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ORIGINAL RESEARCH

Theoretical study of electron-attracting ability of the nitro group: classical and reverse substituent effects
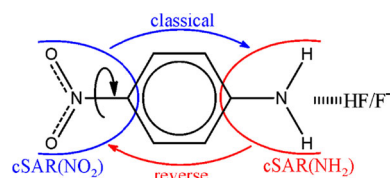
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Abstract This study presents a quantum chemistry modeling of the substituent effect. For this purpose, a uniform approach—the model termed as "charge of substituent active region" (cSAR, defined as a sum of atomic charges at the substituent and the *ipso* carbon atom)—has been used. Its reliability has been confirmed by a quantitative description of the electron-attracting ability of the nitro group, and finally, the reverse substituent effect, showing the influence of reaction site (Y) on the properties of substituent (X), has been introduced and documented. The cSAR model has been applied to *para*-substituted nitrobenzene derivatives in which the nitro group acts either as a reaction site (classical substituent effect, with X = NO$_2$, CN, CHO, COOMe, COMe, CF$_3$, Cl, H, Me, OMe, NH$_2$ and NHMe) or as a substituent (reverse substituent effect, with Y = NH$^-$, NH$_2$, H and NH$_3^+$).

Dedicated to our friend Professor Alexandru T. Balaban of Texas A&M University at Galveston in recognition of his outstanding contribution to theoretical and physical organic chemistry.

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Calculation was performed using BLYP functional with DFT-D3 correction and TZ2P basis set. Application of different assessments of atomic charges (Voronoi, Hirshfeld, Bader, Weinhold and Mulliken) leads to good correlation between calculated cSAR values.

Graphical Abstract Electron-attracting ability of the nitro group depends dramatically on the electron-donating properties of the reaction site

Keywords Substituent effects · Electron-attracting ability · Nitro group · Atomic charges

Introduction

Substituent effect is traditionally regarded in terms of Hammett constants [1], σ (for reviews, see Refs. [2–7]). By definition, these constants rely on the ionization constants of *para*- and *meta*-substituted benzoic acids. The σ constants have been used numerous times for the interpretation of chemical and physicochemical properties of X–R–Y systems (X—substituent, R—transmitting moiety and Y—reaction/process site) by using Hammett equation [2, 3, 5, 6]:

$$\lg k_{p,m} = \lg k_0 + \rho\, \sigma_{p,m} \qquad (1)$$

where $\sigma_{p,m}$ are substituent constants for *para*- and *meta*-positions, and $k_{p,m}$ and k_0 are rate constants for substituted

and unsubstituted systems, whereas ρ is the reaction constant describing the sensitivity of the reaction/process on the substituent effect. In later works, lg k has often been replaced by P(X)—some quantitative characteristic of chemical or physicochemical properties. Soon, it became clear that the original Hammett constants fail in those cases where the electron-donating/attracting ability of the reaction site Y differs greatly from that of COOH/COO⁻ groups in the Hammett's reference reaction. Therefore, for such reaction series in which moieties with strong electron-donating properties (EDP) are involved (e.g., ionization of phenols), new substituent constants have to be introduced, σ_p^- (see Ref. [4]). The same applies to processes in which moieties with strong electron-attracting properties (EAP) participate (e.g., solvolysis of dimethylphenylcarbinyl chloride), yielding new constants [8], σ_p^+. For example, in the case of the nitro group, the original $\sigma_p = 0.78$, whereas $\sigma_p^- = 1.27$ [7], which implies almost doubling EAP of this group in the latter case.

Existence of many various scales of substituent constants [9–13] indicates the dependence of substituent properties on the feature of the reaction center. Therefore, two types of the substituent effects should be taken into account: classical and reverse ones. A general view of substituent effects is presented in Scheme 1. The classical substituent effect describes how X affects properties of Y, whereas the influence of Y (usually a reaction site) on the properties of the substituent X is defined as the reverse substituent effect.

The nitro group [14, 15] is one of the most important substituents in organic chemistry. The variability of its EAP is nicely illustrated by experimental measurements of the polarographic half-wave potentials, $E_{1/2}$, of the reversible one-electron reduction of substituted nitrobenzene derivatives carried out in aprotic solvents to avoid subsequent kinetics [16], as well as by their formal reduction potentials [17], E^0. In this way, the obtained $E_{1/2}$ as well as E^0 values are thermodynamic properties and may serve as reliable descriptors of relations between structure and energetic characteristics of the molecules. A convenient case is reduction of the nitrocompounds where less negative value of the half-wave potential denotes a stronger electron-attracting ability of the nitro group in a given compound. In particular, measured $E_{1/2}$ values are between -0.800 V (for p-CN-nitrobenzene) and

−1.400 V (for p-nitroaniline), and even −1.700 V for 2-nitropropane [16].

