

# $\sigma$ - and $\pi$ -electron contributions to the substituent effect: natural population analysis

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Two independent  $\sigma$ - and  $\pi$ - substituent effect descriptors, *sEDA* and *pEDA*, were constructed using the Natural Population Analysis (NPA) approach. The descriptors are based on parameters of 32 monosubstituted benzene molecules calculated at the B3LYP/6-31G\*\* level which is easily applicable to large molecular systems. The *sEDA* and *pEDA* descriptors have a clear physical meaning—they show to what extent the  $\sigma$  and  $\pi$  electrons are donated or withdrawn by the substituent from the substituted system. The descriptors were successfully tested to be independent of either of the applicable theoretical methods (DFT or MP2), basis set (6-31G\*\* or cc-pVTZ), and solvent presence. We also demonstrated that the *sEDA* descriptor described equally well methane derivatives, whereas the *pEDA* descriptor explained behavior of ethene derivatives. Moreover, the two descriptors work out well for as different molecular systems as triazoles. A comparison of the *sEDA* and *pEDA* descriptors with the selected well-known substituent effect scales shows that the *sEDA* descriptor correlates well ( $R = 0.961$ ) with the Boyd & Boyd/Boyd–Edgcombe  $\chi$  descriptor and that so does also the *pEDA* descriptor ( $R = 0.943$ ) with the Taft–Topsom  $\sigma_R$ -resonance constant. Copyright © 2009 John Wiley & Sons, Ltd.

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**Keywords:** substituent effect; NBO; DFT; electron acceptor; electron donor;  $\sigma$ ;  $\pi$

## INTRODUCTION

A structural unit named ‘substituent’ usually has one of the following meanings<sup>[1]</sup>

- (1) It is a small part of the molecule that can be introduced by a simple chemical operation, particularly when it can directly replace a hydrogen atom.
- (2) It is a smaller and less important part of the molecule which influences the properties of the molecule in quantitative sense but does not alter its chemical character: the latter is determined by another group present there, namely the functional group or reaction site.

The first approach to the substituent effect was introduced by Louis P. Hammett as long ago as 1937.<sup>[2]</sup> He defined substituent constant  $\sigma_X$  as

$$\sigma_X = \log K_X - \log K_H \quad (1)$$

where  $K_H$  is the ionization constant of benzoic acid in water at 25 °C and  $K_X$  is the corresponding constant for either *m*- or *p*-substituted benzoic acid. In the early 1990s, Hansch *et al.*<sup>[3]</sup> published an extensive compilation containing  $\sigma_p$  and  $\sigma_m$  values for as many as 530 substituents.

If we try to understand the nature of the influence that the substituent exerts on reaction center there appears a major drawback of the original Hammett constants—they combine all effects in one variable. Thus, to fully understand and rationalize the substituent effect, there arises the need to partition it into different components.

According to Taft and Topsom scheme,<sup>[4,5]</sup> the substituent effect consists of four components: (i) the field-inductive component, (ii) electronegativity (EN), (iii) polarizability, and (iv) resonance. The ‘field’ or ‘field-inductive’ effect (**F**) is caused by

electrostatic interactions via space. The pole–pole, pole–dipole, and dipole–dipole interactions are distinguished for (**F**). On the other hand, the ‘electronegativity-inductive’ effect, ( $\chi$ ), originating from the difference of EN of two neighboring atoms is transmitted through the molecular bonds. This effect is supposed to diminish quickly as the number of successive C—C bonds is increased. Polarization (**P**) is yet another effect, appearing when a polarizable substituent, such as an alkyl group, is exposed to the electric field generated by the other fragments of the molecule. In comparison to the field effect, the polarization effect is assumed to originate from pole-induced dipole or dipole-induced dipole interaction. In conjugated systems also the resonance effect (**R**) is observed and is often claimed to operate in a direction opposite to the ( $\chi$ ), (**F**), and (**P**) effects.

First trials were concerned with dividing the overall effect into two components: field and resonance (see review by Charton<sup>[6]</sup>).

