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ORIGINAL RESEARCH

How OH and O^- groups affect electronic structure of *meta*-substituted and *para*-substituted phenols and phenolates

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Abstract An application of two independent quantum chemistry-based concepts, a substituent effect stabilization energy (SESE) and a charge of the substituent active region (cSAR), for describing substituent effects allows to investigate a nature of mutual interactions between substituents. The B3LYP/6-311++G(d,p) method is employed to examine changes in properties of a reaction center Y (Y = OH or O^- groups) and a transmitting moiety (the benzene ring) due to substituent effects in a series of *meta*-X-substituted and *para*-X-substituted phenol and phenolate derivatives (X = NMe_2, NH_2, OH, OMe, CH_3, H, F, Cl, CF_3, CN, CHO, COCl, COMe, $CONH_2$, COOH, NO_2, NO). HOMA, NICS(1) and *p*EDA parameters are used to characterize π-electron delocalization of the transmitting moiety. Relations between cSAR(X) and σ constants show almost identical sensitivity of the substituent effect in *meta*-substituted phenol and phenolate derivatives, whereas in *para*-substituted analogs, different kinds of intramolecular interactions have been revealed. Due to electron attractive property of OH group in *meta* position, dependences of cSAR(X) on SESE show a dramatically different picture of interaction in *meta*-substituted phenols as compared to that found for all other series studied. Moreover, this group affects in a different way the electron-attracting and electron-donating substituents in *meta* position. A clear substituent effect on π-electron delocalization of the benzene ring is observed only in *para*-substituted phenolate derivatives. The application of cSAR(X) parameter allows to estimate a difference between its value for a particular substituent in *meta* and *para* derivatives. In some cases, this difference amounts up to ~53% of the range of cSAR(X) variability.

Keywords substituent effects · electronic structure · molecular modeling · substituent effect stabilization energy · charge of the substituent active region

This paper is dedicated to Professor Lou Massa on the occasion of his Festschrift.

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Introduction

There are a lot of reasons causing hydroxy and hydroxylate groups to form a pair of substituents of a great importance. Firstly, they can interchange from one to another depending on the environment [1]. In cases of an interaction with strong bases, OH group is easily transformed into O^- group. Secondly, they have a possibility to act either as the H-bond donor (OH) or acceptor (O^-); for a review, see Gilli and Gilli [2]. As substituents (X) interacting in a classical way with reaction site (Y) through the transmitting moiety R, schematically X-R-Y, both OH and O^- exhibit very different properties exemplified in Table 1 by means of substituent constants [3].

As we see, OH group in *meta* position acts even as an electron-accepting substituent with $\sigma > 0$, whereas in all other cases, $\sigma < 0$, and hence, both OH and O^- groups exhibit electron-donating properties. Hydroxylate group (O^-) is always

Table 1. Substituent constants in dependence on position (*meta*- and *para*-) and nature of a reaction site taken from Ref. [3].

Substituent constant	OH	O^-
σ_m	0.12	-0.47
σ_p	-0.37	-0.81
σ_p^+	-0.92	-2.30
σ_p^-	-0.37	-0.82

much stronger electron-donating substituent than OH group. All these data are obtained from the model reactions: the Hammett constants from acid/base equilibria of benzoic acid derivatives and σ_p^+ from the kinetic data of solvolysis of dimethyl-diphenyl-carbinylchloride [4, 5]. It is important to note that the changeability of electron accepting/donating properties of both groups is very large. An application of the abovementioned substituent constants is somewhat limited to systems in which we are able to assume a similar nature of substituent effect to that which works in an appropriate model reaction. Unfortunately, this kind of a priori assumption is not always justified. A quantum chemical modeling allows to look at these problems independently from the model reactions/processes. The substituent effect may be characterized by quantitative descriptors which can be verified firstly by a comparison with the traditional, empiric substituent constant. Substituent effects in phenol and phenoxide ion derivatives were theoretically described by means of molecular orbital calculations [6], however, without a possibility of an effective estimation of substituent effect descriptors in a given molecular system.

Recently, two quantum chemical-based models have been successfully applied for describing SE: cSAR and substituent effect stabilization energy (SESE). The cSAR(X) approach (an acronym from charge of the Substituent Active Region) describes the electron attracting or donating property of the substituent X. By definition, cSAR(X) is a sum of atomic charges at all atoms of the substituent and the ipso carbon atom [7]. This descriptor correlates well with substituent constants [7–10]. It is important to stress that the cSAR(X) approach realized by the use of different atomic charge schemes leads to the results which are, as a rule, mutually well correlated [11]. The more negative is its value, the more electron attracting is a substituent, and vice versa for electron-donating properties – the more positive cSAR(X), the more electron donating is the substituent. Moreover, the cSAR approach can be applied to both, the varying substituents, [as cSAR(X)], as well as to the reaction site (or a fixed functional group in the series X-R-Y), [cSAR(Y)], and allows to estimate the regression line cSAR(Y) vs. cSAR(X). The slope of this regression describes the strength of interactions between X and Y [9, 10]. It was also shown that changes in geometry of the components of the functional group Y correlate well with cSAR(Y) [12] and hence correlate also with cSAR(X) that was documented for aniline [10], nitrobenzene [13], and benzoic acid [14] substituted derivatives.

Another possibility of the application of quantum chemical computations for the modeling of SE are isodesmic or homodesmotic reactions [6, 15]. They can be used to obtain the SESE characteristic. This approach allows to determine, in an energetic scale, the nature of the interaction between substituents in disubstituted systems. It was documented that the SESE characteristic correlates well with classical substituent constants [9, 10]. SESE is a descriptor of substituent electron donating/attracting properties and takes into account all interactions in the X-R-Y system.

Chemical compounds with hydroxy and phenoxide groups are of great interest in many fields of chemistry, biochemistry, and related fields of science and technology [16–18]. Hydroxy group is also a part of carboxyl group, and hence, it is of great importance for interactions in which proteins participate. This implies its high importance in all branches of life science and medical chemistry [19, 20]. Many nucleic bases may exist in tautomeric form with OH group as their important component [16, 21, 22].