As aforementioned, it is reasonable to introduce a concept of the reverse substituent effect. However, until now, no general and physically well-grounded way was found to describe it numerically. Certain solutions for this problem may come from the concept of the charge of substituent active region (cSAR) proposed by Sadlej-Sosnowska [18–20]. cSAR was originally termed as qSAR but to avoid a confusion with commonly used Quantitative Structure Activity Relationships (QSAR) [21], a new abbreviation was introduced [22, 23]. The value of cSAR(X) is a sum of the atomic charge X, $q(X)$ and $q(C_{ipso})$. Therefore, it is a quantitative measure of the electronic state of X and may depend on the moiety to which X is attached. The more negative cSAR(X) value is, the more electron-attractive is the group X. It was found that there is a linear correlation between the cSAR values and the σ_p Hammett constants for a set of 21 $para$-substituted benzoic acids [18]. The slope of the obtained linear equation is negative with correlation coefficient, cc, and equal to -0.932. It should be noted that for the same reaction series, there is no correlation between the charge at the substituent only, $q(X)$, and σ_p values ($cc = -0.126$). Also in other cases, good correlations have been found for cSAR, both with σ_p for monosubstituted derivatives of benzene [19] and with SESE (substituent effect stabilization energy) for $para$-substituted nitrobenzene derivatives [23], as well as between cSAR(X) and cSAR(Y) for series of X–C_6H_4–Y molecules [22].

The purpose of this paper is to show the effectiveness of the application of the cSAR concept for the description of the electron-attracting/donating properties of not only classical substituents but also to characterization of electronic propensity of any functional group. It will be demonstrated that cSAR concept can be used as a quantitative measure of both classical and reverse substituent effects in systems with two active groups located in $para$-position with respect to each other. To show the classical substituent effect on the reaction site Y, the one-electron reduction of the NO_2 group in p-nitrobenzene-X derivatives (with X = NO_2, CN, CHO, COOMe, COMe, CF_3, Cl, H, Me, OMe, NH_2 and NHMe) have been chosen as a model reaction. In this case, the NO_2 group plays a role of the reaction site. However, much more important and definitely novel is application of cSAR model for description of the reverse substituent effect. For this purpose, the cSAR concept has been applied to p-nitrobenzene-Y derivatives (with Y = NH^-, NH_2, H and NH_3^+), where EDP of the Y has been additionally modified by intermolecular H-bonding. In this case, the NO_2 group plays the role of the substituent X and its properties will be investigated depending on the different electronic ability of the reaction site Y.
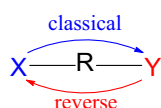
Scheme 1 Two kinds of substituent effects, X denotes substituent, R denotes transmitting moiety and Y denotes reaction/process site

Methodology

Calculations were carried out with the Amsterdam Density Functional (ADF) program [24] using BLYP functional [25, 26] with DFT-D3 correction [27] including Becke–Johnson (BJ) damping [28] and TZ2P basis set [29]. The computed energy minima were verified to be equilibrium structures through vibrational analysis.

For assessment of the atomic charges, five different methods were used: Voronoi [30, 31], Hirshfeld [32], Mulliken [33–36], Bader [37] and Weinhold [38]. The first three of them were calculated using ADF program, whereas the last two types of charges were obtained using Gaussian 09 program [39] at BLYP/6-311++G(d,p) level of theory. Bader's AIM atomic charges were computed using AIMAll program [40]. Weinhold's natural population analysis (NPA) was performed with NBO 5.G program [41].

The charge of the substituent active region (cSAR) was calculated by summing up the atomic charges of all atoms of the group X and the charge at the *ipso* carbon atom to which the X is attached:

$$cSAR(X) = q(X) + q(C_{ipso}) \qquad (2)$$

To study the effect of intermolecular interactions on EAP of the nitro group, two types of H-bonded complexes of *p*-nitroaniline were simulated: (1) with neutral and (2) charge-assisted hydrogen bond. In the first case, $H_2N\cdots HF$ and $HNH\cdots FH$ interactions were considered. In the second one, $HNH\cdots F^-$ and $HN^-\cdots HF$ interactions were taken into account. Different strengths of H-bond were achieved by elongation of the distance between N and F atoms from equilibrium to 4.0 Å

Results and discussion

This section is organized in three parts. In the first one, the assumption that the cSAR values computed by using various assessments of the atomic charges lead to qualitatively equivalent results will be verified. The next part will be devoted to a verification of the hypothesis that such intramolecular characteristic of the electron-attracting ability of the nitro group as the cSAR(NO_2) can be an appropriate description of the external electron transfer properties measured for *para*-substituted nitrobenzene derivatives by the formal potentials or the polarographic half-wave potentials of reversible one-electron reduction. The third part will be focused on application of the cSAR concept to X–R–Y systems, where two kinds of the substituent effect may be observed: (1) the classical one, related to cases where substituent X influences properties of the reaction/process site Y, and (2) the reverse effect,

which is manifested in changes of EAP of NO_2 group depending on the kind of reaction/process site Y.