Thus  $\sigma_p$  and  $\sigma_m$  were expressed as

$$\sigma_p = \sigma_F + \sigma_R \text{ and } \sigma_m = \sigma_F + \alpha \sigma_R \quad (2)$$

where  $\sigma_F$  (or **F**) describes the field-inductive effect,  $\sigma_R$  (or **R**) describes the resonance effect, and  $\alpha$  is the so-called ‘transmission coefficient’.<sup>[7–9]</sup>

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Once the  $\sigma_F$  value is known, one can calculate the resonance component  $\sigma_R$  from the Eqn (2). The field-inductive scale was constructed on the basis of non-aromatic 4-substituted bicyclo [2.2.2] octane-1-carboxylic acids by Roberts and Moreland. This molecule is rigid, free from substituent steric influences, and geometrically resembles the benzene molecule, which makes it a good choice for field effect estimation.<sup>[10–12]</sup> There was also a simpler, although not unproblematic, approach introduced much later by Charton<sup>[6]</sup> who used substituted acetic acids. Field-inductive effects were also estimated by the  $^{19}\text{F}$  NMR chemical shifts of *m*-substituted fluorobenzenes.<sup>[13]</sup> Swain and Lupton<sup>[14]</sup>  $F$  and  $R$  constants, and the later modified Swain and Lupton constants,<sup>[15]</sup> were based on the following equation:  $\sigma_p = \alpha F + R$ , where the field-inductive term was derived from the bicyclo [2.2.2] octane-1-carboxylic acids constants, and the resonance term was calculated from the equation with an assumption that the resonance effect of the  $[\text{N}(\text{CH}_3)_3]$  substituent equaled zero. This assumption and the entire concept of Swain and Lupton were criticized by Charton, who did not recommend the use of their values.<sup>[6,16]</sup> On the other hand, resonance parameters were also obtained by means of the difference between the  $^{19}\text{F}$  NMR chemical shifts of *p*- and *m*-substituted fluorobenzenes as it was found that these values were highly sensitive to  $\pi$ -electron distribution.<sup>[13]</sup>

A more exact way of dividing substituent effect into inductive and resonance components, which was shown to be sufficient for the majority of applications, can be expressed by the following equation:

$$\log k = \log k^0 + \rho_F \sigma_F + \rho_R \sigma_R \quad (3)$$

referred to in the literature as the Taft or extended Hammett equation.<sup>[17]</sup> The  $\sigma_F$  and  $\sigma_R$  parameters are considered to be fixed for various reactions while the  $\rho_F$  and  $\rho_R$  parameters are adjusted for every reaction separately. This approach was later denoted as Dual Substituent Parameter (DSP) treatment.<sup>[4,5]</sup>

Finally, the full classification of the substituent effect was given by Taft and Topsom<sup>[4,5]</sup> and it accounted for field, polarization, EN, and resonance effects

$$\log k = \log k^0 + \rho_F \sigma_F + \rho_\alpha \sigma_\alpha + \rho_\chi \sigma_\chi + \rho_R \sigma_R \quad (4)$$

At first, only two components had been considered, namely the field-inductive one and resonance.<sup>[18]</sup> Later, the field-inductive component was shown to be insufficient for describing non-resonance contributions to the substituent effect, and EN factor was recognized as responsible for short-range perturbation of the  $\sigma$ -electron structure of the substituted molecule. In this way, the classical stream of studies of atom EN initiated by Pauling<sup>[19]</sup> was embedded into the mainstream investigations of the substituent effect.<sup>[20]</sup> Since the substituent EN is of primary interest to this paper, we briefly describe the development of the EN concept below.

The concept of EN was always one of the most important but also one of the most difficult to define. At the beginning Linus Pauling defined EN as 'the power of an atom in a molecule to attract electrons to itself.'<sup>[19]</sup> Pauling based his scale on thermochemical data and this approach was quite successful in explaining various structural features such as chemical bonding.<sup>[21]</sup> However, as some difficulties arose<sup>[21,22]</sup> the focus was switched to other approaches. Wells<sup>[23]</sup> built his scale based on vibrational data, Mulliken<sup>[24]</sup> utilized combination of ground state ionization energies and electron affinities, and then

Ichkowski and Margrave<sup>[25]</sup> also proposed incorporation of higher ionization potentials into EN. Furthermore, Hinze and Jaffe<sup>[26–28]</sup> derived their EN scale from orbital energies and effective charges, while the Allen<sup>[29]</sup> scale was based on average energy of valence electrons. The Sanderson scale<sup>[30,31]</sup>, created much later, was actually a modification of the original Pauling scale.

Another possible approach is to consider EN to be a function of the size and charge of an atom. On this basis, the Allred–Rochow,<sup>[32]</sup> Gordy,<sup>[33]</sup> and Boyd and Markus<sup>[34]</sup> scales were established.

EN scales were at first created for atoms, and then in a natural way extended to groups. A scale based on full EN equalization scheme was proposed by Huheey.<sup>[35,36]</sup> Inamoto and Masuda<sup>[37]</sup> proposed an empirical scale which was an extension of Gordy's original<sup>[33]</sup> concept.

