptors, etc.); and quantum (reactivity indices, dipole moment, HOMO and LUMO energies, etc.)

The heuristic multilinear regression procedures available in the framework of the CODESSA program were used to find the best correlation models. These procedures provide collinearity control (i.e., any two descriptors intercorrelated above 0.8 are never involved in the same model) and implement heuristic algorithms for the rapid selection of the best correlation, without testing all possible combinations of the available descriptors. After the heuristic reduction the pool of descriptors was reduced to 219. A variety of subset sizes was investigated to determine the optimum number of descriptors in a model. When adding another descriptor did not improve significantly the statistics of a model, it was determined that the optimum subset size had been achieved. The optimum model size in this study was seven descriptors. The goodness of the correlation is tested by the coefficient regression ( $R^2$ ), the  $F$ -test, the standard deviation (SD), the relative standard deviation (RSD), that is, the SD divided by the mean experimental BDE, and by the average of the absolute relative error. The stability of the correlations was tested against the cross-validated coefficient,  $R^2_{cv}$ . The  $R^2_{cv}$

**Table 1.** Experimental and Calculated BDE (kJ mol<sup>-1</sup>) for the Working and the Prediction Sets

no.	compd <sup>a</sup>	exptl	calcd	error <sup>b</sup>	no.	compd <sup>a</sup>	exptl	calcd	error <sup>b</sup>
1	PhOH	371.3	372.4	0.30	40	2,6-Ph <sub>2</sub>	360.3	359.8	0.15
2	2-Me	362.3	358.5	1.06	41	2,6-(OMe) <sub>2</sub>	350.3	354.5	1.19
3	4-Me	363.3	365.1	0.49	42	3,5-(OMe) <sub>2</sub>	364.3	364.6	0.07
4	4- <i>t</i> -Bu	364.3	358.3	1.65	43	2,6-(NO <sub>2</sub> ) <sub>2</sub>	397.3	398.8	0.37
5	4-Ph	359.3	364.6	1.46	44	3,5-Cl <sub>2</sub>	385.3	379.1	1.60
6	2-OH	341.3	347.7	1.88	45	2,4,6-Me <sub>3</sub>	348.3	346.3	0.56
7	3-OH	372.3	364.8	2.01	46	2,6- <i>t</i> -Bu <sub>2</sub> -4-Me	339.3	339.2	0.04
8	4-OMe	349.3	353.7	1.25	47	2,4,6- <i>t</i> -Bu <sub>3</sub>	334.3	329.4	1.46
9	2-CH <sub>2</sub> OH	361.3	352.4	2.46	48	2,4,6-Ph <sub>3</sub>	348.3	352.6	1.25
10	2-COMe	365.3	362.3	0.83	49	2,6- <i>t</i> -Bu <sub>2</sub> -4- <i>Or</i> Bu	322.3	312.8	2.95
11	4-COMe	380.3	377.8	0.65	50	2,6- <i>t</i> -Bu <sub>2</sub> -4-COMe	345.3	353.1	2.25
12	3-COEt	380.3	375.3	1.32	51	2,6- <i>t</i> -Bu <sub>2</sub> -4-OCOMe	345.3	342.9	0.69
13	4-COPh	382.3	387.4	1.32	52	2,6- <i>t</i> -Bu <sub>2</sub> -4-CH <sub>2</sub> NMe	333.3	333.9	0.18
14	4-OCOMe	360.3	366.9	1.85	53	2,4,6-(OMe) <sub>3</sub>	336.3	342.0	1.70
15	3-COOEt	378.3	377.3	0.27	54	2,6-Me <sub>2</sub> -4-NO <sub>2</sub>	371.3	375.2	1.05
16	2-NH <sub>2</sub>	340.3	342.8	0.72	55	2,6- <i>t</i> -Bu <sub>2</sub> -4-NO <sub>2</sub>	352.3	361.1	2.50