Since OH/O^- groups are present in so many important compounds, a systematic study of their electron donating/attracting properties can give a possibility to get a wider and deeper knowledge on their influence on molecular systems containing them. Additionally, it is important to stress that acid base equilibria $PhOH/PhO^-$ constitutes the reference reaction for estimating σ_p^- substituent constants which are necessary to describe reactions with negatively charged reaction sites [23].

The application of the abovementioned quantum chemical-based models of substituent effect to series of *meta*-substituted and *para*-substituted derivatives of phenol and phenolate allows to recognize the changeability of electron donating/attracting properties of OH and O^- groups resulted from an action of various substituents. A comparison of the SE characteristics based on physical models with the traditional SC can enables a presentation of data expressed in SESE or cSAR in the scale of well-known σ constants. Finally, since both functional groups, OH and O^-, are known as strongly interacting with moieties to which they are attached, we intend to estimate their reverse substituent effects. This means to evaluate the impact of these groups on the electron donating/attracting properties of substituents attached in *meta* and *para* positions in phenol and phenolate derivatives.

Methodology

The molecular geometries of phenol and phenolate as well as their monosubstituted derivatives (X = NO, NO_2, CN, COCl, CF_3, COMe, COOH, CHO, $CONH_2$, Cl, F, H, Me, OMe, OH, NH_2, and NMe_2) have been fully optimized at the B3LYP [24, 25] level of theory and 6-311++G** basis set [26] with the GAUSSIAN09 program [27]; for

branched substituents, several conformations have been taken into account to find the global minimum energy structure. Each stationary point was then characterized at the same level of theory by computing the vibrational frequencies within the harmonic approximation to ensure that the resulting structures were the minima with no imaginary frequencies. Moreover, their effective wavefunctions at the same level of theory have been used to characterize topological properties of the electronic charge density.

For each system studied, the energy-based descriptor SESE has been evaluated using a homodesmotic reaction which is based on total energies of optimized systems [15, 28–30] (eq. (1)):

$$\mathrm{X–}\mathbf{R}\mathrm{–Y} + \mathbf{R} \rightarrow \mathbf{R}\mathrm{–X} + \mathbf{R}\mathrm{–Y} \quad (1)$$

By using this model, the energetic effect of the interaction between a substituent (X) and a reaction site (Y), which is OH or O^- group in this work (**R** denotes the benzene ring), could be described. The greater stabilization energy due to the substituent effect leads to the greater SESE value and indicates the stronger stabilization in disubstituted system (see eq. (2)).

$$\mathrm{SESE} = \mathrm{E}(\mathbf{R}\mathrm{–X}) + (\mathbf{R}\mathrm{–Y}) - \mathrm{E}(\mathrm{X}\mathrm{–}\mathbf{R}\mathrm{–Y}) - \mathrm{E}(\mathbf{R}) \quad (2)$$

Another parameter used to describe the substituent effect is cSAR(X) – a substituent active region parameter [7, 31] which can be calculated according to eq. (3)

$$\mathrm{cSAR(X)} = q(\mathrm{X}) + q\left(\mathrm{C_{ipso}}\right) \quad (3)$$

where q(X) and $q(C_{ipso})$ are charges of atoms belonging to the substituent X and the *ipso* carbon atom to which the substituent is attached, respectively.

An assessment of atomic charges has been performed through three different methods: (a) Hirshfeld [32], (b) Bader [33], and (c) Weinhold [34]. The AIM2000 package [35] has been employed for calculation of Bader's AIM atomic charges. Weinhold's natural population analysis (NPA) has been performed with NBO 6.0 program [36].

The NBO 6.0 program has been also used for calculating a *p*EDA descriptor (eq. 4) [37] for the transmitting moiety (**R**) – the benzene ring. The π-effect is defined by the sum of occupancies of p_z orbitals of all C atoms in the ring (located in the *xy* plane) contributing to the benzene π-electron system.

$$p\mathrm{EDA} = \sum_{i=1}^{6} \pi^i_{\mathbf{R}} - \sum_{i=1}^{6} \pi^i_{\mathrm{C6H6}} \quad (4)$$

where π^i denotes sums of occupancies of all atomic orbitals of the *i*th C-atom in the benzene ring contributing to the valence π-molecular orbitals.

To characterize an effect of the substituent on the transmitting moiety, a geometry-based aromaticity index Harmonic Oscillator Model of Aromaticity (HOMA) [38, 39] has been used. It is defined as

$$\mathrm{HOMA} = 1 - \frac{\alpha}{n}\sum\left(d_{opt} - d_i\right)^2 \quad (5)$$

where n is the number of bonds taken into account; α is a normalization factor which is for CC bond fixed to 257.7 to give HOMA = 0 for a model nonaromatic system and 1 for the system with all bonds equal to the optimal value (d_{opt} = 1.388 Å), and d_i stands for a running bond length.

Additionally, the GIAO/B3LYP/6-311++G** method [40] has been used to calculate NMR shielding and also NICS at the geometric center of a ring defined as NICS(0), at 1 Å above the center denoted as NICS(1) as well as its component corresponding to the principal axis perpendicular to the ring plane denoted as NICS(1)zz [41–43].

Results and Discussion

The obtained results and subsequent analysis are presented in subsections devoted to: (i) quantitative characteristics of the substituent effect and their mutual interrelations, (ii) the classical substituent effect – the influence of substituents X on the properties of OH and O^- groups, (iii) the influence of a substituent on the transmitting moiety properties, and (iv) the reverse substituent effect, i.e., how the electron attracting/donating properties of the substituent X depend on the nature of a moiety to which it is attached. The values of all obtained characteristics are gathered in Tables 1S and 2S for phenol and phenolate derivatives, respectively.

Quantitative characteristics of the substituent effect

In studies of substituent effects in *meta*-substituted and *para*-substituted phenol and phenolate derivatives, it is reasonable to look firstly at the mutual relations between the substituent effect descriptors. In this work, we have used: the traditional Hammett's substituent constant, cSAR, and SESE descriptors. To get a deeper insight, the mutual interrelations are shown for three methods of the atomic charge assessment: Hirshfeld, Weinhold (NBO), and Bader (AIM). The statistics of the linear regressions are given in Tables 2, 3S, and 4S.