Even for atoms, calculating EN scales leads to difficulties, but in the case of chemical groups (substituents), the problems are much more serious. Despite the fact that the EN of the composed group is mostly affected by the EN of the atom connecting the group to the rest of the molecule, there are other factors, like hybridization of that atom or influence of other atoms in the substituent, modifying the main EN component. For the  $-X$  composite groups Reynolds<sup>[38]</sup> created a simple scale based on the HF/6-31G\* calculated Mulliken hydrogen charge in the HX molecules. This scale was later extended by Marriott and Reynolds.<sup>[39]</sup> They were the first to suggest dividing EN into two scales:  $\sigma_F$  measuring field effects and  $\sigma_\chi$  for through-bond-inductive effect, and they calculated  $\sigma_\chi$  for numerous substituents. Then, another group of EN scales appeared: Mullay's<sup>[40]</sup> bond orbital EN formulation, Boyd and Edgecombe<sup>[41,42]</sup> application of AIM topological electron partitioning, and Bratsch's<sup>[43]</sup> definition using the harmonic mean of Pauling's atomic scale. Later, Reed and Allen<sup>[44]</sup> proposed a scale based on Bond Polarity Index and Xie *et al.*<sup>[45]</sup> proposed one founded on iterative summation of energies of valence orbitals and effective charges. The recently developed Suresh and Koga scale<sup>[46]</sup> also refers to Bader's AIM theory and defines EN as electrostatic potential at the C—X bond critical point. Domenicano's geometrical approach is also worth mentioning.<sup>[47–50]</sup> According to this model, EN is defined as a function of some angles of the substituted benzene ring, mainly the angle of the *ipso*-carbon atom and its neighboring carbon atoms. In recent years there have also been some efforts to define EN through application of density functional theory.<sup>[51–53]</sup>

The disadvantage of these EN scales is that they are not compatible with each other, as they seem to describe various aspects of interaction between substituent and core-molecule.<sup>[40,47,48]</sup> Thus, a uniform EN description with a clear physical interpretation would still be desirable.

Nowadays, theoretical calculations offer a quick and inexpensive way of obtaining various molecular properties with good accuracy and low computational cost, whereas experimentally these properties could be obtained with great difficulty and cost.<sup>[54]</sup> Therefore currently, numerous quantum chemical descriptors which can be useful for studying the substituent effect are used in *Quantitative Structure-Activity Relationship* (QSAR) and *Quantitative Structure-Property Relationship* (QSPR) analyses.<sup>[55]</sup>

In recent years many research groups have pursued the goal of explaining the nature of substituent effect by means of theoretical calculations. In a series of papers, Exner group

focused on field-inductive effect<sup>[34,56–60]</sup> reasoning that discussion: ‘whether the electronic transmission is through space or through bonds’, is meaningless, and that although the effects are mainly electrostatic in nature (in the sense of multipole expansion), the EN component can be separated and can play a substantial role. Exner *et al.*<sup>[61–65]</sup> also devoted several computational papers to resonance effect and to EN itself.<sup>[66]</sup> Recently, Wiberg obtained plausible correlation of calculated dipole moments and calculated acidities of some organic acids and claimed that there was a good correlation between the C—X bond dipole moment and the field substituent parameter.<sup>[67]</sup> There were also attempts to correlate substituent constants with atomic charges<sup>[68–70]</sup> electrostatic potential<sup>[71]</sup> and NMR shifts.<sup>[72]</sup> Lately, Krygowski *et al.*<sup>[73]</sup> reviewed the investigations of connections between the substituent effect and the  $\pi$  electron delocalization.

The aim of this study was to check whether a simple  $\sigma$  and  $\pi$  electron shift between the core molecule and a substituent can reflect important components of the substituent scales used so far. To this aim, a set of 32 substituents was chosen to express diverse electron donor–acceptor (EDA) properties, and two descriptors, sEDA and pEDA, have been constructed to reveal the  $\sigma$  and  $\pi$  electron shift, respectively, between the substituent and the core-molecule.

Three model molecules were considered in this paper, namely benzene, methane, and ethene. Additionally, the substituent effect was tested on C5-substituted-2H-1,2,3-triazoles. The substituents, when acting on benzene, account either for field-inductive-electronegativity effects or for resonance effects. On the other hand, when the substituents are attached to methane, they solely offer an explanation for field-inductive-EN effects, whereas for ethene they again stimulate both field-inductive-EN effects and resonance effects.