17	4-NH <sub>2</sub>	331.3	337.8	1.96	56	2,6- <i>t</i> -Bu <sub>2</sub> -4-CHNOH	328.3	339.6	3.46
18	3-NMe <sub>2</sub>	363.3	344.3	5.24	57	3,4,5-Cl <sub>3</sub>	384.3	379.1	1.35
19	4-NMe <sub>2</sub>	321.3	335.6	4.45	58	2,6-(NO <sub>2</sub> ) <sub>2</sub> -4-Cl	396.3	394.2	0.54
20	2-CN	371.3	377.1	1.57	59	2,3,6-Me <sub>3</sub> -4-OMe	333.3	333.6	0.09
21	3-CN	384.3	382.7	0.42	60	2,3,5,6-Me <sub>4</sub> -4-OMe	344.3	341.5	0.82
22	4-CN	389.3	381.7	1.95	61	2,3,5,6-F <sub>4</sub>	385.3	375.7	2.49
23	2-NO <sub>2</sub>	366.3	372.8	1.78	62	2,3,4,5,6-F <sub>5</sub>	360.3	369.5	2.56
24	3-NO <sub>2</sub>	390.3	385.0	1.35	63	2,4,6-Cl <sub>3</sub> <sup>c</sup>	369.3	369.0	0.08
25	4-NO <sub>2</sub>	396.3	390.3	1.50	64	2,6-Cl <sub>2</sub> <sup>c</sup>	370.3	372.7	0.66
26	2-F	363.3	365.0	0.47	65	2,6-Me <sub>2</sub> -4-OMe <sup>c</sup>	329.3	336.9	2.32
27	3-F	377.3	376.5	0.21	66	2,6- <i>t</i> -Bu <sub>2</sub> -4-Et <sup>c</sup>	328.3	335.9	2.30
28	4-Cl	370.3	371.8	0.40	67	2-CH=CH <sub>2</sub> <sup>c</sup>	361.3	360.1	0.34
29	2-Br	364.3	372.4	2.23	68	2-Cl <sup>c</sup>	368.3	369.7	0.38
30	4-Br	373.3	375.9	0.69	69	2-OMe <sup>c</sup>	354.3	357.3	0.86
31	4-I	370.3	379.4	2.45	70	3-COMe <sup>c</sup>	376.3	377.8	0.40
32	4-CF <sub>3</sub>	388.3	386.6	0.44	71	3-Cl <sup>c</sup>	376.3	374.2	0.57
33	3-SO <sub>2</sub> Me	382.3	380.5	0.46	72	3-Me <sup>c</sup>	368.3	368.3	0.00
34	4-SO <sub>2</sub> Me	393.3	396.0	0.69	73	3-NH <sub>2</sub> <sup>c</sup>	366.3	355.0	3.09
35	2,6-Me <sub>2</sub>	357.3	355.6	0.48	74	3-OMe <sup>c</sup>	371.3	362.1	2.47
36	3,5-Me <sub>2</sub>	368.3	363.1	1.41	75	4-F <sup>c</sup>	367.3	367.1	0.05
37	2,4- <i>t</i> -Bu <sub>2</sub>	349.3	346.5	0.79	76	4-OH <sup>c</sup>	344.3	348.4	1.18
38	2,6- <i>t</i> -Bu <sub>2</sub>	345.3	347.7	0.70	77	2,6- <i>t</i> -Bu <sub>2</sub> -4-CHO <sup>c</sup>	343.3	353.2	2.89
39	3,5- <i>t</i> -Bu <sub>2</sub>	365.3	349.5	4.32	78	3-CF <sub>3</sub> <sup>c</sup>	384.3	382.5	0.46

<sup>a</sup> Substituent on phenol. <sup>b</sup> Absolute Relative Error: absolute value of 100[(calc-exp)/exp]. <sup>c</sup> Prediction set (pset).

**Table 2.** Seven-Parameter Correlation Equation for the Working Set<sup>a</sup>

descriptor	coefficient	SD	beta	<i>t</i> -test	sig	VIF
intercept	1310.90	225.60		5.81	0.000	
HOMO energy	-21.78	2.21	-0.60	-9.86	0.000	1.96
topographic electronic index (all bonds)	-44.62	6.81	-0.65	-6.55	0.000	5.26
min atomic state energy for a C atom	-11.34	2.13	-0.29	-5.32	0.000	1.53
RPCS relative positive charged SA (Zefirov)	1.77	0.61	0.22	-9.86	0.000	3.02
min (>0.1) bond order of a C atom	7.61	3.56	0.12	2.14	0.037	1.78
ZX shadow	0.58	0.15	0.36	3.85	0.000	4.55
FPSA-3 fractional PPSA (Zefirov)	843.72	337.39	0.19	2.50	0.015	2.94

<sup>a</sup>  $R^2 = 0.8978$ ;  $F = 67.75$ ;  $s = 6.67$ ;  $n = 62$ ;  $R^2_{cv} = 0.8661$ .