A few results are worth mentioning. Firstly, consider relations of the data independent of the atomic charge assessment method – the case of SESE vs. Hammett's substituent constants. It is important to stress that both Hammett-like substituent constants and SESE descriptors take into account all interactions in the substituted systems. For *para*-substituted phenols and phenolates and for *meta*-substituted phenolates, the correlations are excellent as shown in Fig. 1. This is not a case of *meta*-substituted phenols for which a very small variability of SESE values has been found. It is also noted

Table 2. Interrelations between characteristics of substituents in phenol and phenolate anion derivatives.

	R^2	a	b	a_p/a_m	Δ1	$\Delta1_p/\Delta1_m$	Δ2	$\Delta2_p/\Delta2_m$
	SESE = $a \cdot \sigma + b$				SESE		σ	
m	0.218	-0.515	0.323	-5.19	0.84	5.02	0.87	2.00
	0.942	**21.361**	**0.916**	**1.04**	**17.05**	**1.96**	**0.87**	**2.00**
p	0.847	2.671	-0.427		4.22		1.74	
	0.864	**22.131**	**5.977**		**33.50**		**1.74**	
p^*	0.860	2.160	-0.954		4.22		2.00	
p^*	**0.971**	**18.818**	**1.169**		**33.50**		**2.00**	
m+*p*	0.572	1.972	-0.335					
	0.804	**21.196**	**3.558**					
	$cSAR(X)_{Hirsh} = a \cdot \sigma + b$				$cSAR(X)_{Hirsh}$		σ	
m	0.870	-0.306	0.055	0.55	0.28	0.93	0.87	2.00
	0.817	**-0.299**	**-0.092**	**0.74**	**0.26**	**1.31**	**0.87**	**2.00**
p	0.961	-0.169	-0.030		0.26		1.74	
	0.788	**-0.220**	**-0.237**		**0.34**		**1.74**	
p^*	0.847	-0.128	-0.001		0.26		2.00	
p^*	**0.960**	**-0.194**	**-0.185**		**0.34**		**2.00**	
m+*p*	0.771	-0.192	-0.002					
	0.549	**-0.219**	**-0.176**					
	$cSAR(X)_{Hirsh} = a \cdot SESE + b$				$cSAR(X)_{Hirsh}$		SESE	
m	0.219	0.139	-0.056	-0.40	0.28	0.93	0.84	5.02
	0.911	**-0.014**	**-0.077**	**0.71**	**0.26**	**1.31**	**17.05**	**1.96**
p	0.846	-0.055	-0.058		0.26		4.22	
	0.983	**-0.010**	**-0.173**		**0.34**		**33.50**	
m+*p*	0.309	-0.047	-0.041					
	0.875	**-0.012**	**-0.128**					

In the equation $f(x) = a \cdot x + b$, Δ1 and Δ2 denote ranges of variability $f(x)$ and x, respectively. Data for phenolate anion derivatives are in bold (cSAR data related to Hirshfeld charge)

*equation with σ_p^- constants

that the use of σ_p^- for *para* series leads to better correlations than the application of the original Hammett σ_p constants, particularly in the case of phenolates.

In two other cases, cSAR(X) vs. σ and cSAR(X) vs. SESE, regression lines are more acceptable for *para*-substituted than for the *meta*-substituted derivatives. As a rule, these relationships reveal weaker correlations. This may result from the fact that cSAR(X) describes rather local electron properties of substituents, whereas both, the Hammett substituent constants and SESE, take into account all intramolecular interactions in a substituted molecule.

Additionally, both abovementioned relationships depend on the method of atomic charge assessment (see Tables 2, 3S, and 4S and Fig. 1S). To estimate these dependences, let us consider regression lines for *meta* and *para* derivatives of phenols and phenolates in the case of cSAR(X) vs. original Hammett σ constant relations. The determination coefficients are the best for Hirshfeld estimation of charges (0.788-0.961), followed by AIM (0.726-0.940) and then NBO (0.648-0.867). Figure 2 presents comparison of cSAR(X) vs. σ relations for *meta*-substituted and *para*-substituted species and for Hirshfeld charge of atoms assessment. It is important to note the almost identical sensitivity of the substituent effect in *meta*-substituted phenol and phenolate derivatives: the slopes are equal to -0.306 and -0.299, respectively, indicating a similar nature of interactions in both series. Contrary to this, values of the slopes for *para*-substituted species are different: -0.169 and -0.220, respectively, indicating different kinds of intramolecular interactions in these series. The application of σ_p^- instead of σ_p in the latter case and different charge assessments leads to qualitatively similar results (Fig. 1S). In further discussion, the Hirshfeld assessment of atomic charges will be used.

The dependences of cSAR(X) on SESE for *para*-substituted phenol and phenolate derivatives and for *meta* derivatives of phenolates are presented in Fig. 3. As expected, in all three cases, increase of SESE is associated with an increase of a negative charge at the substituent which is in line with its increasing electron-attracting properties.