The Natural Population Analysis (NPA) based on Natural Bond Orbital (NBO) theory<sup>[74–76]</sup> was used as a method revealing the  $\sigma$  and/or  $\pi$  shift from the core molecule to the substituent or vice versa. We checked validity of the constructed sEDA and pEDA descriptors by using different theoretical methods and basis sets. We also ensured that the descriptors were applicable to solvated molecules modeled by using Polarizable Continuum Model (PCM) approach.<sup>[77–79]</sup> Finally, we compared our sEDA and pEDA descriptors with the selected well-known substituent effect scales and showed that the sEDA descriptor correlates fairly well with the Boyd&Boyd/Boyd–Edgecombe<sup>[41,42]</sup> scale, expressing the inductive effect, while the pEDA descriptor definitely correlates well with the Taft–Topsom  $\sigma_R$ -resonance constant.<sup>[4,5]</sup> Thus, the sEDA and pEDA descriptors describe the two aspects of substituent effect which can be related to EN and the resonance effect.

## CALCULATIONS

Essential calculations were performed at the B3LYP/6-31G\*\* level. In order to confirm that each of the calculated structures corresponded to the minimum on Potential Energy Surface (PES) the vibrational frequencies were calculated at the same level and then their positivity was controlled.<sup>[80]</sup> Several conformations of branched substituents were calculated with the aim of choosing a global minimum energy structure for which further analysis was performed. To estimate the  $\sigma$  and  $\pi$  electrons shift from/toward the substituent, the NPA was carried out. We also performed the

B3LYP/cc-pVTZ and MP2/6-31G\*\* calculations to ensure that the basis set and the electron correlation effects did not influence quality of the constructed substituent effect descriptors. Finally, to find out whether the solvent presence affected our descriptors water environment was simulated by using the IEF-PCM (Integral Equation Formalism PCM) approach. All the calculations were carried out using the Gaussian 03 suite of programs.<sup>[81]</sup> Data correlations were effected using SigmaPlot2000 software.<sup>[82]</sup>

## RESULTS AND DISCUSSION

Further, we apply the NPA methodology to find a change in occupancies of the  $\sigma$ - and  $\pi$ -orbitals on C atoms of the substituted molecule due to substituent effects. We are testing the assumption that a significant part of the substituent effect can be explained by the  $\sigma$ - and  $\pi$ -charge redistribution between the core molecule and the substituent. To this aim, each studied molecule is oriented in such a way that the atomic orbitals contributing to the  $\pi$ -molecular orbitals are directed parallelly to the z-axis. Then, for the selected atoms of the core molecule, occupancies of the s,  $p_x$ , and  $p_y$  atomic orbitals are summed up and occupancies of the  $p_z$  atomic orbitals are separately summed up as well. The former sum reflects changes in the  $\sigma$ -orbitals, whereas the latter reflects modification of the  $\pi$ -orbitals. The  $\sigma$ -effect can be observed for the methane, ethene, and benzene derivatives, while the  $\pi$ -effect only for the latter two sets of molecules. The difference of the summed  $\sigma$ - and  $\pi$ -occupancies of the substituted molecule and the same values of the reference molecule gives rise to the substituent descriptors defined below.

### Substituent effect in methane derivatives

#### Effect on the C atom $\sigma$ orbitals occupancies

Since in a vast majority of cases the carbon atom in methane monoderivatives forms only the  $\sigma$  bonds, the substituent influences the electron distribution of the rest of the molecule only via  $\sigma$ -inductive interactions. Thus, we can introduce a descriptor measuring the influence of the substituent based solely on the  $\sigma$ -electrons of the methane C-atom. We call it the sEDA(CH<sub>4</sub>) descriptor. The sEDA(CH<sub>4</sub>) descriptor is obtained by adding up the occupancies of the 2s, 2p<sub>x</sub>, 2p<sub>y</sub>, 2p<sub>z</sub> Natural Atomic Orbitals (NAOs) of methane carbon in monosubstituted methane from which the analogous sum of occupancies for unsubstituted methane is subtracted

$$\text{sEDA}(\text{CH}_4) = \sigma_{R-\text{CH}_3} - \sigma_{\text{CH}_4} \quad (5)$$

where  $\sigma_i$  denotes sum of the occupancies of the  $\sigma$ -bonding valence orbitals of the C-atom in the molecule indexed by  $i$ .

Although the sEDA(CH<sub>4</sub>) descriptor (Table 1) is expressed in electron units (e), it does not express charge itself but the methane C atom occupancy changes (electron shift between substituent and methane). Therefore, the electron withdrawing substituents have negative sEDA(CH<sub>4</sub>) values, whereas the electron donating substituents exhibit positive ones. Note that the range of changes of sEDA(CH<sub>4</sub>) is quite broad (approximately 1.2 e), thus enabling good discrimination of diverse substituents.