Do cSAR values depend on the charge analysis method?

It is well known that the Voronoi [30, 31], Hirshfeld [32], Mulliken [33–36], Bader [37] and Weinhold [38] methods for calculation of atomic charges give often qualitatively similar insights but quantitatively values differ [31, 42, 43]. Therefore, to avoid unreliable treatment in using of cSAR approach, we have computed cSAR(X) and cSAR(NO_2) values for *p*-nitrobenzene-X derivatives (X = NO_2, CN, CHO, COOMe, COMe, CF_3, Cl, H, Me, OMe, NH_2 and NHMe) using all aforementioned assessments of the atomic charges. The cSAR(X)^{VDD} values (the Voronoi Deformation Density method is used for computing atomic charges) plotted against the data obtained from Hirshfeld, Mulliken, Bader and Weinhold approaches are well correlated (Fig. 1, data in Tables S1,S2). Thus, it can be concluded that *qualitatively all these approaches are nearly equivalent* for estimation of cSAR(X) values. Furthermore, the slopes for these linear regressions are close to 1 and amount to 0.86, 1.22, 1.01 and 1.24, respectively. However, these regressions are not sufficiently precise to recalculate cSAR(X) values from one method to the values of another one. Nevertheless, it confirms that within a given method, the final results are quite reliable.
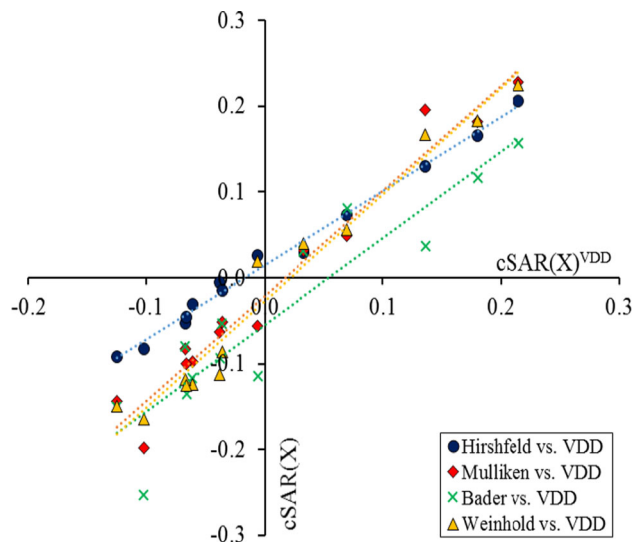

Fig. 1 Linear regressions between cSAR(X) values calculated by VDD method and data from Hirshfeld, Mulliken, Bader and Weinhold approaches for *p*-nitrobenzene-X derivatives with X = NO_2, CN, CHO, COOMe, COMe, CF_3, Cl, H, Me, OMe, NH_2 and NHMe (cc = 0.996, 0.981, 0.923 and 0.982, respectively)

A rather good agreement between cSAR(X) values estimated by different approaches results from the fact that the substituent active region includes C_{ipso}, and the region boundary of cSAR(X) goes through two CC bonds which are less polarized. This is not the case when the charges of only the substituent are taken into account. The C–X bond is usually much more strongly polarized, and the partitioning of space between the C and X atom can have there a large effect on q(X) [31].

Figure 2 presents the analogous results for the cSAR(NO_2) values treated in the same way (data in Table S3). Correlations are even better due to a uniformity of the substituent active region (only for NO_2 group). Importantly, the values of cSAR(NO_2) and cSAR(X) are strongly correlated (Figure S1) which agrees with results obtained by Siodla et al. [22].