However, since OH group in *meta* position has electron-accepting properties (Table 1) the situation in the case of *meta*-

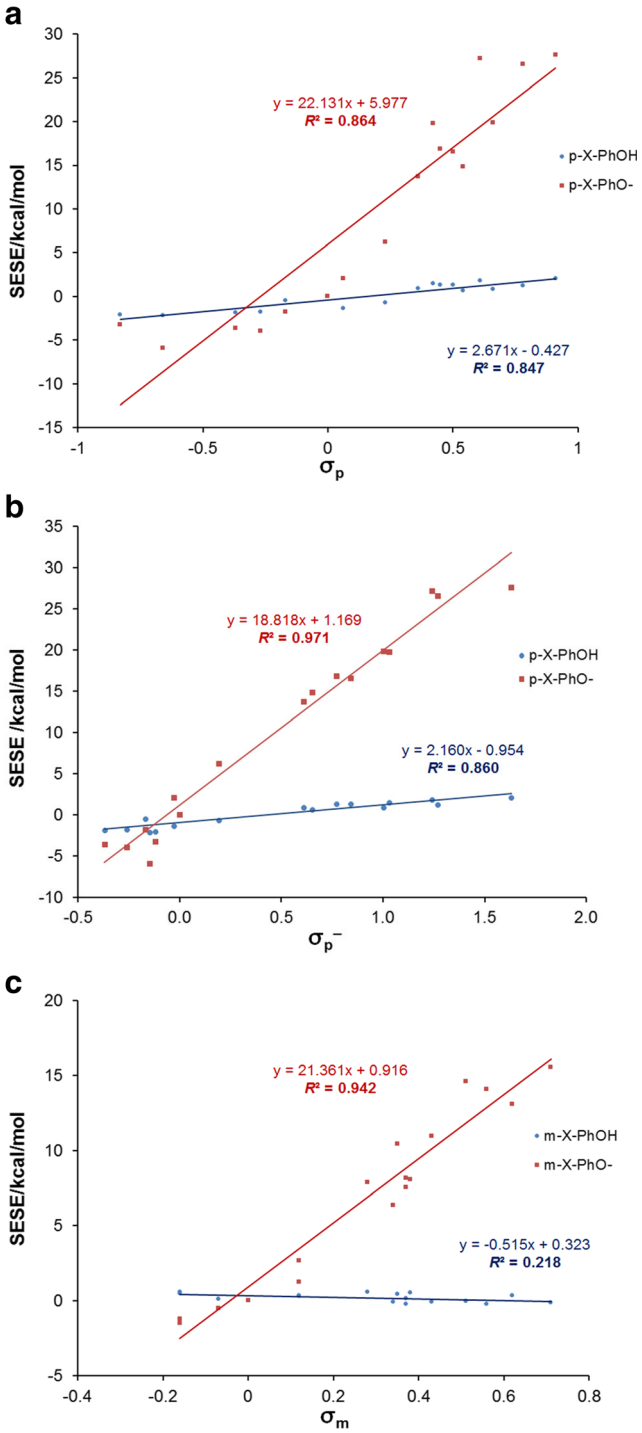

Fig. 1. Dependences of SESE on (**a**) σ_p and (**b**) σ_p^- for *para* and (**c**) on σ_m for *meta* in substituted phenol and phenolate derivatives.

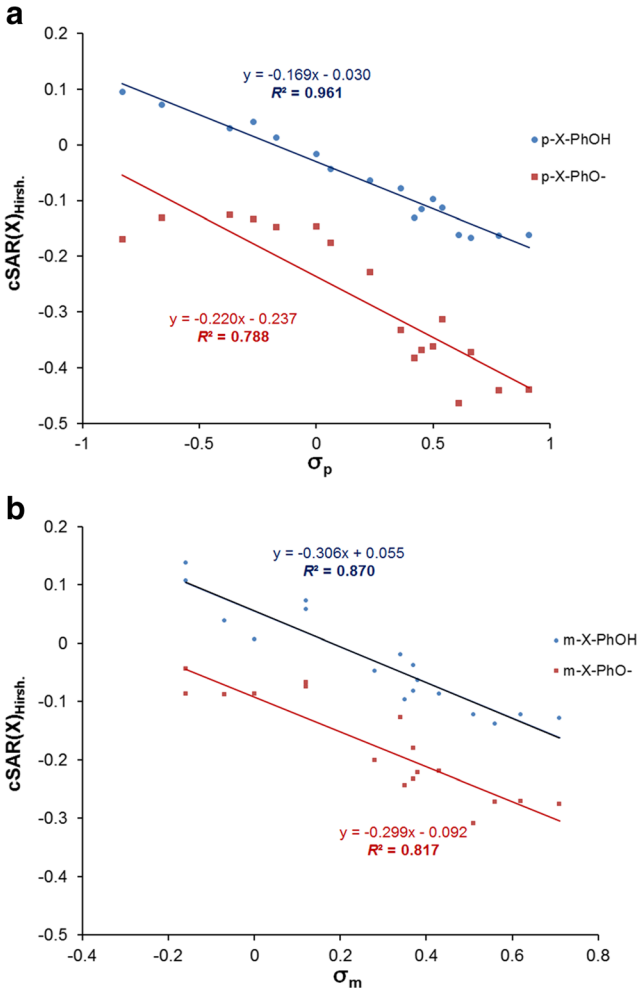

Fig. 2. Relations between cSAR(X) and σ_p and σ_m for (**a**) *para*-substituted and (**b**) *meta*-substituted phenols and phenolates obtained for the Hirshfeld charge assessment.

substituted phenol derivatives is quite different. The dependence of cSAR(X) on SESE is presented in Fig. 4 and suggests a division of substituents into two groups: (i) electron-donating substituents with negative resonance substituent constants $R \leq 0.0$ (R taken from [3]) and (ii) the remaining substituents ($R > 0.0$). In contrast to the relations shown in Fig. 3 for both groups, positive values of the slopes and almost the same ranges of SESE values are observed. Therefore, a decrease of cSAR(X) (an increase of the negative charge) is associated with a decrease in stability of the systems in question (a decrease of SESE values), but two equations are needed to describe these relationships.

The upper line with $R^2 = 0.982$ indicates that an increase of cSAR(X) (denoting an increase of electron-donating properties of the substituent) is strongly associated with an increase in stabilization of di-substituted species. This stabilization can be explained by an electron-attracting property of *meta* position in phenol (Table 1), and hence, stronger intramolecular interactions are observed with increasing electron-donating ability of substituents. A similar trend is observed (but with a worse determination coefficient) for electron-attracting substituents presented by the lower line in Fig. 4.