Seemingly, the sEDA(CH<sub>4</sub>) values (Table 1) suggest that most of the substituents are  $\sigma$ -electron-withdrawing and only five out of 32 (—BeH, —Li, —SiH<sub>3</sub>, —BF<sub>2</sub>, and —BH<sub>2</sub>) are the  $\sigma$ -electron donors. This is due to the fact that sEDA(CH<sub>4</sub>) is related to the —H ‘substituent’ which is considerably less electronegative than the

**Table 1.** The methane carbon atom orbital populations ( $e$ ) and sEDA descriptor for methane derivatives. Values are sorted with the increasing  $\sigma$ -electron acceptor ability of the substituent

Substituent	Total occupancy	sEDA descriptor
–BeH	5.375	0.446
–Li	5.372	0.443
–SiMe <sub>3</sub>	5.203	0.274
–SiH <sub>3</sub>	5.160	0.231
–BF <sub>2</sub>	5.129	0.200
–BH <sub>2</sub>	5.082	0.153
–MeSO <sub>2</sub>	4.932	0.003
–H	4.929	0.000
–MeSO	4.899	–0.030
–MeS	4.830	–0.098
–CFO	4.812	–0.117
–SH	4.811	–0.118
–CN	4.792	–0.137
–COOH	4.790	–0.139
–CHO	4.789	–0.140
–CF <sub>3</sub>	4.782	–0.147
–COCH <sub>3</sub>	4.777	–0.152
–CONH <sub>2</sub>	4.775	–0.154
–COCN	4.771	–0.158
–Br	4.726	–0.202
–CH=CH <sub>2</sub>	4.708	–0.221
–Ph	4.693	–0.236
–Me	4.682	–0.247
–tBu	4.674	–0.255
–Cl	4.653	–0.276
–NO	4.562	–0.367
–NO <sub>2</sub>	4.532	–0.396
–NH <sub>2</sub>	4.474	–0.455
–NMe <sub>2</sub>	4.470	–0.459
–Ac	4.324	–0.605
–OH	4.305	–0.623
–F	4.182	–0.747

methane C atom. If our descriptor was referred to the –CH<sub>3</sub> group then only –Cl, –NO, –NO<sub>2</sub>, –NH<sub>2</sub>, –OH, –F, and substituents would be electron-withdrawing.

Note that the fact that some sEDA(CH<sub>4</sub>) values are close to each other, e.g., –NO<sub>2</sub> and –NH<sub>2</sub> or –Cl and –CH<sub>3</sub>, is sometimes counterintuitive. Similar values of sEDA(CH<sub>4</sub>) for –NH<sub>2</sub> and –NO<sub>2</sub> substituents originate from the fact that the sEDA(CH<sub>4</sub>) descriptor is sensitive principally to the EN of the first atom connecting the substituent to the core molecule. As a result, for instance, the sEDA(CH<sub>4</sub>) values are similar also for the –CHO, –CFO, and –COOH substituents.

#### Computational validation of the sEDA(CH<sub>4</sub>) descriptor

To check whether the choice of a basis set, computational method, and presence of solvent significantly affected the sEDA(CH<sub>4</sub>) descriptor or not, we calculated descriptors using: a much larger cc-pVTZ basis set, the MP2/6-31G\*\* calculations which better reproduce dispersion interactions,<sup>[83]</sup> and the

IEF-PCM calculations modeling water environment. In all cases, very good correlations between the sEDA(CH<sub>4</sub>) descriptor and its new versions were obtained (Figs S1A, S1B, and S1C, supplementary materials). The fact that, for all correlations presented in this paper, except for those with the other substituent descriptors, we use the whole set of the 32 studied substituents, is worth noticing. Thus, the simple B3LYP/6-31G\*\* method offers a good compromise between computational costs and accuracy of description of the substituent influence on the  $\sigma$  electron structure.

#### Substituent effect in benzene derivatives

##### Effect on the $\sigma$ and $\pi$ orbital occupancies in the benzene ring

In benzene monoderivatives, the substituent influences charge distribution via two independent effects:  $\sigma$ -inductive and  $\pi$ -resonance. The benzene sEDA and pEDA descriptors are defined in full analogy to the sEDA(CH<sub>4</sub>) descriptor assuming that the unsubstituted benzene is the reference molecule. The  $\sigma$ -effect is now defined as the sum of occupancies of  $s$ ,  $p_x$ , and  $p_y$  valence orbitals of all the ring C atoms (where  $xy$  is the ring plane). The  $\pi$ -effect is defined by the sum of occupancies of the  $p_z$  orbitals of all the ring C atoms contributing to the benzene  $\pi$ -electron system.

