

A single theoretical descriptor for the bond-dissociation energy of substituted phenols

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Abstract Relative to the corresponding value of phenol, the bond-dissociation energies (BDE) of substituted phenols correlate well with a single descriptor: the Mulliken charge on the oxygen atom of the phenoxyl radical. However, the correlation fails for phenols ortho-substituted with polar groups. Internal reaction coordinates (IRC) for the model reaction of hydrogen abstraction by the hydroperoxyl radical from various 2- and 4-substituted phenols were calculated in order to investigate the role of intra-molecular hydrogen bonds and steric effects on the process. Calculations yielded theoretical values in good agreement with experimental Δ BDE values. The hydrogen-abstraction process was further analyzed in terms of density functional theory (DFT)-based reactivity indices such as local electrophilicity, the Fukui function for nucleophilic attack, and dual descriptor values of the phenolic hydroxyl oxygen along the IRC.

Keywords Quantitative structure–property relationship · Bond-dissociation energy of phenols · Phenoxyl radicals · Hydrogen abstraction · DFT-based reactivity indices

Introduction

Phenols are a class of compounds with wide occurrence in nature, and are responsible for the antioxidant activities of drinks or food extracts [1, 2]. Such activity may be traced back to their ability to quench free radicals, being a source of hydrogen atoms to radical species. The measurement of bond-dissociation energies (BDEs) of phenols has therefore attracted the interest of various groups. BDEs of substituted phenols have been determined using a variety of methods, and compilations of these values, together with their antioxidant activities, have been the subject of monographies and reviews in recent decades [1–3].

The substitution pattern of phenols, and the nature of the substituents, have been analyzed and rationalized theoretically by calculating these energies using quantum chemical methods [4–6], or searching for adequate theoretical descriptors capable of reproducing and predicting BDEs in terms of quantitative structure–property relationships (QSPR) [7, 8].

Though covering, in some cases, a wide range of substituted phenols, these relationships can be criticized for the number of employed descriptors in the regression equations, or for their obscure meanings, which may have little to do with the actual chemical process under investigation.

As an example, the QSPR proposed by Bosque and Sales [7] based on the BDEs of 62 phenols, employed seven parameters, many of which, like the shadow projected by the phenol molecule on a ZX plane, can hardly be associated with the homolytic dissociation of a substituted phenol. The principle of Occam's razor, which requires models that are as simple as possible, and avoids unnecessary concepts to explain reality, was again violated by a different group in a subsequent publication [8]. In this latter article, for a similar number of compounds in a training set, the authors claimed a significant improvement by including six, instead of seven descriptors in the regression equation. Geometrical, electrostatic and

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quantum-chemical descriptors were employed, some of them having little connection with the actual chemical process under investigation.

Reasonable correlations have been obtained between BDE values of some substituted phenols and the corresponding Hammett substituent σ^+ constants [9]. Surprisingly, this observation led the authors to shift their interest to descriptors such as the proton affinity of the corresponding phenolates, and the negative charge $q(\text{O}^-)$ on their oxygen atom. Correlations with data originating from a homolytic process were sought, with descriptors derived from heterolytic dissociations. Here again, the choice of descriptors was not justified by consideration of the process under study.

In a search for theoretical descriptors that might correlate with the homolytic bond-dissociation energies of substituted phenols, we looked for variables that would follow rather closely the hydrogen-abstraction process. In the present work, we show that the charge on the oxygen atom of the product radical $\text{ArO}\cdot$, $q(\text{O}\cdot)$, yields good correlations with the homolytic dissociation energy of various substituted phenols. The resulting regression equation, with one single descriptor, offers a simple and chemically meaningful QSPR for the BDEs of these compounds.

The use and limitations of this descriptor were further investigated by the study of a model reaction: the hydrogen-abstraction process of para- and ortho-substituted phenols by the hydroperoxyl radical (Scheme 1).

Descriptors derived from density functional theory (DFT)-based concepts have been widely employed in past decades [10–12]. Good correlations have been obtained between BDEs of *p*-substituted phenols and some of these descriptors, such as chemical potential or atomic hardness [13]. Fukui functions, f_k , have been suggested as useful reactivity descriptors for organic reactions. Analyses of simple model processes have been carried out, based on profiles of these reactivity descriptors along the intrinsic reaction coordinate (IRC) [14]. In the present communication, this approach was used to study the hydrogen-abstraction process depicted in Scheme 1. The analysis of a “real” chemical process thus revealed the scope and limitations of this theoretical approach based on reactivity descriptors.

Methods

Calculations were performed with the Gaussian 09 package [15], employing the hybrid DFT method B3LYP/6-31G(d,p) for geometry optimizations and determination of the atomic charge $q(\text{O}\cdot)$ on the oxygen atom of the phenoxy radical. The stationary points were confirmed as minima or transition states (TS) by frequency calculations at the same level of theory of geometry optimization. The pathways were subjected to IRC analysis to confirm that the optimized TS structures

connected the correct reagents and products. The final enthalpy values were obtained from single-point calculations using the larger basis set 6-311+G(2d,2p) and included zero-point vibrational and thermal corrections at 298K.