According to the work by Fonseca Guerra et al. [31], the VDD method is basis set independent and yields chemically meaningful atomic charges. Therefore, all further cSAR data will be calculated using this approach [30, 31], and the superscript VDD will be omitted.

cSAR(NO_2) as a numerical characteristic of the EAP of the NO_2 group

As mentioned in the Introduction, the experimental potentials of the reversible one-electron reduction of the nitro group in different nitrocompounds are in a wide range of measured values. These data may be used for answering the question: Does the electron acceptance of the nitro group (i.e., electroreduction) in various chemical species
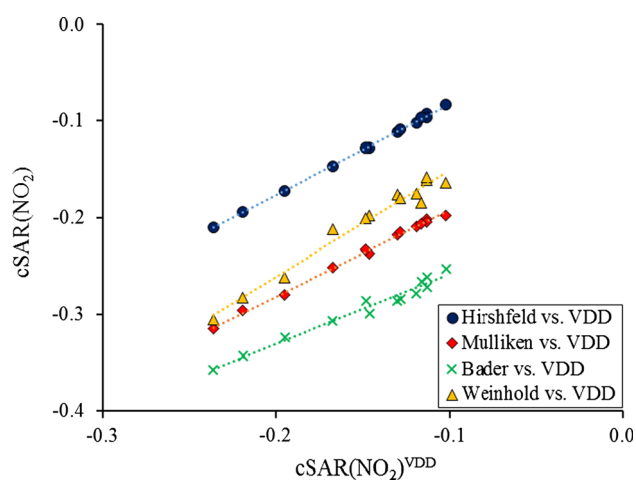
follow the trend in EAP values estimated by using of the cSAR concept?

Table 1 presents the half-wave potentials ($E_{1/2}$) for p-nitrobenzene-X derivatives measured in dimethylformamide with tetrammonium perchlorate as a supporting electrolyte [16] as well as the formal reduction potentials (E^0) measured in dry acetonitrile with tetra-n-butylammonium hexafluorophosphate as supporting electrolyte [17], substituent X constants (σ_p, σ_p^+) and cSAR values. Since both sets of experimental data are highly correlated to each other with $cc = 0.998$ (see Figure S2), we will apply only E^0 values in the rest of this study. Additionally, good linear dependencies of the formal reduction potentials on Hammett's $\sigma_p(X)$ and $\sigma_p^+(X)$ have been also found with $cc = -0.956$ and -0.940, respectively (Figure S3).

The most interesting is relationship between experimental (E^0) and theoretical (cSAR) characteristics of the nitro group presented in Fig. 3. As can be seen, there is a qualitative equivalence between these two properties ($cc = -0.957$). This means that the cSAR concept can be used for numerical characteristic of electronic properties of the nitro group. Deeper analysis of the scatter plot presented in Fig. 3 reveals that total dependence can be formed by two groups of substituted systems: the first one—by the systems with electron-donating substituents and the other one (steeper)—by the systems with electron-accepting groups. The same effect is also observed for other methods of charge assessment (see Figure S4). This can be explained from the fact that E^0 values represent a whole molecule property related to LUMO energy ($cc = 0.997$ for E^0 vs. LUMO, see Figure S5), whereas cSAR(NO_2) is a local description of the electronic state of the nitro group.

As mentioned earlier, substituent effect means a description of the influence of X on the properties of Y in the X–R–Y systems. This may be named as a *classical substituent* effect that is usually treated by original Hammett approach. If the reaction site Y affects, in turn, the properties of the substituent X, we deal with a *reverse substituent effect*. It should be stressed that in the former case charge distribution is based only on the intramolecular interactions, whereas in the latter one intermolecular interactions also influence electronic properties of the reaction site. *para*-Substituted nitrobenzene can be considered as a vivid example of both effects.

To show the classical substituent effect on the reaction site Y, the one-electron reduction of the NO_2 group in p-nitrobenzene-X derivatives (Table 1) have been chosen as a model reaction. In this case, the NO_2 group plays a role of the reaction site (Y = NO_2).

Manifestation of the classical substituent effect can be observed when we change the EAP/EDP of the substituent X and look at the response of the reaction site Y. As a

Fig. 2 Correlation between cSAR(NO_2) calculated from VDD charges and data from Hirshfeld, Mulliken, Bader and Weinhold methods for p-nitrobenzene-X derivatives with X = NO_2, CN, CHO, COOMe, COMe, CF_3, Cl, H, Me, OMe, NH_2 and NHMe ($cc = 0.999$, 0.998, 0.986 and 0.986, respectively)