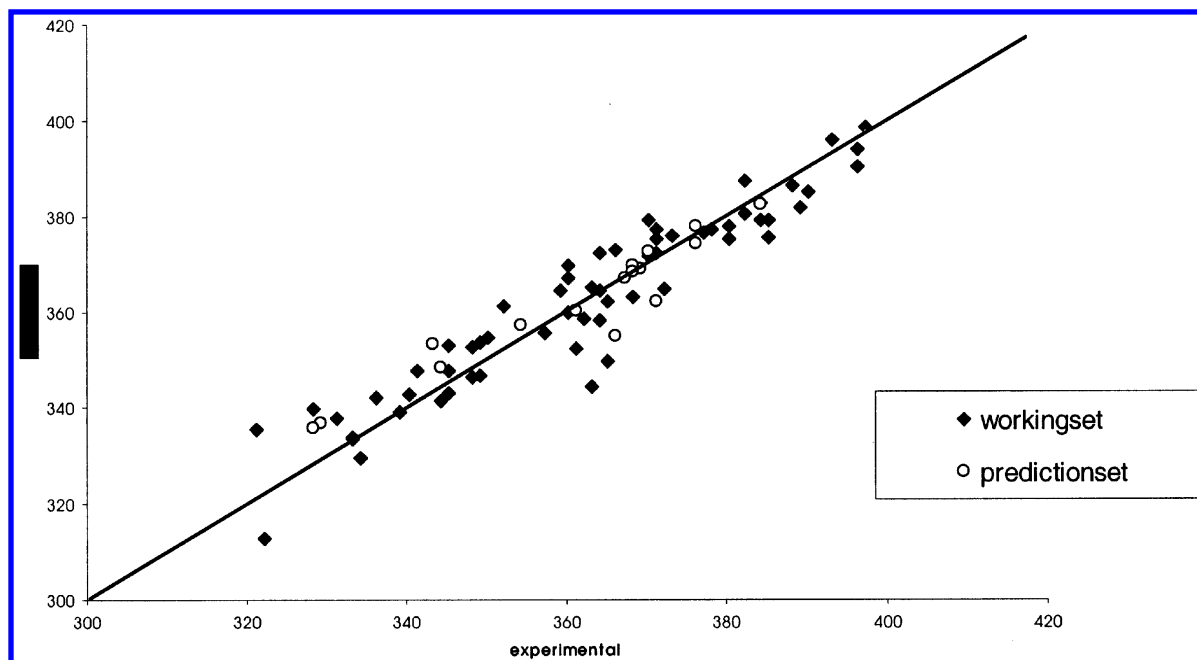
describes the stability of a regression model obtained by focusing on the sensitivity of the model to the elimination of any single data point.

## RESULTS AND DISCUSSION

The QSPR analysis of the BDE values for the 62 phenols of the working set resulted in the seven-parameter model summarized in Table 2. The correlation obtained is good,  $R^2 = 0.8978$ ,  $F = 67.8$ ,  $R^2_{cv} = 0.8661$ , with a standard deviation (SD) of 6.67, which represents a relative standard deviation (RSD) of 1.84%. The average absolute relative error is 1.37%. The level of significance associated to the *t*-student coefficient shows that there is a linear relation

between BDE and the descriptors. In all instances the probability of linear relation is higher than 98%, except with the descriptor Min (>0.1) bond order of a C atom, which is higher than 95%. To further validate the model other tests were performed. The pairwise correlations for the seven descriptors ranged from 0.021 to 0.762, with an average value of 0.30. The variance inflation factors (VIF), defined as  $(1 - R^2)^{-1}$ , was determined for each descriptor as well. The mean VIF' value was 3.0. A VIF larger than 10 is indicative of multicollinearity.

This model contains one geometrical (ZX shadow), three quantum-chemical (HOMO energy, minimum atomic state energy for a C atom, and minimum (>0.1) bond order for a



**Figure 1.** Plot of calculated vs experimental BDE (kJ/mol) of the working and prediction sets.

C atom), and three electrostatic (topographic electronic index, relative positive charged SA, and FPSA-3 fractional PPSA) descriptors.