The Fukui function for nucleophilic attack on atom k (f_k^+) was calculated with the aid of Eq. (1),

$$f_k^+ = q_k(N+1) - q_k(N) \quad (1)$$

where $q_k(N)$ and $q_k(N+1)$ are the Mulliken charges on atom k , calculated for a system with N and $N+1$ electrons, respectively [16]. In an analogous way, the Fukui function for electrophilic attack on atom k (f_k^-) was calculated with Eq. (2), where $q_k(N-1)$ is the Mulliken charge on atom k , calculated for a system with $N-1$ electrons [16].

$$f_k^- = q_k(N) - q_k(N-1) \quad (2)$$

The global electrophilicity of a molecule (ω) was calculated from Eq. (3)

$$\omega = \mu^2/2\eta \quad (3)$$

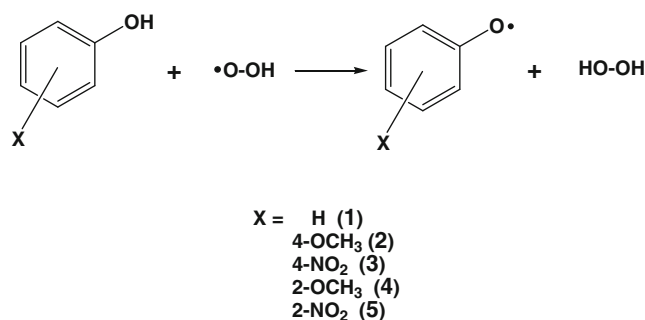
where μ is its chemical potential, and η its hardness [17]. By adopting Koopman's approximation, μ and η were obtained from Eqs. (4) and (5),

$$\mu \approx (\epsilon_{\text{LUMO}} + \epsilon_{\text{HOMO}})/2 \quad (4)$$

$$\eta \approx \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}} \quad (5)$$

where ϵ_{HOMO} and ϵ_{LUMO} are the HOMO and LUMO energies of the molecule, respectively [18, 19].

The electrophilicity of a particular atom k in a molecule (ω_k) was calculated by multiplying the global electrophilicity



Scheme 1 Gas-phase hydrogen-abstraction of substituted phenols 1–5 by the hydroperoxyl radical, studied theoretically with the B3LYP/6-31G(d,p) // B3LYP/6-311+G(2d,2p) method

of the molecule by the Fukui function for nucleophilic attack on atom k [18–20].

$$\omega_k = f_k^+ \cdot \omega \quad (6)$$

Experimental values of the BDEs of phenols were taken from the literature [7].

Results and discussion

Correlations with a single descriptor

Table 1 lists the relative bond-dissociation energies (Δ BDE) for 26 phenols [7], together with the charges on the oxygen atom of the corresponding phenoxyl radicals, $q(\text{O}\cdot)$, calculated with the B3LYP/6-31G(d,p) method.

Although the choice of this method and of Mulliken charges was ultimately arbitrary, it was suggested by a comprehensive comparison of methods for the calculation of atomic charges in substituted phenols, as effective descriptors for the prediction of their pKa values [21]. The observation that most of the QSAR models built from 83 different approaches yielded good correlations with experimental values was rather encouraging. Among these methods, HF/6-31G(d,p)/Mulliken was among the best, for a set of 124 molecules. A slightly weaker correlation was obtained with DFT charges, and the best performing DFT functional was B3LYP.

We based our choice of our method [B3LYP/6-31G(d,p)/Mulliken] for the calculation of the atomic charges $q(\text{O}\cdot)$ on the phenoxyl radicals on the above observations.

The plot of Δ BDE versus $q(\text{O}\cdot)$, where Δ BDE is the BDE of a substituted phenol relative to the BDE of phenol, is shown in Fig. 1. The data comprise the 24 phenols shown in Table 1, with the omission of two ortho-substituted compounds with hydrogen-bond-accepting groups (2-OCH₃ and 2-NO₂).

A good regression line was obtained, with a correlation coefficient $r=0.998$.

$$\Delta\text{BDE} = 506.9 + 1063.6q(\text{O}\cdot) \quad (7)$$

$N = 24$

The regression Eq. (7), yielding a good correlation for 24 para-, meta- and ortho-substituted phenols, supports the choice of the calculated charge $q(\text{O}\cdot)$, as a good descriptor for the BDEs of phenols. In the absence of other effects, such as inter- or intra-molecular hydrogen bonds, the charge on the oxygen atom of a phenoxyl radical should measure the degree of electron delocalization in the molecule and, consequently, of the radical stability

in the gas phase. This delocalization should depend on the nature and position of the substituent, in the case of para- and meta-substituted phenols. A more complex picture may emerge in the case of ortho-substituents, where steric effects should play a significant role. The presence of phenols ortho-substituted by alkyl groups in the set suggests that purely steric effects are also accommodated by the $q(\text{O}\cdot)$ descriptor. However, besides steric interactions, intra-molecular hydrogen bonds between the phenolic O–H group and a neighboring hydrogen-bond-accepting (HBA) substituent like *o*-nitro or *o*-alkoxy, may also significantly affect the linear correlation of Eq. (7).

Table 1 Relative bond-dissociation energies (Δ BDE) of substituted phenols, with the charge on the oxygen atom of the corresponding phenoxyl radical

Phenol substituent	Relative bond-dissociation energies Δ BDE / kJ mol ⁻¹ ^a	$q(\text{O}\cdot)$ ^b
4-NO ₂	25	-0.453
4-CN	18	-0.462
4-Cl	-1	-0.476
4-F	-4	-0.481
H	0	-0.477
4-CH ₃	-8	-0.486
4-OCH ₃	-22	-0.501
4-NH ₂	-40	-0.515
4-OH	-27	-0.498
4-CF ₃	17	-0.464
3-NO ₂	19	-0.457
3-CN	13	-0.461
3-Cl	5	-0.467
3-F	6	-0.473
3-CH ₃	-3	-0.482
3-OCH ₃	0	-0.482
3-NH ₂	-5	-0.494
3-OH	1	-0.481
3-CF ₃	13	-0.465
2-CH ₃	-9	-0.481
2,6-di(CH ₃)	-14	-0.485
2,4,6-tri(CH ₃)	-23	-0.491
2,6-di-(<i>t</i> -Bu)	-26	-0.495
2,6-di-(<i>t</i> -Bu)-4(CH ₃)	-32	-0.502
2-NO ₂	-5	-0.425
2-OCH ₃	-17	-0.508