Table 1 Experimental data of negative values of polarographic half-wave potentials[a] ($E_{1/2}$), formal reduction potentials[b] (E^0) for *p*-nitrobenzene-X derivatives, as well as characteristics of the substituents: σ_p^c, σ_p^{+c}, cSAR values

| X	$-E_{1/2}$/V	$-E°$/V	σ_p (X)	σ_p^+ (X)	cSAR(NO$_2$)	cSAR(X)
NO$_2$	0.580	1.056	0.78	0.79	−0.102	−0.102
CN	0.800	1.228	0.66	0.66	−0.113	−0.125
CHO	0.800	1.236	0.42	0.73	−0.113	−0.067
COOH	–	–	0.45	0.42	−0.119	−0.061
COOMe	0.885	–	0.45	0.49	−0.130	−0.038
COMe	–	1.292	0.50	–	−0.128	−0.036
CF$_3$	–	1.302	0.54	0.61	−0.116	−0.066
Cl	1.020	1.412	0.23	0.11	−0.148	−0.006
H	1.100	1.492	0.00	0.00	−0.146	0.033
Me	–	1.547	−0.17	−0.31	−0.167	0.070
OMe	–	1.615	−0.27	−0.78	−0.195	0.136
NH$_2$	1.400	1.691	−0.66	−1.31	−0.219	0.180
NHMe	–	1.739	−0.70	−1.81	−0.236	0.215

[a] Data taken from Ref. [16]

[b] Data taken from Ref. [17]

[c] Substituent constants taken from Ref. [7]

measure of electronic properties of the substituents Hammett's constants, $\sigma_p(X)$ and $\sigma_p^+(X)$, as well as cSAR(X) values can be used, whereas a reply of the nitro group on electronic changes can be evaluated by two characteristics—reduction potentials and cSAR(NO$_2$) values.

The most important dependence supporting the classical substituent effect is a linear correlation between calculated cSAR(X) and experimental E^0 as well as obtained cSAR(NO$_2$) values (Figs. 4, 5, S6). Therefore, it can be

concluded that for *p*-nitrobenzene-X derivatives any modification in the electronic properties of substituent X implies the changes in the cSAR values of the reaction site, i.e., X influences the properties of the nitro group in a direct way.

Additionally, in support of the idea presented by Sadlej-Sosnowska [18], good linear correlations between cSAR(X) values and Hammett's constants, σ_p and σ_p^+, have been found with $cc = -0.985$ and -0.979, respectively (see Figure S7).
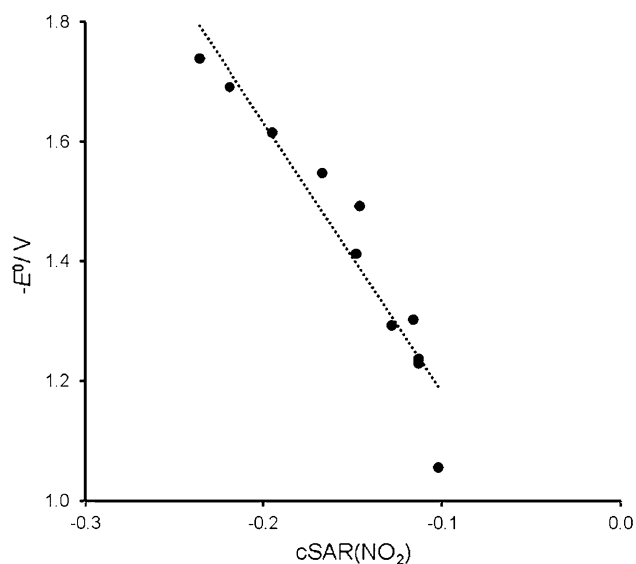
Fig. 3 Relationship between formal reduction potentials [17] (E^0) and cSAR values of the nitro group for *p*-nitrobenzene-X derivatives with X = NO$_2$, CN, CHO, COOMe, COMe, CF$_3$, Cl, H, Me, OMe, NH$_2$ and NHMe ($cc = -0.957$)
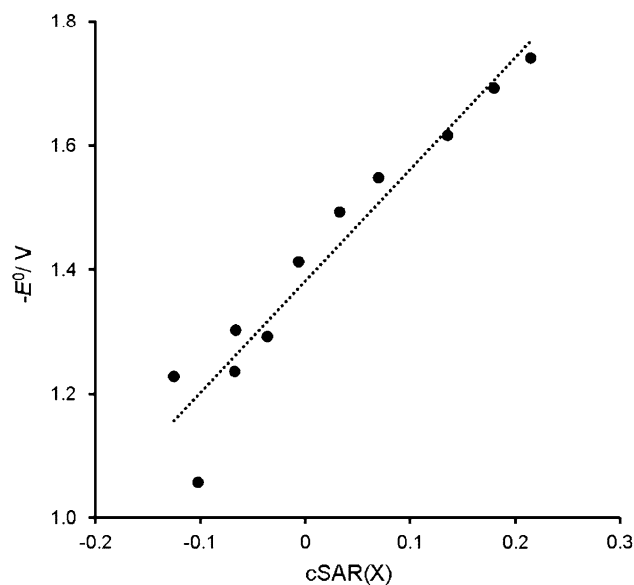
Fig. 4 Relationship between formal reduction potentials [17] and cSAR(X) values for *p*-nitrobenzene-X derivatives with X = NO$_2$, CN, CHO, COOMe, COMe, CF$_3$, Cl, H, Me, OMe, NH$_2$ and NHMe ($cc = 0.962$)
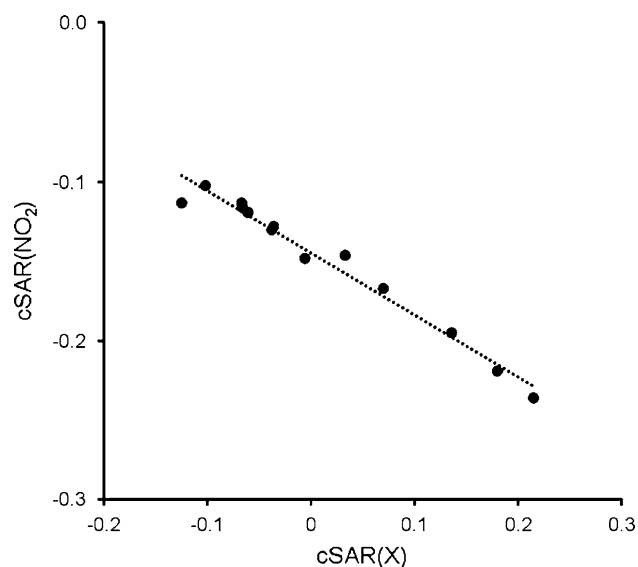
Fig. 5 Linear correlation between cSAR(X) and cSAR(NO$_2$) values for *p*-nitrobenzene-X derivatives ($cc = -0.986$)