$$sEDA = \sum_{j=1}^6 \sigma_{R-C_6H_5}^j - \sum_{j=1}^6 \sigma_{C_6H_6}^j \quad (6)$$

$$pEDA = \sum_{j=1}^6 \pi_{R-C_6H_5}^j - \sum_{j=1}^6 \pi_{C_6H_6}^j \quad (7)$$

where  $\sigma_j^i$  and  $\pi_j^i$  denote sums of occupancies of all atomic orbitals of the  $j$ th benzene ring C-atom contributing to the valence  $\sigma$ - and  $\pi$ -molecular orbitals (respectively) in the molecule indexed by  $i$ .

The total  $\sigma$ - and  $\pi$ -occupancies as well as the occupancies with respect to the unsubstituted benzene (the benzene pEDA and sEDA descriptors) are presented in Table 2. First and foremost, juxtaposition of the benzene sEDA and pEDA descriptors shows the descriptors to be definitely different from each other: we can assume that there is no correlation between the sEDA and pEDA descriptors,  $R=0.35$ . What follows, they really describe diverse electron distribution in the benzene ring perturbed by substituents. And thus, for instance, the sEDA descriptors of the –BH<sub>2</sub>, –Li, –BeH, and –SiH<sub>3</sub> groups show that they are  $\sigma$  electron-donating groups, whereas the pEDA descriptors show that they are  $\pi$  electron-withdrawing groups. On the other hand, in view of these two descriptors, the –F and –NH<sub>2</sub> substituents are the  $\sigma$  electron-withdrawing, whereas they are the  $\pi$  electron-donating. And then, the –NO<sub>2</sub>, –CN, and –COOH groups are simultaneously  $\sigma$  and  $\pi$  electron withdrawing.

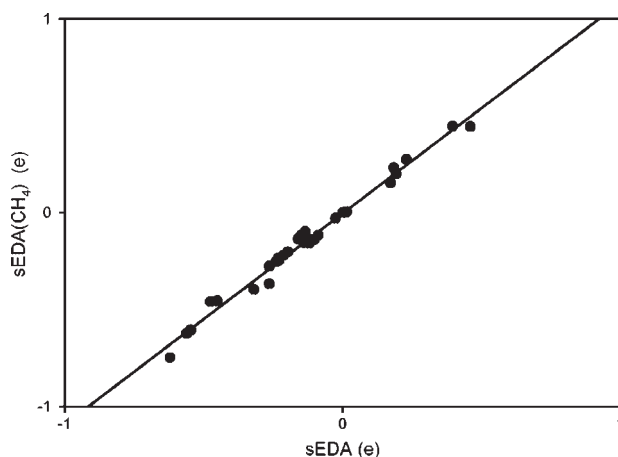
Secondly, it is important to observe whether the sEDA(CH<sub>4</sub>) and sEDA descriptors express the substituent effect on the  $\sigma$  electrons system of the core molecule in a similar manner or not. For 32 substituents, the differences between the sEDA(CH<sub>4</sub>) and sEDA descriptors are only slight (Tables 1 and 2). Indeed, even if the substituent order is marginally different, in the majority of cases the substituents close on one scale are also close on the other (Fig. 1). For example, on both scales the –BeH and –Li substituents are neighbors, although for methane the –BeH group is the strongest electron-donating group, whereas for benzene it is the –Li substituent. In both cases, the strongest withdrawing substituents are the –OH and –F groups. The



**Table 2.** The ring carbon atoms orbital populations (e) and sEDA and pEDA descriptors for benzene derivatives. Values are sorted according to decreasing effect