The above conclusion allows to assume that the substituent effect mechanism in *meta* position is different for electron-attracting and electron-donating substituents. To check this statement, the relation between substituent field/inductive constant (F) and Hammett's σ_m is shown in Fig. 5. It is known that

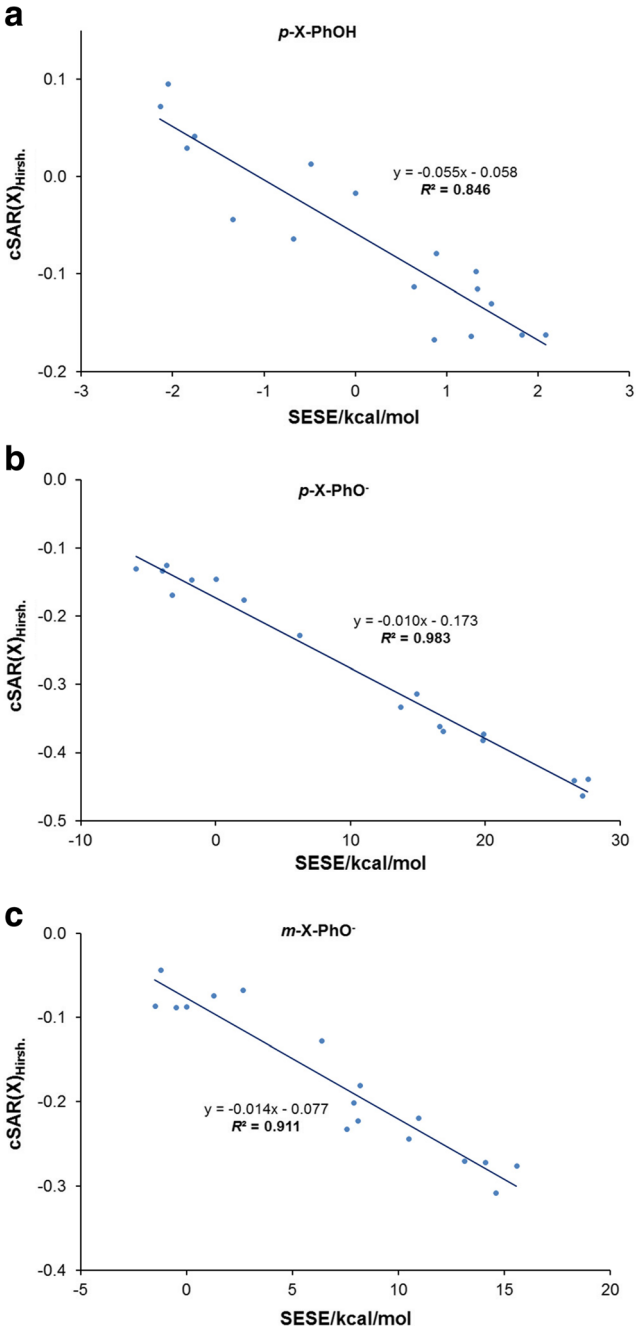

Fig. 3. Dependences of $cSAR(X)_{Hirsh}$ on SESE for *para*-substituted phenol (**a**) and phenolate (**b**) and *meta*-substituted phenolate (**c**) series.

interactions described by σ_m consist of two main components: the resonance effect and the inductive/field one [44, 45]. Data presented in Fig. 5 suggest that there are two substituent groups for which the regression lines are separated, indicating different dependences of F on σ_m. It indicates different contributions of the aforementioned components for interactions described by σ_m, therefore, confirms the different mechanism of interactions for *meta* position. Note that the same kind of separation is observed for electron-attracting and electron-donating substituents in Fig. 4.

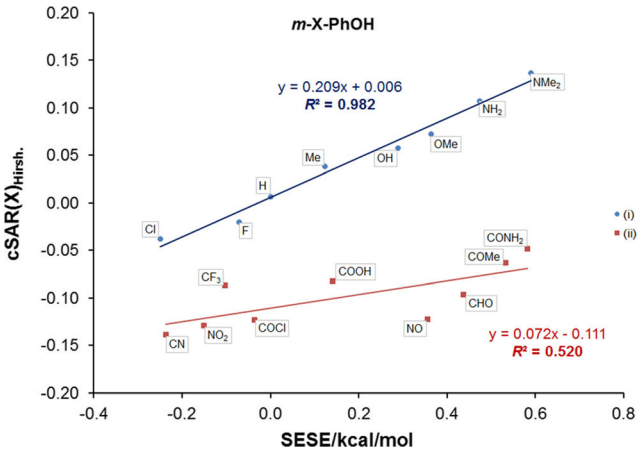

Fig. 4. Regression of $cSAR(X)_{Hirsh}$ vs. SESE for *meta*-X-PH-OH derivatives.

Classical substituent effect

Consider now a traditional Hammett scheme of analyses applying cSAR descriptors for substituents and for the "reaction site" (i.e., OH and O^- groups). Figure 6 shows dependences of cSAR(OH) and cSAR(O^-) on cSAR(X).

The classical Hammett's approach deals with relations between chemical property of a reaction site Y and substituent constants. Here, we present another view of this kind of relation showing dependences of cSAR(Y) on cSAR(X), where Y = OH or O^-. In the presented dependences in Fig. 6, both variables are in the same scale of magnitude, and hence, comparisons of slopes are justified. For *para*-substituted species, determination coefficients are very high ($R^2 > 0.971$) and the slope for phenolate data is higher (as the absolute value) than for the phenols, -0.376 and -0.337, respectively, indicating stronger interactions between substituents and the reaction site Y in phenolates. The opposite situation is encountered for *meta* derivatives. Determination coefficients are lower (0.675 and 0.909, respectively), but values of the slopes

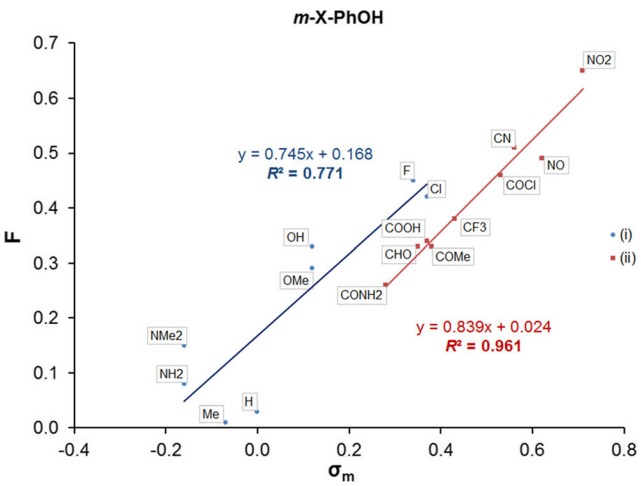

Fig. 5. Dependence of field/inductive constant F on σ_m for (i) and (ii) groups of substituent (see text; ED and EA substituents, respectively).