As was already shown by σ_p and σ_p^- values, the EAP of the nitro group depends on the reaction site and changes almost twice. Therefore, to illustrate how the EAP of substituent X can vary depending on the presence of another active group Y (reverse substituent effect), we have applied the cSAR concept to the *p*-nitrobenzene-Y derivatives. In this case, we change the electronic properties of the reaction site Y and observe changes in EAP of the nitro group, which here acts as substituent. For this purpose, following Y have been chosen: H, NH$_3^+$, NH$_2$ and NH$^-$. Additionally, EDP of the last two Y has been modified by introducing the intermolecular H-bonding with HF/F$^-$(see Scheme 2). In order to investigate the effect of H-bond strength on the electronic properties of the NO$_2$ group, both equilibrium ($d_{N\cdots F} = $ opt) and simulated ($d_{N\cdots F} = 4.0$ Å) complexes have been regarded.

As a starting point of the discussion on reverse substituent effect, cSAR(NO$_2$) = -0.146 for nitrobenzene
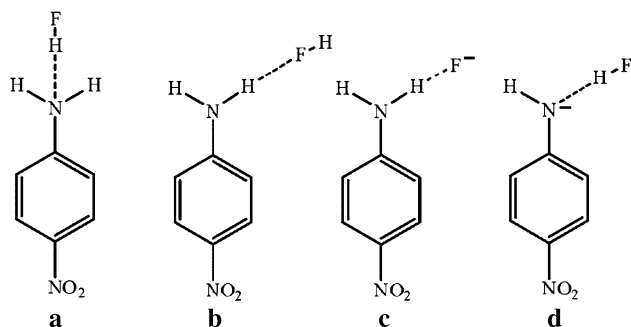
Scheme 2 Schematic representation of the studied H-bonded complexes

should be chosen (row 2 in Table 2), where the electron flow takes place only between benzene ring and the nitro group and the possibility of an external electron flow is absent. This value of cSAR indicates the moderate EAP of the nitro group, which can be modified by introducing an electron-donating/attracting group in the *para*-position.