The geometrical descriptors describe the size of the molecules and are derived from the three-dimensional coordinates of the atomic nuclei and the atomic masses and/or the atomic radii in the molecule. The only descriptor contained in the model that belongs to this group is the ZX shadow, that can be derived in the following way: by orientation of the molecule in the space along the axes of inertia (X coordinate defined along the main axis of inertia, Y coordinate defined along the next longest, Z coordinate along the shortest axis of inertia), the areas of the shadows  $S_1$ ,  $S_2$ , and  $S_3$  of the molecule as projected on the XY, YZ, and XZ planes are calculated. The shadow areas are calculated by applying a two-dimensional square grid on the molecular projection and by summation of the areas of squares overlapped with the projection.<sup>26</sup> The three quantum-chemical descriptors are as follows: HOMO energy, minimum atomic state energy for a C atom, and minimum ( $>0.1$ ) bond order of a C atom. The HOMO energy is the energy of the highest occupied molecular orbital. The minimum atomic state energy for a C atom corresponds to the value of the atomic valence state energy for the given atomic species in the molecule. The valence state energy characterizes the magnitude of the perturbation experienced by an atom in the molecular environment in comparison to the isolated atom. The minimum ( $>0.1$ ) bond order of a C atom is the lowest order of the bonds between one carbon atom and any other atom. The electrostatic descriptors reflect the characteristics of the charge distribution of the molecule. The empirical partial charges in the molecule are calculated using the approach proposed by Zefirov,<sup>27</sup> based on the Sanderson electronegativity scale. The topographic electronic index<sup>28</sup> (all bonds) is the sum of the absolute differences in electronic excess charges on all atomic parts in a given molecule, divided by the squares of the respective interatomic distances

$$T_2^E = \sum_{(i < j)}^{N_B} \frac{|q_i - q_j|}{r_{ij}^2}$$

The other two electrostatic descriptors belong to the charged partial surface area descriptors (CSPA), developed by Jurs et al.,<sup>29</sup> in terms of the whole surface area of the molecule or its fragments and in terms of the charge distribution in the molecule. The relative positive charged surface area, RPCS, is the product of the solvent accessible surface area of the most positive charged atom,  $SA_{MPOS}$ , and the relative positive charge, RPCG. The fractional partial positive surface area, FPSA-3 fractional PPSA, is defined as the ratio of the atomic charge weighted partial positive surface area (PPSA3), which is obtained by summation of products of the individual atomic partial charges and the atomic solvent-accessible surface areas and the total molecular surface area, TMSA. According to the beta values (Table 2), the more relevant descriptors are the topographic electronic index and the HOMO energy.

With the prediction set (Table 1) very good results are obtained, showing the high prediction capacity of the model. The statistical parameters are  $R^2 = 0.9076$ ;  $F = 137.4$ ;  $n = 16$ ;  $SD = 4.26$ , and the average absolute relative error is 1.13%. Figure 1 shows a plot of the calculated versus observed values for all the 78 phenols studied, the working set and the prediction set.

Table 3 gives the results obtained for different subsets of compounds according to the number (mono- and polysubstituted) and position (*ortho* and *no-ortho*) of their substituents in the aromatic ring. It is clearly shown that the capacity of prediction of the QSPR approach here proposed is very similar in all the cases, independently of the number of substituents. More importantly, there are no significant differences between the BDE predicted for the *ortho*-derivatives and the other compounds containing only substituents in the *meta*- and/or the *para*-position.



**Table 3.** Statistics of O–H BDE Determination for the Different Subsets of Phenols

subset	<i>n</i>	<i>R</i> <sup>2</sup>	<i>F</i>	SD	error <sup>a</sup>
mono	44	0.8514	240.7	5.6	1.30
poly	33	0.9058	298.3	5.9	1.37
no-ortho	37	0.8295	170.3	6.1	1.39
ortho	40	0.9117	392.5	5.3	1.28

<sup>a</sup> Average absolute relative error (%).**Table 4.** Statistics of Different Methods of O–H BDE Estimation

method (reference)	<i>n</i>	<i>R</i> <sup>2</sup>	<i>F</i>	SD	error <sup>a</sup>
DFT-additivity (10)	49	0.6869	103.1	14.8	3.03
QSPR (this work)	49	0.9202	542.3	4.8	1.17
phenol-model (14)	35	0.8454	180.4	6.9	1.41
phenoxy-model (14)	35	0.7668	108.5	8.6	1.75
QSPR (this work)	35	0.8939	278.5	5.5	1.25
additivity Hammett (this work)	69	0.7332	187.9	9.5	1.88
QSPR (this work)	69	0.9024	619.7	5.1	1.32

<sup>a</sup> Average absolute relative error (%).