Substituent	σ-total	sEDA	Substituent	π-total	pEDA
–Li	19.826	0.460	–NMe <sub>2</sub>	6.165	0.174
–BeH	19.762	0.396	–NH <sub>2</sub>	6.136	0.145
–SiMe <sub>3</sub>	19.596	0.230	–OH	6.112	0.121
–BF <sub>2</sub>	19.559	0.193	–MeS	6.097	0.106
–SiH <sub>3</sub>	19.550	0.184	–SH	6.084	0.093
–BH <sub>2</sub>	19.539	0.173	–F	6.069	0.078
–MeSO <sub>2</sub>	19.382	0.016	–Cl	6.053	0.062
–H	19.366	0.000	–Br	6.047	0.057
–MeSO	19.342	–0.024	–Ac <sup>a</sup>	6.043	0.052
–CFO	19.278	–0.088	–MeSO	6.008	0.018
–CHO	19.264	–0.102	–Me	6.005	0.014
–COOH	19.256	–0.110	–tBu	5.999	0.008
–COCN	19.247	–0.119	–Ph	5.991	0.001
–COCH <sub>3</sub>	19.247	–0.119	–H	5.991	0.000
–CF <sub>3</sub>	19.237	–0.130	–CH=CH <sub>2</sub>	5.982	–0.008
–MeS	19.232	–0.134	–SiMe <sub>3</sub>	5.976	–0.015
–CONH <sub>2</sub>	19.226	–0.140	–MeSO <sub>2</sub>	5.975	–0.017
–SH	19.217	–0.149	–SiH <sub>3</sub>	5.974	–0.017
–CN	19.207	–0.159	–Li	5.971	–0.020
–Br	19.169	–0.197	–CF <sub>3</sub>	5.967	–0.024
–CH=CH <sub>2</sub>	19.153	–0.213	–CN	5.955	–0.035
–Me	19.137	–0.229	–CONH <sub>2</sub>	5.947	–0.044
–Ph	19.134	–0.232	–BeH	5.938	–0.052
–tBu	19.126	–0.240	–COOH	5.923	–0.068
–NO	19.102	–0.264	–NO <sub>2</sub>	5.922	–0.069
–Cl	19.102	–0.264	–COCH <sub>3</sub>	5.920	–0.071
–NO <sub>2</sub>	19.046	–0.320	–BF <sub>2</sub>	5.914	–0.077
–NH <sub>2</sub>	18.915	–0.451	–CFO	5.910	–0.081
–NMe <sub>2</sub>	18.891	–0.475	–CHO	5.903	–0.087
–OH	18.805	–0.561	–COCN	5.874	–0.117
–Ac <sup>a</sup>	18.820	–0.546	–NO	5.861	–0.129
–F	18.745	–0.621	–BH <sub>2</sub>	5.849	–0.142

<sup>a</sup> Ac = –OOCCH<sub>3</sub>



**Figure 1.** Linear correlation between the sEDA and sEDA(CH<sub>4</sub>) descriptors,  $R = 0.993$ . Standard Error of Estimate = 0.0337 Correlation equation:  $sEDA(CH_4) = 1.09 (\pm 0.02) \cdot sEDA - 0.004 (\pm 0.007)$   $F = 2124.9$  (95% confidence level)

groups of substituents attached to the core molecule either through the C atom or through the N atom are close on the two scales as well.

The sEDA (benzene) descriptor is expressing the  $\sigma$  electrons perturbation produced by a substituent more selectively and accurately than the sEDA(CH<sub>4</sub>) one. This is because, in substituted benzenes, perturbation by a substituent can be spread out between the  $\sigma$  and  $\pi$ -electron system, while for the substituted methanes this cannot occur. As a result, part of the perturbation by a substituent can be gathered in the pEDA descriptor and another part in the independent sEDA descriptor. This is why in our further study we shall use the sEDA and pEDA descriptors. However, we would like to emphasize the fact that the sEDA and sEDA(CH<sub>4</sub>) descriptors (Fig. 1) define practically the same effect.

The sEDA descriptor, describing  $\sigma$  electron withdrawing strength, is simply related to the EN of the binding atom of the substituent. For example, boron and fluorine are positioned at two opposite limits of the benzene sEDA descriptor and the Pauling EN of boron atom is equal to 2.04, whereas for the fluorine atom it is equal to 3.98. Moreover, the substituents attached by the same binding atom exhibit similar sEDA values: the sEDA descriptors of very different –NO<sub>2</sub> and –NH<sub>2</sub> groups are close to each other. The same is true for –CFO, –CHO, –COOH, –CONH<sub>2</sub>, and –CN groups (Table 2).