^a Values taken from [7] relative to the BDE of phenol, made equal to 0 kJ mol⁻¹

^b Charge on the oxygen atom of the phenoxyl radical, calculated with the B3LYP/6-31G(d,p) method

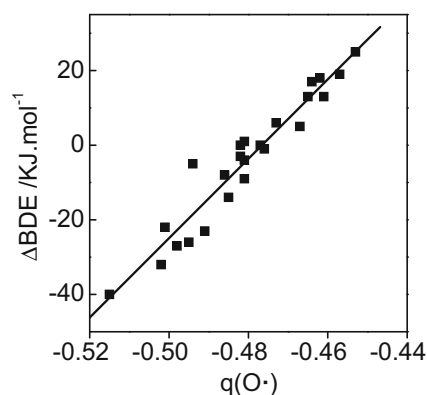


Fig. 1 Linear dependence of the variation of the bond-dissociation energy (BDE) of substituted phenols on the charge on the oxygen atom of the corresponding phenoxyl radical, calculated with the B3LYP/6-31G(d,p) level of theory

Theoretical study of a hydrogen-abstraction process

In order to shed light on the interplay of these effects, we next studied the reaction between a phenol and the hydroperoxyl radical $\text{HOO}\cdot$ (Scheme 1).

The electronic contribution of the substituent to the hydrogen-transfer process was studied by comparing the IRCs for three phenols: unsubstituted phenol, 4-nitro-phenol and 4-methoxy-phenol. The same substituents were then investigated when ortho to the phenolic hydroxyl group, so that a comparison could be made between purely electronic effects and other effects arising from the proximity between the two HBA substituents and the OH group.

Table 2 lists the calculated transition (ΔH^\ddagger) and equilibrium (ΔH°) enthalpies for the gas-phase process, with the enthalpy differences $\Delta\Delta H^\circ$ relative to phenol **1**

Table 2 Calculated values of the transition (ΔH^\ddagger) and equilibrium (ΔH°) enthalpies for the gas-phase hydrogen-abstraction of phenols **1-5** by the hydroperoxyl radical

Compound	Substituent	Transition enthalpy ΔH^\ddagger , kJ mol^{-1}	Equilibrium enthalpy ΔH° , kJ mol^{-1}	$\Delta\Delta H^\circ$, kJ mol^{-1} ^a
1	H	27.1	-12.7	0
2	4-MeO	9.8	-36.2	-23.5
3	4-NO ₂	41.6	17.5	30.2
4(a)^b	2-MeO	13.2	-33.6	-20.9
4(t)^c	2-MeO	20.5	-22.8	-10.1
5(a)^b	2-NO ₂	38.2	9.7	22.4
5(t)^c	2-NO ₂	67.0	61.6	74.3

^a Equilibrium enthalpies relative to phenol **1**, taken as reference

^b Reagents positioned in an “away” conformation, with no hydrogen bonds between the substituent and the hydroxyl group (see text)

^c Reagents positioned in a “towards” conformation, with hydrogen bonds between the substituent and the hydroxyl group (see text)

We employed in our calculations the same optimization method [B3LYP/6-31G(d,p)] used for calculation of the charges $q(\text{O}\cdot)$ listed in Table 1, performing a single-point correction with a larger basis set [6-311+G(2d,2p)] and including zero-point vibrational and thermal corrections at 298K.

The B3LYP/6-31G(d,p) method for calculations of molecular thermochemistry has been criticized recently. It has been suggested that this widely used method should be replaced by a modified scheme, B3LYP-gCP-D3/6-31G(d,p), which corrects the so-called basis set superposition error (BSSE) and missing London dispersion interactions, at no additional computational cost [22].

In our case, we compared the calculated data shown in Table 2 with transition and equilibrium enthalpies calculated with the B3LYP-gCP-D3/6-31G(d,p) scheme [23].

Corrections for the equilibrium enthalpies ΔH° of Table 2 were fairly constant, amounting to positive variations of ca. 2 kJ mol^{-1} . These corrections did not seem too large. Nevertheless, our main reason for not adopting them, making the appropriate changes in the values of Table 2, was the fact that we were not interested in absolute values, but in the differences in $\Delta\Delta H^\circ$ relative to the equilibrium enthalpy of compound **1**. Corrections in these enthalpy differences were cancelled out, requiring no refinement of the calculated data listed in Table 2.