As mentioned in the Introduction, some theoretical calculations have been applied for the BDE determination of phenols. To test the suitability of the QSPR approach proposed, we have compared the obtained BDE with those calculated by other procedures. Table 4 shows the statistical parameters of the results obtained from the methods described in the literature and those obtained from our approach for the same set of compounds. Wright et al. using DFT have calculated the BDE in gas phase of some phenols containing methyl, methoxy, and amino substituents and of several chromanols and dihydrobenzofuranols.<sup>8</sup> More recently,<sup>10</sup> using also DFT and locally dense basis sets (LDBS), a simple group additivity scheme has been derived to compute the BDE. Values for 12 substituents in each of the *ortho*-, *meta*-, and *para*-positions have been proposed. The obtained BDE for several mono and polysubstituted phenols are in good agreement with the experimental values. Table 4 contains the results obtained with the 49 phenols, 25 monosubstituted, and 23 polysubstituted, for which the additivity values of each substituent are known, showing that the results obtained from the QSPR approach are better, with significantly higher correlation coefficient and lower standard deviation and average absolute relative error. Recently,<sup>14</sup> the bond dissociation energy of a set of phenols has been calculated using a three-dimensional quantitative structural activity relationship method incorporating electron densities computed using the semiempirical AM1 method, followed by a correlation of the electron density with the bond dissociation energies. The QSAR was determined for both the ground-state phenol as well as the singlet phenoxy radical with a set of compounds for which the bond dissociation energies have been measured; the model developed using the ground-state phenol model is more predictive. The comparison has been done with a set of 35 substituted phenols, 28 monosubstituted, and 7 polysubstituted. The estimations derived by the QSPR method are significantly better. Hammett parameters and its variants have been used in the prediction of BDE of phenols. This approach also enables the study of the relative effect of the nature and position of the different substituents. The best results have been obtained from Brown's parameters,  $\sigma^+$ . With a set of 34 phenols containing only *meta*- and *para*-substituents, for which  $\sigma_m^+$  and  $\sigma_p^+$  were well-known, a good

correlation was obtained,<sup>22</sup>  $R^2 = 0.9801$ . Due to the irregular interactions between *ortho* substituents and the OH group, the assignment of  $\sigma_o^+$  is less clear and fewer values of these  $\sigma_o^+$  have been collected. In general, a relation of the type  $\sigma_o^+ = a\sigma_p^+$  is accepted, and the value of  $a = 0.66$  has been proposed for phenol derivatives.<sup>16</sup> Fitting the experimental bond dissociation energies with  $\sigma^+$  for the 69 compounds, 38 monosubstituted, and 30 polysubstituted phenols, for which  $\sigma^+$  are known,<sup>30</sup> the following equation is obtained

$$\text{BDE(O-H)} = 22.04(\pm 1.6)\sigma^+ + 365.2(\pm 1.0)$$

The average absolute relative error of the calculated values by this equation is 1.32%. These results are good taking into account that in the set of phenols studied there are 36 *ortho*-substituted derivatives, for which the  $\sigma_o^+$  parameter is not very accurate. However, the QSPR approach gives better results.

## CONCLUSIONS

A quantitative structure–property relationship was derived to predict the bond dissociation energy of substituted phenols based on the correlation analysis of the proposed O–H bond dissociation energy for a diverse set of 78 phenols. The model contains seven descriptors, which are calculated solely from the chemical structure of compounds. Therefore, the prediction of the BDE can now be made for any phenol derivative. The equation has a squared correlation coefficient of 0.8978 and a standard error of 6.67 for the working set and of 0.9076 and 4.26 for the prediction set. The average absolute relative error for all the phenols studied is 1.33%. The goodness of the method and its prediction capacity is practically the same for any kind of phenol derivative, independently of the number and position of the substituents in the aromatic ring. These results are better than those obtained from other theoretical methods based on DFT, QSAR incorporating electron densities, and even from additivity of Hammett parameters. Consequently, this approach currently constitutes the simplest and most accurate method to estimate the BDE of phenols.

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