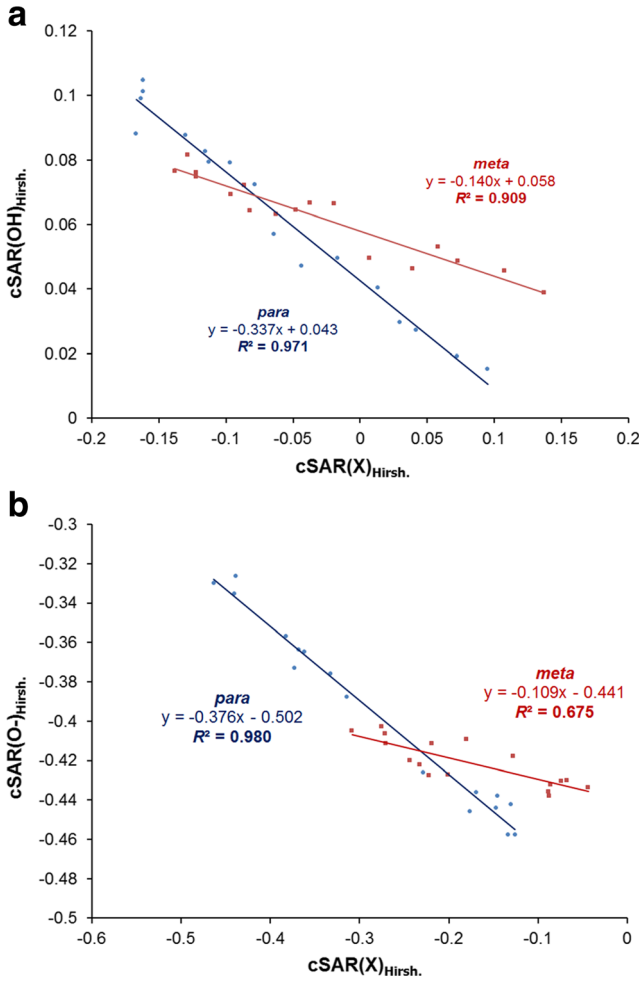

Fig. 6. Dependences of cSAR(Y) on cSAR(X), for Y = OH (**a**) or O^- (**b**) in *meta*-substituted and *para*-substituted series.

suggest a better communication for phenol derivatives than for the phenolates, with the slopes equal to -0.140 and -0.109, respectively.

Substituent effects on transmitting moiety properties

To characterize changes in π-electron delocalization of the benzene ring (the transmitting moiety of the studied systems), HOMA [38, 39], NICS [41–43], and *p*EDA [37] parameters were used.

In accordance with the earlier studies [46] in the case of phenol derivatives, HOMA and NICSs present a very low variability and no clear dependences on SE characteristics are observed. Nevertheless, the ranges of the variability of HOMA and NICS aromaticity characteristics are dramatically greater for *para*-substituted phenolates than for phenols (~10 and 2 times, respectively). Scatter plots of these indices vs. SESE or cSAR(X) for phenolates have acceptable determination coefficients ($R^2 > 0.81$, Figs. 2S and 3S) and document an increase of aromaticity with increasing cSAR(X) values (Fig. 2S). For *meta*-substituted phenolates, the variability of HOMA and NICS is very low and no clear dependences on substituent characteristics are observed.

It has been already shown that changes in the π-electron structure may be well described by *p*EDA [9, 37, 47]. In the case of strong substituent effect, as in *para*-substituted phenolate derivatives, *p*EDA is well correlated with HOMA as shown in Fig. 7. The increase of π-electron population in the ring described by *p*EDA values is associated with an increase of aromaticity indicated by HOMA. Low range of variation of HOMA for *meta* derivatives does not allow for the strong conclusion; nevertheless, a reverse picture might be found.

Reverse substituent effect

A nonequivalent character of interactions in *meta*-substituted and *para*-substituted phenols and phenolates is also well illustrated by relations between cSAR(X) values for *para* and *meta* series. As presented in Fig. 8 for phenol derivatives, the slope close to 1.0 indicates a highly similar reverse substituent effect from *meta* and *para* positions. However, this is not the case for phenolate series, where the reverse substituent effect for *meta*-substituted derivatives is 0.687 times weaker than for the *para* ones. A very similar result is found for the regression of differences in energy between phenols and appropriate phenolates, [E(X-Ph-OH) – E(X-Ph-O^-)]. This is shown in Fig. 9, where the slope is 0.525. Undoubtedly, this indicates a different nature of the substituent effect from *para* and *meta* positions.

One more illustration of the reverse substituent effect is provided by a comparison of cSAR(X) values in phenol and phenolate series with the values of cSAR(X) for monosubstituted benzene derivatives (Fig. 10). In all cases, $R^2 > 0.89$ indicates reliable results. For phenol derivatives (Fig. 10a), a minor difference between slopes for *meta*-substituted and *para*-substituted systems is observed – it means that the reverse substituent effects are very similar. The difference appears for phenolate series (Fig. 10b). The observed reverse substituent effect for both *meta* and *para* derivatives is greater than in the phenol series (slopes greater than 1.0). Additionally, the obtained slope for the *para* phenolates is larger than that for the *meta* one. The above presented analyses are understandable since O^- group undoubtedly affects strongly electron donating/attracting properties of substituents.