A comparison of phenols **1-3**, where any steric effects may be ruled out, reveals a transition from a significantly exergonic hydrogen-abstraction ($\Delta H^\circ = -36.2 \text{ kJ mol}^{-1}$), for compound **2**, with an electron-donating 4-methoxy substituent, through a less exergonic reaction for phenol **1** ($\Delta H^\circ = -12.7 \text{ kJ mol}^{-1}$), to an endergonic process for the 4-nitrosubstituted phenol **3** ($\Delta H^\circ = 17.5 \text{ kJ mol}^{-1}$). The corresponding theoretical $\Delta\Delta H^\circ$ values, where $\Delta\Delta H^\circ$ is the difference between the calculated enthalpy of a substituted phenol and that of phenol itself, agrees reasonably well with the experimental ΔBDE values of Table 1. For compound **2**, $\Delta\Delta H^\circ = -23.5 \text{ kJ mol}^{-1}$, $\Delta\text{BDE} = -22 \text{ kJ mol}^{-1}$; for compound **3**, $\Delta\Delta H^\circ = 30.2 \text{ kJ mol}^{-1}$, $\Delta\text{BDE} = 25 \text{ kJ mol}^{-1}$. In addition, the corresponding transition states occur at an increasingly late stage along the reaction coordinate, as the nature of the 4-substituent shifts from donor to acceptor. For the 4-methoxy derivative **2**, bond breakage of the O–H bond in the transition state takes place rather early, with an $\text{O}\cdots\text{H}$ bond distance of 1.115 Å; for phenol **1**, it increases to 1.171 Å, taking place rather late for the 4-nitrophenol **3**, with an $\text{O}\cdots\text{H}$ bond distance of 1.229 Å. Finally, charges on the oxygen atom of the phenoxyl radicals, calculated at the B3LYP/6-31G(d,p) level of theory, reproduce the trend shown in Fig. 1. ΔBDEs decrease with an increase in the absolute value of the negative charge on the oxygen atom: 25 kJ mol^{-1} (–0.406, compound **3**) $>$ 0 kJ mol^{-1} (–0.428, compound **1**) $>$ -22 kJ mol^{-1} (–0.450, compound **2**).

Our results may be compared with calculations reported previously, either at a lower level of theory, or in the study of a similar process. Yamada et al. [24] were able to reproduce

the dependence of the position of the TS on the nature of the substituent for the same reaction, at a lower level of theory (STO-3G). However, their result of a linear binding between the O–H hydrogen atom and the oxygen atom of the peroxy radical in the transition state of **2** was at variance with our result of an O–H–O angle of ca. 165° for the TS of the same reaction. Mulder et al. [25] were not able to obtain a TS for the reaction of 4-methoxyphenol with the methoxyl radical at a higher level of theory [B3LYP/6-31G(d,p)], but arrived at an angle of ca. 170° for the same reaction with 2-methoxyphenol, arguing that, for the 4-methoxy derivative, this value was close to that expected for the transition structure. DFT calculations of the hydrogen abstraction from various phenols by the DPPH radical in general yielded BDEs in good agreement with experimental ArO–H BDEs, with significant deviations when an intramolecular H-bond to the O• center was present in the phenoxyl radical [26].

DFT calculations were also employed to rationalize the surprising observation that the hydrogen abstraction from substituted phenols gave an excellent correlation with Hammett σ_p^+ values [27, 28]. This observation points to the very strong electrophilic character of the phenolic oxygen in these dissociations. Prompted by these observations, a study of the variations in local electrophilicity of the phenolic oxygen atom $\omega(O)$ along the IRC of the reaction of Scheme 1 was conducted in the present work. Profiles of $\omega(O)$ values along the IRC are shown in Fig. 2.

Values of $\omega(O)$ increased from reagents to products for the three phenols, confirming the electrophilic nature of the phenoxyl radical formed. The variation in local electrophilicity followed a sigmoidal pattern, with the largest difference between reagents and products being observed for 4-nitrophenol **3** (ca. 1.0 eV), followed by phenol **1** (ca. 0.47 eV) and 4-methoxyphenol **2** (ca. 0.40 eV). The steepest initial variation of $\omega(O)$ was also observed for the electron-donating 4-methoxy substituent. In the transition state of **2**, 72% of the final electrophilicity of the oxygen atom in the 4-

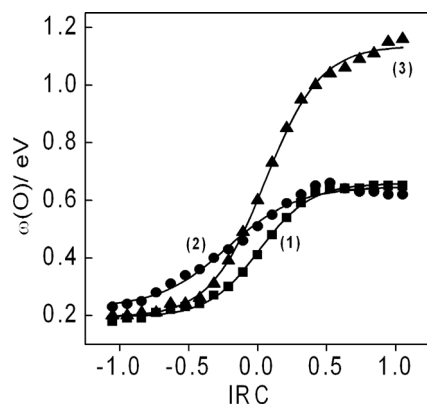


Fig. 2 Variation in local electrophilicity $\omega(O)$ of the hydroxyl oxygen of phenols **1–3** along the intrinsic reaction coordinate (IRC) of the reaction depicted in Scheme 1

methoxyphenoxyl radical was already attained. This value reduces to 47% in the case of the phenoxyl radical, and to 42% in the case of the 4-nitrophenoxyl radical. This result parallels the relative stages of transition states of phenols **1–3**: the strongest electron-donating substituent (4-OMe) promotes the earliest transition state, with the largest developed electrophilicity on the oxygen atom of the incipient radical. O–H breakage occurs at a later stage for the electron-withdrawing 4-NO₂ substituent, with the least developed electrophilicity on the oxygen atom of the corresponding radical.

The approach developed by Chattaraj and Roy [14], based on variations of reactivity descriptors along the IRC, was next applied to the reaction depicted in Scheme 1. Similarly to the examples presented by the latter authors, the present study looked at both endo- and exo-thermic reactions. Energy profiles for these processes, together with the Fukui functions for nucleophilic attack at the two oxygen atoms involved in the ArO•••H•••OOH transfer (f_{ArO}^+ and f_{HOO}^+) are shown in Fig. 3a–c. The values of the Fukui functions f_{ArO}^+ for all three phenols increase from reagents to products, while the f_{HOO}^+ values for the peroxy radical follow the opposite behavior. The corresponding curves for these variations intersect at IRC_{eq} points where $f_{ArO}^+ = f_{HOO}^+$, defined as “equireactivity configurations” [14]. In general, this IRC_{eq} configuration will be different from that of the reagent, TS and product for an unsymmetrical reaction. Following a reactivity-based Hammond postulate, Chattaraj and Roy suggested that, for an endothermic reaction, the equireactivity configuration should