As expected, EAP of the NO$_2$ group in the *p*-nitroanilinium cation (row 1 in Table 2) is the weakest among all studied cases with cSAR(NO$_2$) = -0.019. The reason of such lowering of this group attracting properties lies on a strong electron-withdrawing inductive effect of the positively charged NH$_3^+$ which promotes small positive charges on the *ortho*- and *para*-positions, and prevents the resonance effect between ring and the nitro group. In turn, NH$_2$ in *p*-nitroaniline (pNA, 5) causes a decrease of the cSAR(NO$_2$) value down to -0.219, via extra electrons donating through the ring. Such donating effect of the nitrogen lone pair in NH$_2$ can be disturbed by intermolecular interactions involving H-bonding (**a**, **b** and **c** in Scheme 2). N···H interactions result in a monotonic increase of cSAR(NO$_2$) with strengthening of the H-bond (rows 3 and 4 in Table 2). In these cases, an electron outflow from pNA is observed which supplies electrons to the region of the intermolecular interactions. However, **b** and **c** types of complexes with H···F interactions shown in Scheme 2 demonstrate an opposite effect on EAP of the nitro group. This is confirmed by the cSAR(NO$_2$) value decreasing down to -0.399 (rows 6–9 in Table 2). This can be explained by an electron transfer from HF/F$^-$ to pNA which helps the nitro group to reveal stronger electron-attracting properties.

In the last type of complexes (**d** in Scheme 2), the negative charge at the nitrogen atom promotes even smaller (more negative) cSAR(NO$_2$) values (see rows 10 and 11 in Table 2). The participation of NH$^-$ in the H-bonding slightly reduces its donating properties; however, this can be compensated by weakening or total removal of the intermolecular interactions. Lengthening of the N···F distance allows negatively charged nitrogen atom to donate more electron density to the π-system, which results in stronger EAP of the NO$_2$ group with cSAR(NO$_2$) = -0.489. And finally, in *p*-nitroanilide anion (row 12 in Table 2), where on the moiety in question no external perturbations exist, the negative charge at the nitrogen atom is able to fully participate in resonance interactions with the nitro group making its EAP the greatest, with cSAR(NO$_2$) = -0.509. All trends mentioned above are well illustrated by Fig. 6 (black diamonds). It can be seen that, depending on electronic properties of the reaction site Y, EAP of the nitro group changes significantly, yielding cSAR(NO$_2$) values in the range from -0.019 to -0.509. Two monotonic trends are observed that correspond to different types of the studied systems (neutral and charged).

Table 2 cSAR(NO$_2$) characteristics in simulated systems

N	System	Interaction	$d(\text{N}\cdots\text{F})$/Å	$\varphi = 0$	$\varphi = 30$	$\varphi = 60$	$\varphi = 90$
1	pNA cation[a]	Free	–	−0.019	−0.022	−0.022	−0.018
2	Nitrobenzene	Free	–	−0.146	−0.149	−0.143	−0.131
3	**a**	N$\cdots$HF	Opt[b]	−0.173	−0.171	−0.159	−0.142
4	**a**	N$\cdots$HF	4.0	−0.198	−0.197	−0.183	−0.158
5	pNA	Free	–	−0.219	−0.216	−0.198	−0.170
6	**b**	NH$\cdots$FH	4.0	−0.235	−0.223	−0.205	−0.183
7	**b**	NH$\cdots$FH	Opt[b]	−0.239	−0.228	−0.210	−0.187
8	**c**	NH$\cdots$F$^-$	2.8	−0.311	−0.302	−0.277	−0.231
9	**c**[c]	NH$\cdots$F$^-$	Opt[c]	−0.399	−0.395	−0.373	−0.280
10	**d**	N$^-\cdots$HF	Opt[b]	−0.445	−0.444	−0.423	−0.299
11	**d**	N$^-\cdots$HF	4.0	−0.489	−0.485	−0.470	−0.333
12	pNA anion[a]	Free	–	−0.509	−0.507	−0.494	−0.348

Symbols of H-bonded systems correspond to the Scheme 2

[a] *p*-Nitroanilinium cation and *p*-nitroanilide anion, respectively

[b] Distance in equilibrium complex

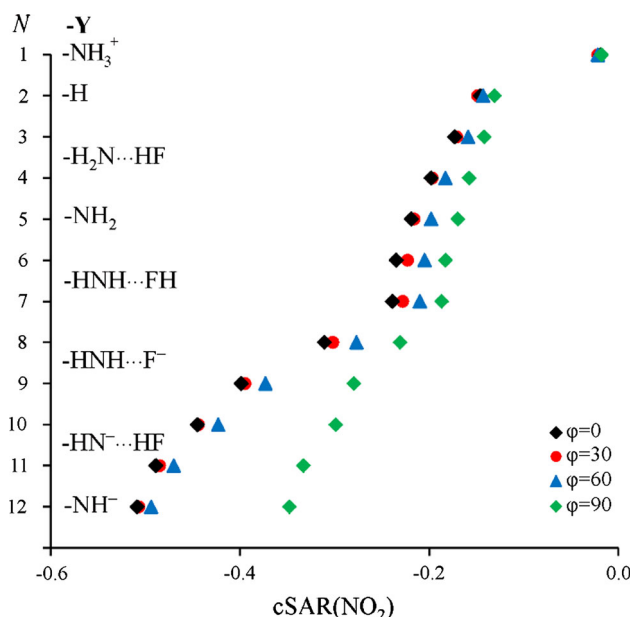[c] Distance in complex without proton transfer, $d(\text{N}\cdots\text{F}) = 2.65$ Å