The reverse substituent effect is the most clearly presented by numerical data from Table 3. Comparisons of cSAR(X) for a particular substituent are facilitated by values of Δ1 and Δ2 which inform how much cSAR(X) in *meta* and *para* positions in phenol and phenolate series, respectively, differ.

In the case of the phenol series for particular substituents, these differences account for 11-15% of the cSAR(X) variability range, **Δ**. For phenolates, these differences are significantly greater and vary from 23 to 53% of **Δ**. When all studied series are taken together into account then the range of the cSAR(X) variation is 0.600, whereas the greatest value of

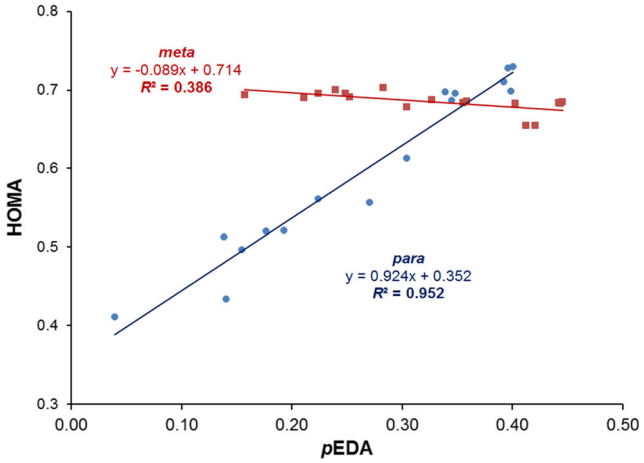

Fig. 7. Dependences of HOMA on *p*EDA in *meta*-substituted and *para*-substituted phenolates.

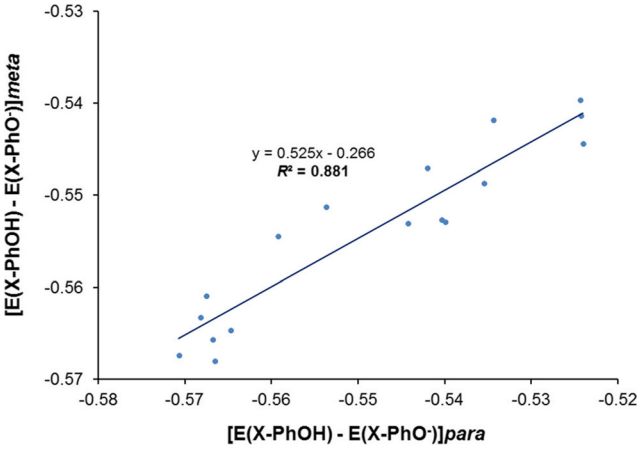

Fig. 9. Dependence of [E(X-Ph-OH) - E(X-Ph-O⁻)]*meta* values on [E(X-Ph-OH) - E(X-Ph-O⁻)]*para* for studied derivatives.

$\Delta = 0.340$, which constitutes 56.6% of the total variability of cSAR(X). This is a very good illustration how dramatically electron donating/attracting properties of substituents can be modified depending on the moiety to which they are attached.

One more very important meaning of Δ values is that they allow to quantify the range of a potential variability in electron attracting/donating properties of any substituent, as shown in Table 3. Let us illustrate this in practice. The substituents with the greatest ability for changing their electron attracting/donating properties are: COCl, NO, NO_2, and NMe_2 with $\Delta > 0.300$, whereas H, F, OH, and Me (with $\Delta < 0.190$) may be indicated as the substituents with a weaker ability for changing their electronic properties. This information may be particularly important in cases of not well-recognized electronic properties (electron attracting or donating) of the moiety to which the substituent is to be attached. The high value of Δ for NMe_2 substituent needs a comment. Firstly, let us note that $\Delta 1$ has the highest value for NMe_2 (0.042), even higher than for a strongly electron-attracting NO group (0.040). This is due to the electron-attracting property of *meta* position in phenol, as shown in Table 1. This is a reason why Δ for NMe_2 substituent is so large. One more information comes from the comparison of ranges of cSAR(X) values in the dependence on the kind and the position of Y (OH or O⁻). Usually, it is accepted that

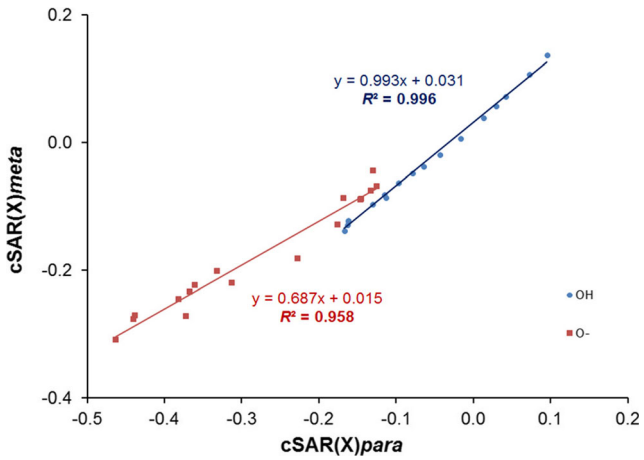

Fig. 8. Dependences of $cSAR(X)_{Hirsh}$ of *meta* derivatives on the *para* ones for phenols and phenolates.