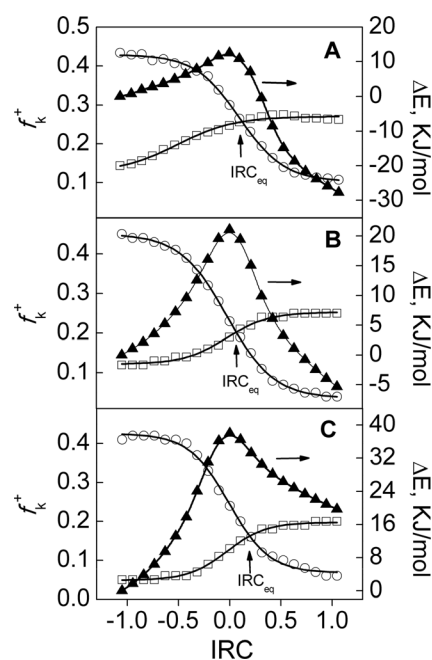


Fig. 3 Energy (▲) and Fukui function profiles for nucleophilic attack at the phenoxyl (f_{ArO}^+) (□) and hydroperoxyl (f_{HOO}^+) (○) oxygen atoms involved in the ArO•••H•••OOH transfer, for the reaction of **a** 4-methoxyphenol, **b** phenol and **c** 4-nitrophenol

also lie to the left of the TS, with a negative IRC value. This was not verified by our examples, where all equireactivity configurations, including the endothermic H-abstraction from 4-nitrophenol (Fig. 3c), had small, positive IRC values. For the present reaction, the Hammond postulate is verified if the variations of the f_{HOO}^+ values along the IRC for the three phenols are compared. The variations of the f_{HOO}^+ values constitute a more reliable reference, since the hydroperoxyl radical is a constant reagent in all three processes. In all cases, values of f_{HOO}^+ decrease from ca. 0.4 in the HOO• reagent, to ca. 0.1 in the HOOH product. As the process becomes more endothermic, from Fig. 3a to Fig. 3c, the closer its f_{HOO}^+ value in the equireactivity configuration is to its final value in the product. Thus, for the more reactive 4-methoxyphenol, the equireactivity configuration occurs when f_{HOO}^+ decreases by nearly 47% (Fig. 3a); for phenol, this decrease amounts to 54% (Fig. 3b), reaching 71% for the less reactive 4-nitrophenol (Fig. 3c).

The reason for the discrepancies between our observations and what was originally postulated by Chattaraj and Roy may be sought in the greater structural complexity of our system, as compared to the rather simple three- and four-atom model reactions presented by the latter authors [14]. Their assumption that the total reactivity of the reaction, expressed as a sum of the f_k^+ values of the two atoms intervening in the H-transfer, remains roughly constant throughout the whole process, is no longer verified in the present example. Abstraction of a hydrogen atom from substituted phenols 1–3 entails a reduction in total reactivity of the two oxygen atoms involved in the H-transfer ($f_{\text{ArO}}^+ + f_{\text{HOO}}^+$), because of the increased charge delocalization by the aryl ring, as the reaction proceeds.

Another useful DFT-based reactivity index that has found increasing applications is the dual descriptor [29, 30], defined as the partial second derivative, at a constant potential, of the electronic density ρ of an atom with respect to the number N of electrons of the system. The index incorporates both the electrophilicity and the nucleophilicity of an atomic center in a chemical reaction, from its calculation as the difference between the Fukui functions for a nucleophilic (f_k^+) and electrophilic attack (f_k^-):

$$\Delta f_k = f_k^+ - f_k^- \quad (8)$$

A positive value of Δf_k indicates a site where a nucleophilic attack should be favored, a negative value a site where an electrophilic attack should take place [12].

From Eq. (8), we calculated dual descriptor values Δf_{ArO} for the phenolic oxygen atom of 4-methoxy- (2) and 4-nitrophenol (3) along the IRC with the hydroperoxyl radical (see [Supplementary Material](#)). In both cases, Δf_{ArO} values were negative at the start of the reaction—an indication of the nucleophilic nature of the oxygen atom of the two phenols. As

the hydrogen-abstraction proceeds, Δf_{ArO} values become less negative, changing to positive values at IRC = -0.5 for the 4-methoxy derivative 2 and at IRC = 0.1 for the 4-nitrophenol 4. The earlier attainment of an electrophilic character by the oxygen atom of 2 reflects the greater stability of this phenoxyl radical, due to the electron-donating 4-methoxy substituent. The variations of the dual descriptor index for the two phenols thus parallel the consequences of the Hammond postulate: the more stable the product, the earlier its transition from reactant- to product-like character.

The effect of ortho-substituents

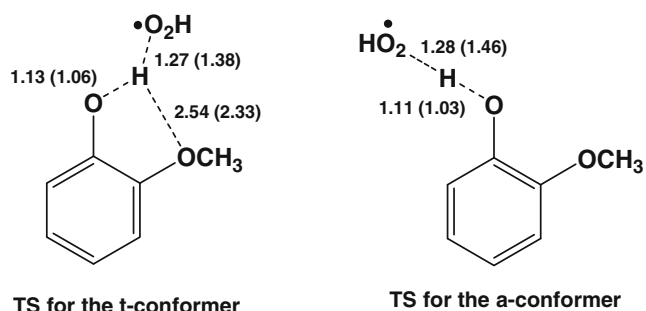
The inclusion of some mono- and di-ortho substituted phenols in the set shown in Table 1 did not affect the good correlation obtained with the para- and meta-substituted derivatives when the ortho substituents were alkyl groups. This may be taken as an indication that steric effects due to the proximity of bulky alkyl groups are incorporated into the calculated $q(\text{O}^\bullet)$ values of Eq. 6.