Fig. 6 Graphical illustration of cSAR(NO$_2$) values, for *p*-nitrobenzene-Y derivatives (with Y = NH$^-$, NH$_2$, H and NH$_3^+$), as a measure of reverse substituent effects. *N* corresponds to the index number in Table 2

Additionally, to present that this approach can be generalized for estimation of the electronic properties of other substituents with varying EAP, the properties of the NO$_2$ group were modified by rotation from coplanar to perpendicular orientation with respect to the benzene ring by angle φ ($0 \leq \varphi \leq 90$) with step of 30° (Table 2; Fig. 6). It can be observed that their responses to the change of the Y electronic properties show similar trends, but with different sensitivity. This means that the same reactive site Y influences the different substituents X to varying degrees. This is particularly visible for the cases 2–7 (neutral systems), where the trends are very similar. As expected, substituent X with $\varphi = 0$ can withdraw more charge from the system than X with $\varphi = 90$. The smallest effect of rotation is observed for the pNA cation (ΔcSAR = 0.004), and the greatest one is for the pNA anion (ΔcSAR = 0.161). Such substantial effect in the latter case can be explained by a significant lowering of the resonance effect between the NH$^-$ and perpendicular NO$_2$ group.

Conclusions

Uniform approach to quantitative characteristics of both the reaction site (Y) and substituent (X) is presented. For this purpose, the charge of the substituent active region (cSAR) concept is used and applied for description of *para*-disubstituted benzene derivatives (X–C$_6$H$_4$–Y). It has been shown that:

1. Different assessments of atomic charges (Voronoi, Hirshfeld, Mulliken, Bader and Weinhold) used for calculating the cSAR(X) and cSAR(NO$_2$) values lead to a good qualitative agreement between them.

2. cSAR(NO$_2$) parameter is a reliable descriptor of the EAP of the nitro group as the reaction site at the same level of reliability as the classical Hammett approach.

3. The EAP of the NO$_2$ group as a substituent changes in a range 0.49 units of cSAR (Table 2). Applying a

simple proportion,[1] it is equivalent to the range of changes in the scale of the Hammett substituent constants ~ 2.5 units of σ. It is a measure how dramatically may change EAP of the group due to the moiety to which this is attached.

Therefore, application of the cSAR concept to quantitative measure of both classical and reverse substituent effects has been proposed. It should be stressed that the reverse substituent effect (showing the influence of reaction site Y on the properties of substituent X) is expressed in a quantitative and unified way. Moreover, the presented method is not sensitive to errors inherent in secondary substituent constants [2], which were usually obtained from different reference reactions [4] and hence might comprise not only experimental errors but also errors involved in fitting of these data to the primary standards, i.e., to σ constants defined for *meta*-substituted benzoic acids. Application of the cSAR method makes the concept of substituent effects more understandable and might have a practical advantage for organic chemistry, in particular for targeted organic synthesis.

Perspectives

A good agreement between results in estimation of EAP/EDP of substituents by application of the cSAR and Hammett-like approaches allow us to postulate a possibility of estimating EAP/EDP of a given group in any new molecular systems.

In particular, if a substituent, or more generally a functional group, is attached to a less known molecular moiety (i.e., with no possibility of application a typical Hammett-like approach), its electronic properties can be evaluated using linear regression between cSAR(X) values and Hammett constants for typical Hammett-like series: X–Ph–COOH, NH_2–Ph–COOH and NO_2–Ph–COOH. Then, based on this regression, we may "translate" cSAR(X) value calculated for a new system into the much more familiar numerical characteristic of the substituent—the Hammett constant. Certainly, other "normalization" procedures are also recommended in order to approach the cSAR values to other scales describing substituent effects.

Another fruitful field of research seems to be comparison of the cSAR characteristics of the substituent with quantum topological molecular descriptors of the substituents [44, 45] and of the transmitting moiety (ring) [46].

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[1] In the case of the nitro group, the difference of its σ constants for *p*-nitroaniline and *p*-nitrobenzoic acid is $1.27 - 0.78 = 0.49$, whereas the appropriate cSAR values are -0.219 and -0.119, respectively (Table 1). The ratio of these differences is ~ 5. Thus, the ranges of cSAR values in Table 2 correspond to 2.5 units of σ.

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