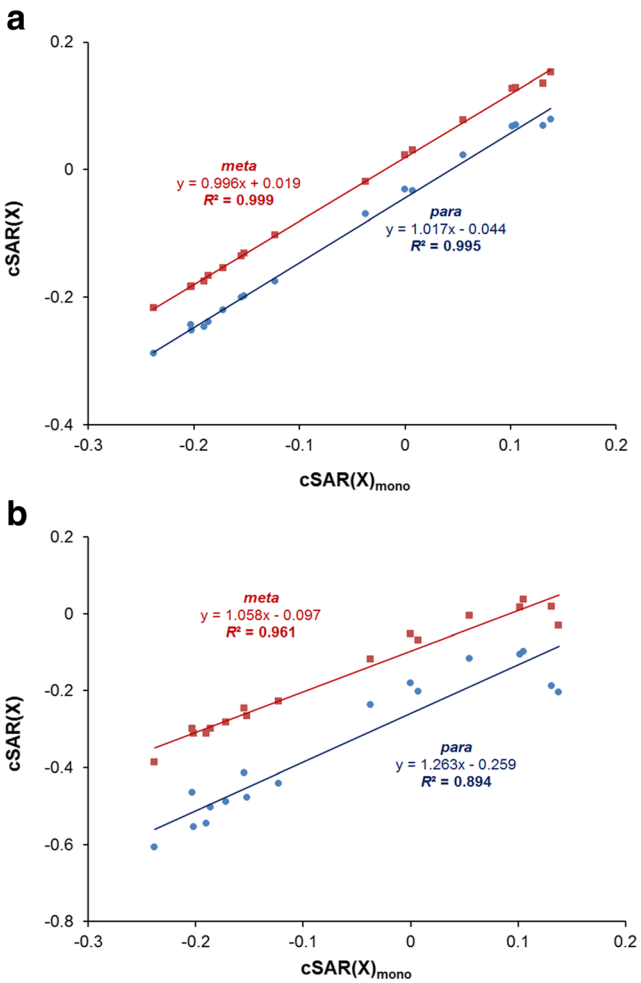

Fig. 10. Dependences of $cSAR(X)_{NBO}$ for phenol (**a**) and phenolate (**b**) derivatives on cSAR(X) in monosubstituted benzene derivatives.

Table 3. cSAR(X) for X-Ph-OH and X-Ph-O^- (Hirshfeld charges).

X	X-Ph-OH			X-Ph-O^-			**Δ**
	para	*meta*	Δ1	*para*	*meta*	Δ2	
NO	-0.162	-0.122	0.040	-0.439	-0.270	0.169	0.317
NO_2	-0.163	-0.129	0.035	-0.441	-0.276	0.165	0.312
CN	-0.167	-0.138	0.029	-0.373	-0.272	0.101	0.235
COCl	-0.162	-0.123	0.039	-0.463	-0.308	0.155	0.340
CF_3	-0.113	-0.087	0.026	-0.314	-0.219	0.095	0.227
COMe	-0.097	-0.063	0.034	-0.362	-0.222	0.139	0.299
COOH	-0.115	-0.082	0.033	-0.368	-0.232	0.136	0.286
CHO	-0.130	-0.096	0.034	-0.382	-0.244	0.138	0.286
$CONH_2$	-0.079	-0.048	0.031	-0.333	-0.201	0.132	0.285
Cl	-0.064	-0.037	0.027	-0.228	-0.180	0.048	0.191
F	-0.044	-0.019	0.024	-0.176	-0.128	0.049	0.157
H	-0.017	0.007	0.024	-0.146	-0.087	0.059	0.152
Me	0.013	0.039	0.026	-0.147	-0.088	0.059	0.186
OMe	0.042	0.073	0.031	-0.133	-0.074	0.059	0.206
OH	0.030	0.058	0.028	-0.126	-0.067	0.058	0.184
NH_2	0.072	0.108	0.035	-0.130	-0.044	0.087	0.238
NMe_2	0.095	0.137	0.042	-0.169	-0.086	0.083	0.306
range	0.262	0.275	0.018	0.337	0.265	0.121	

Δ1, Δ2, and **Δ** denote range of cSAR variability for particular X in phenols, phenolates, and both series, respectively

interactions (effects) of substituents from *para* position are stronger than from *meta* ones as observed for phenolates (0.337 and 0.265, respectively). This not the case for phenol derivatives. The impact of OH group on electron attracting/donating properties of the substituents is greater in *meta* position (range 0.275) than in *para* one (0.262).

Conclusions

The quantum chemical-based modeling of substituent effects in *meta*-substituted and *para*-substituted phenol and phenolate derivatives (SESE and cSAR characteristics) as well as the comparison of the obtained results with σ constants allow for the deeper recognition of the nature of mutual interactions between substituents.

Firstly, it should be stated that the application of various atomic charge assessments (Hirshfeld, NBO, and AIM) for calculation of cSAR characteristics leads to a qualitatively equivalent picture of the studied problem.

The results of the analysis of interdependences of the substituent effect descriptors have demonstrated their usefulness for characterization of the substituent. For *para*-substituted systems, σ_p^- constants have been found to be better substituent effect parameters than σ_p ones, particularly in the case of phenolate derivatives. The relations of cSAR(X) vs. σ have shown almost identical sensitivity of the substituent effect in *meta*-substituted phenol and phenolate derivatives, whereas they have indicated different kinds of intramolecular interactions in *para*-substituted phenols and phenolates.

The electron-attractive property of OH group in *meta*-substituted phenol derivatives causes the dramatically different picture of dependences of cSAR(X) on SESE as compared to that observed for all others (*meta* phenolate systems and *para* derivatives of phenols and phenolates). Moreover, it has been documented that OH group affects the electron-attracting and electron-donating substituents in *meta* positions in a different way.

The obtained Hammett-type dependences of cSAR(Y) on cSAR(X), where Y = OH or O^-, have revealed a stronger intramolecular interactions in *para*-substituted phenolates than phenol derivatives, whereas the opposite situation has been encountered for *meta* derivatives.

A clear substituent effect on π-electron delocalization of the benzene ring (the transmitting moiety of the studied systems) has been observed only in *para*-substituted phenolate derivatives – aromaticity of the ring increases in line with increasing cSAR(X) of the substituent. Additionally, it has been shown that the *p*EDA parameter is useful to indicate changes in the π-electron structure of the ring due to the substituent effect.

An application of cSAR(X) for phenol derivatives has allowed to estimate that difference between cSAR(X) for *meta* and *para* derivatives may be as large as ~15% of the range of the cSAR(X) variability, **Δ**. In the case of phenolates, this difference may be even greater and amounts up to ~53%. The value of **Δ** for a particular substituent represents its potential variability of its electron attracting/donating properties dependent on the moiety to which it is attached. This may have some general significance and should be taken into account when new systems are subject of studies.

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Compliance with ethical standards

Conflict of interest The Authors declare that they have no conflict of interest.

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