However, for hydrogen-bond-accepting groups, like 2-methoxy or 2-nitro, experimental BDEs may depart considerably from theoretically estimated values, depending on how the experimental BDE value was determined. Kinetic measurements that incorporate the possible breakage of an intramolecular hydrogen-bond may yield BDE values that are very different from other methods where the effect of these hydrogen-bond interactions should be absent [31].

We therefore investigated the effect of hydrogen-bonds between the OMe and/or NO₂ substituent and the hydroxyl group for the reaction shown in Scheme 1, by comparing the results obtained for para- with those of ortho-substituted phenols.

Previous attempts to interpret the effect of ortho substituents on the BDEs of phenols have made a distinction between two conformations: one in which the hydrogen atom of the OH group points towards the 2-substituent, and the other in which it points away from the neighboring group [25, 32]. The TS geometries for the two conformers, termed henceforth the “towards”, or t-conformer, and the “away” or a-conformer, are represented below for the case of the 2-methoxy derivative 4.

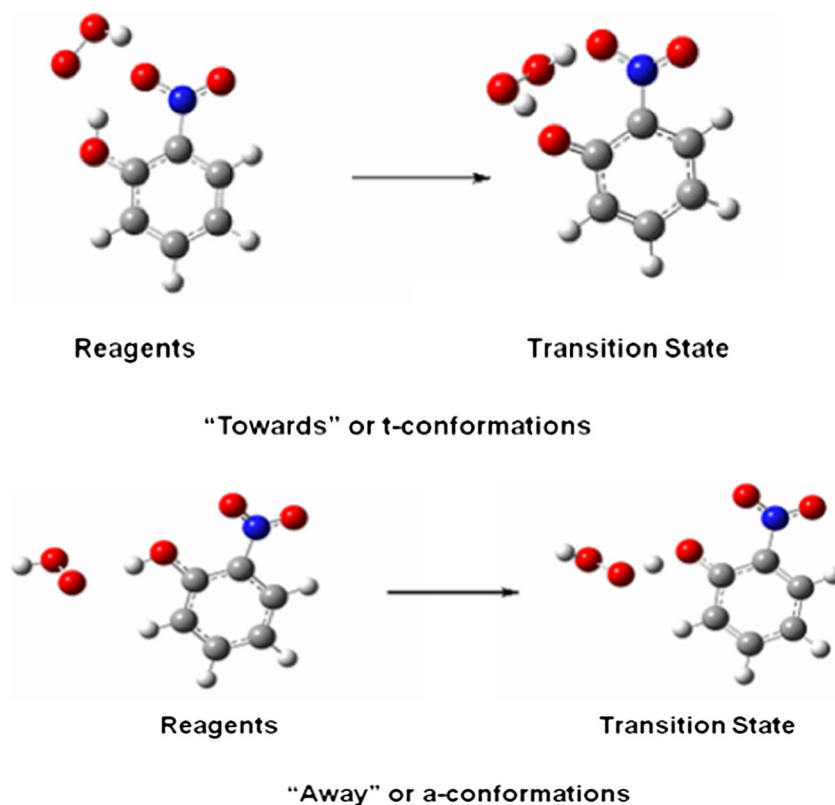
The hydrogen-abstraction of compound 4 by the methoxyl radical CH₃O• was studied by Mulder et al. at the B3LYP/6-31G(d,p) level of theory [25]. The authors considered the two conformations shown in Scheme 2, for which they obtained TS geometries similar to those obtained here, which are shown in Scheme 2. Differences in bond distances reflect the different nature of the abstracting radicals. The more reactive MeO• radical attains an earlier transition state than the HO₂• radical, leading to TS structures where the ArOH...•OMe bond is longer, for both conformers, than the ArOH...•O₂H bond.



Scheme 2 Transition state (TS) geometries for the “towards” (t) and “away” (a) conformers of phenol **4**, with distances in Ångstroms. Values between brackets correspond to distances for a similar hydrogen abstraction from a $\text{CH}_3\text{O}^\bullet$ radical [25]

Inspection of the values in Table 2 shows that the a-conformation leads to a more exergonic process ($\Delta H^\circ = -33.6 \text{ kJ mol}^{-1}$) than the t-conformation ($\Delta H^\circ = -22.8 \text{ kJ mol}^{-1}$). This is in line with the expectation that hydrogen abstraction from the t-conformer is a more costly process, because it involves, in addition to homolysis of the O–H bond, breakage of the intramolecular hydrogen-bond with the neighboring 2-methoxy group. A comparison of the relative BDEs of the isomeric 4- and 2-methoxyphenols (Table 1) shows that OH homolysis is slightly favored in the former ($\Delta \text{BDE} = -22 \text{ kJ mol}^{-1}$) over the latter ($\Delta \text{BDE} = -17 \text{ kJ mol}^{-1}$). The corresponding variations of the calculated reaction enthalpies of Table 2, taking the ΔH° value for phenol as a reference, are

Fig. 4 Conformations of reagents and transition states (TS) for the hydrogen-abstraction reaction of 2-nitrophenol **5** with the hydroperoxyl radical, with an indication of the “towards” or t-conformations and the “away” or a-conformations



$\Delta \Delta H^\circ = -23.5 \text{ kJ mol}^{-1}$ for phenol **2** and $\Delta \Delta H^\circ = -20.9 \text{ kJ mol}^{-1}$ for species **4(a)**, in good agreement with the experimental values of Table 1 (ΔBDE values of -22 kJ mol^{-1} for compound **2** and -17 kJ mol^{-1} for compound **4**).

In non-HBA solvents, the t-conformer of **4** should predominate. Calculations predict less than 0.1% of the a-conformer in saturated hydrocarbons [25]. This, however, does not imply that the hydrogen-abstraction process takes place from the more stable t-conformer. The Curtin-Hammett principle should operate here, with the expectation that the OH hydrogen-abstraction should proceed via an “away”, or a-transition state, with a smaller transition energy barrier ($\Delta H^\ddagger = 13.2 \text{ kJ mol}^{-1}$) than the t-TS ($\Delta H^\ddagger = 20.5 \text{ kJ mol}^{-1}$) (Table 2).

The hydrogen-abstraction from 2-nitrophenol **5** by the hydroperoxyl radical was studied by consideration of the two possible starting a- and t-conformations. Figure 4 reproduces the optimized geometries of reagents and TSs for the two conformations. The corresponding calculated enthalpies for the TS and final equilibrium between reagents and products are given in Table 2.

In compound **5**, the internal hydrogen-bond between the phenolic OH and the neighboring NO_2 is much stronger than that with the 2-methoxy substituent in **4**. This may be one explanation why the two processes depicted in Fig. 4 differ so much in energy compared with the corresponding pathways for the 2-methoxy derivative. According to the data in

Table 2, the difference between the calculated equilibrium enthalpies ΔH_{O} was 10.8 kJ mol⁻¹ for the **4(a)/4(t)** pair, and 51.9 kJ mol⁻¹ for **5(a)/5(t)**. The larger difference in stability between the reagents for the **5(a)/5(t)** pair, when compared with **4(a)/4(t)** may also explain such a large enthalpy difference. As can be seen in Fig. 4, an additional intermolecular hydrogen-bond between the hydroperoxyl radical and the nitro group is formed in the t-conformation of the starting reagents. This hydrogen-bond was absent in the t-conformation of the starting reagents of 2-methoxyphenol **4**.

Following the Curtin-Hammett principle, we may assume that the hydrogen-abstraction process takes place via the a-TS, despite the fact that the more stable t-conformation should predominate for the reagents. The calculated values of Table 2 allow the estimation of theoretical $\Delta\Delta H^{\circ}$ values for 4-nitrophenol (compound **3**) and 2-nitro-phenol [compound **5(a)**], assuming the ΔH° of phenol **1** as a reference. As stated above, theoretical $\Delta\Delta H^{\circ}$ and experimental ΔBDE values were in good agreement for 4-nitrophenol **3**. The agreement was much poorer, however, for the 2-nitro derivative **5(a)**, with values of $\Delta\Delta H^{\circ}=22.4$ kJ mol⁻¹, and $\Delta\text{BDE}=-5$ kJ mol⁻¹. A previous theoretical estimation of the BDE of 2-nitrophenol, employing the B3LYP level and the 6-31+G(3pd) basis set, arrived at a relative bond dissociation enthalpy of 11.5 kJ mol⁻¹ (2.76 kcal mol⁻¹) [32], in line with a less labile O–H bond for the 2-nitro derivative than for phenol. Calculated BDEs for compound **5**, in the gas phase and in seven solvents, were consistently larger than the calculated BDE for phenol [32], at variance with the experimental value of $\Delta\text{BDE}=-5$ kJ mol⁻¹ (Table 1). This discrepancy between theory and experiment, observed by other workers and by us, has puzzled other researchers before. Thus, after compiling ΔBDE values of phenols by various methods from the literature, Santos and Simões admitted that “the negative value” reported for the 2-nitrophenol “is hardly justifiable”, suggesting that “the problem may be in the VLPP (very low pressure pyrolysis) result for 2-NO₂” [31]. Our calculations, together with the results of other authors [32], reinforce their observations and their mistrust of the reported experimental value, which is, unfortunately, the only one available for this compound in the literature.

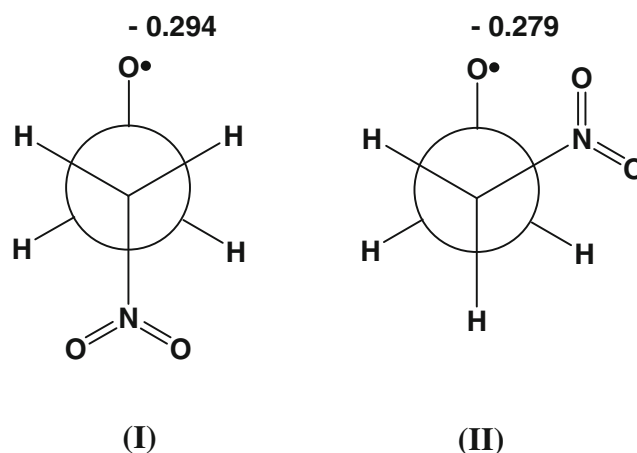
The results of the calculated charges $q(\text{O}^{\bullet})$ of Table 1 for the 2-nitro- and 4-nitrophenols are nevertheless at variance with those of Table 2, which are also theoretical. According to the calculated $q(\text{O}^{\bullet})$ values of Table 1, homolysis of the OH bond should be more difficult for 2-nitrophenol, when compared with the 4-nitro isomer. According to the calculated enthalpies of Table 2, the reverse should be observed. Trends from the literature, though regarded with some mistrust, favor the second conclusion.

As argued above, steric effects cannot account for major discrepancies of phenols with ortho-substituted groups like OMe and NO₂ in regression Eq. 7. The degree of coplanarity between the ortho-nitro substituent and the ring may doubtless

affect the calculated $q(\text{O}^{\bullet})$ value: the value listed in Table 2 (−0.425) corresponds to complete coplanarity between ring and substituent. Calculations with the same method for another conformation with an ortho NO₂ group orthogonal to the ring yielded a $q(\text{O}^{\bullet})$ value of −0.454. This more negative $q(\text{O}^{\bullet})$ value reflects both a reduction in conjugation between the nitro group and the phenoxy oxygen, and also a more reduced field effect due to the proximity of the NO₂ and the phenoxy oxygen atoms. Effects on the $q(\text{O}^{\bullet})$ value due to conjugation with the nitro group should be present in the 2- and the 4-nitro isomer. By contrast, field effects should not be present in the 4-nitrophenoxyl radical, and could be the cause of the discrepancies between the $q(\text{O}^{\bullet})$ values of the 2-nitro isomer ($q(\text{O}^{\bullet})=-0.425$), where this effect is present, and the 4-nitro derivative ($q(\text{O}^{\bullet})=-0.453$), where it is absent.

To verify this, we performed calculations with different conformations of the 2-nitroethoxyl radical O₂N-CH₂-CH₂-O[•], a structure where, unlike what happens with the 2-nitrophenoxyl radical, effects of conjugation, but not field effects of the nitro group on the neighboring alkoxy oxygen, may be ruled out. Employing the same B3LYP/6-31G(d,p) method, $q(\text{O}^{\bullet})$ values for these ethoxyl radicals varied with the distance between one NO₂ oxygen and the alkoxy O[•]. Negative $q(\text{O}^{\bullet})$ charges decreased in absolute value as this distance decreased, as can be seen in Scheme 3, where the antiperiplanar (I) is compared with the staggered conformation (II). The greater proximity of the NO₂ group to the oxygen radical, observed with structure (II), with the consequent larger field effect, reduces the absolute value of the charge on O[•].

Thus, these results are in agreement with the difference in $q(\text{O}^{\bullet})$ values observed for the 2- and the 4-nitrophenoxyl radicals of Table 1, and help explain why the $q(\text{O}^{\bullet})$ value is not a good descriptor for ΔBDE values of phenols with ortho-substituted nitro or methoxy substituents.



Scheme 3 Mulliken charges $q(\text{O}^{\bullet})$ on the oxygen atom of the 2-nitroethoxyl radical O₂N-CH₂-CH₂-O[•], calculated for two different conformations, with the B3LYP/6-31G(d,p) method

Conclusions

The above theoretical study of the hydrogen-abstraction process of substituted phenols **2–5** by the hydroperoxyl radical in the gas phase yielded results that were, in general, in fairly good agreement with the experimental Δ BDE values of these compounds. The electrophilic nature of the incipient phenoxyl radical is reflected in the dependence of the O–H BDE on the nature of the phenol substituent. Donor groups, like 4-OMe, promote earlier TSs, with relatively smaller bond-breakage, than electron-withdrawing groups like 4-NO₂. As the O–H hydrogen-abstraction proceeds, the electrophilicity of the oxygen atom increases along the IRC, following a sigmoidal pattern. This variation, from reagents to products, of the local electrophilicity of the oxygen atom decreased with the electron-releasing nature of the substituent, in the order 4-NO₂>H>4-OMe. Profiles of the variations of Fukui functions for nucleophilic attack at the two oxygen atoms involved in the hydrogen transfer (f_{ArO}^+ and f_{HOO}^+) were also sigmoidal, increasing for the phenoxyl (f_{ArO}^+) and decreasing for the hydroperoxyl oxygen (f_{HOO}^+) along the IRC. For the three phenols, and regardless of being exo- or endo-thermic processes, the intersection of the two curves occurred at equireactivity configurations with positive IRC values. This contrasts with the postulates of Chattaraj and Roy [14], and was rationalized by the fact that, in the present study, the sum of f_{ArO}^+ and f_{HOO}^+ does not express the total reactivity of the reaction. Values of the dual descriptor Δf_{ArO}^+ for the hydroxylic oxygen atom of 4-methoxy- and 4-nitrophenol changed from negative to positive, indicating the ambiphilic nature of the O atom of the incipient phenoxyl radical along the IRC; its nucleophilic nature in the undissociated O–H changes to increasingly electrophilic behavior in the free phenoxyl radical. This change occurs earlier for 4-methoxyphenol than for the 4-nitrophenol, reflecting the greater stability of the electrophilic 4-methoxyphenoxyl radical.

The charge on the oxygen atom of the substituted phenoxyl radical $q(\text{O}\cdot)$ is a good descriptor for the BDEs of the corresponding phenols, when the electronic effect of the substituent is the major factor affecting these energies. When other factors, such as intramolecular hydrogen-bonds between the phenolic OH and neighboring HBA groups come into play, the $q(\text{O}\cdot)$ parameter may no longer be an adequate descriptor. The reason for this is probably not steric, since the observed good correlation between experimental Δ BDE values and $q(\text{O}\cdot)$ (Eq. 7) holds for voluminous ortho-alkyl groups. A more reasonable explanation may be sought in the sensitivity of the $q(\text{O}\cdot)$ parameter to field effects by neighboring polar groups like OMe or NO₂. Small changes in their orientation or proximity to the oxygen radical may induce significant charge variations in the phenoxyl oxygen atom, leading to deformations that no longer correlate with the OH bond dissociation. Calculations performed on the product phenoxyl radical are

no longer reliable in such cases, and a more detailed analysis of the whole hydrogen-abstraction process is required, to arrive at results that agree reasonably well with experimental values.

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