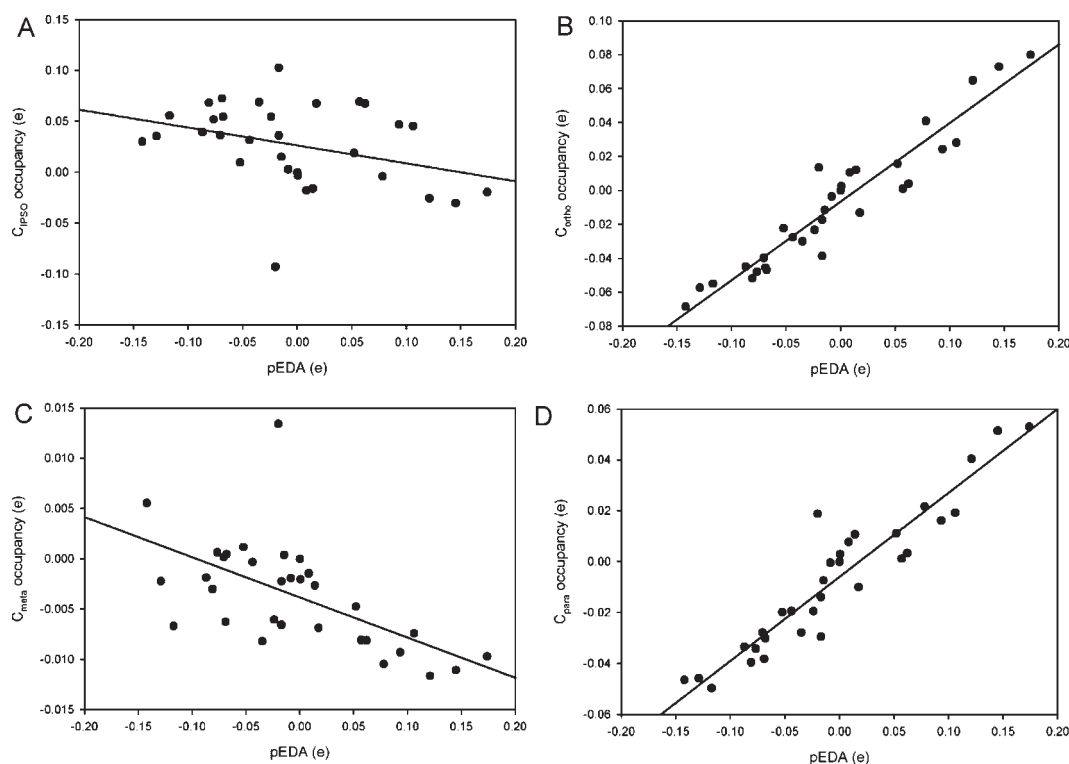
Also, let us stress the obvious substituent properties that influence the  $\pi$  electron structure revealed by the pEDA descriptors. In terms of the pEDA descriptor, the substituents possessing lone electron pair(s), –NH<sub>2</sub>, –OH, –F, –Cl, and –Br are  $\pi$  electron-donating groups. For a substituent to be  $\pi$  electron-withdrawing it is necessary to exhibit either a non-occupied  $p_z$  atomic orbital as in –BH<sub>2</sub> group, or a low-energy antibonding  $\pi^*$  orbital as in –CHO or –CN substituents.

The assumptions made in order to define the benzene sEDA and pEDA descriptors require some more information and clarification as to, for instance, why summation of occupancies is used over all carbon ring atoms or whether the basis set, presence of solvent, or computational method influence the results. These and the other questions are addressed in the sections which follow.

#### Why summation over the ring carbon atoms?

One could suppose that the definition of the pEDA descriptor is too arbitrary and that the  $\pi$ -electron occupancy summation over all the ring carbon atoms can be replaced by the occupancy of the  $p_z$  orbital of just one of the C-atoms—for example the *ipso*-atom.

To prove that the pEDA descriptor is correctly defined, the correlations of the pEDA with the *ipso*-, *ortho*-, *meta*-, and *para*-carbon atom occupancies are presented in Fig 2A–D. In the case of *ortho*- and *meta*- positions the mean occupancy of two atoms were taken. Different substituents exert diverse changes on  $\pi$  electron distribution at various ring positions. At first glance, inspection of Fig. 2A shows clearly that there is no correlation between the  $\pi$ -electron occupancy of the *ipso*- carbon atom and the pEDA descriptor. Nearly the same can be said about dependence between occupancy of the *meta*-carbon atom and the pEDA descriptor (Fig. 2C). However, there exist satisfactory correlations between the pEDA descriptor and occupancies of the *ortho*- and *para*- carbon atoms (Fig 2B and D,  $R = 0.952$  and  $0.940$ , respectively), as well as between the occupancies of the



**Figure 2.** (A) *ipso*- carbon atom occupancy against the *pEDA* descriptor,  $R = 0.344$ . Standard Error of Estimate = 0.0386, Correlation equation:  $C_{ipso} \text{ occupancy} = -0.18 (\pm 0.09) * pEDA + 0.027 (\pm 0.007)$ .  $F = 4.0$  (95% confidence level), (B) *ortho*- carbon atom occupancy plotted against the *pEDA* descriptor,  $R = 0.952$ , Standard Error of Estimate = 0.0119. Correlation equation:  $C_{ortho} \text{ occupancy} = 0.46 (\pm 0.03) * pEDA - 0.007 (\pm 0.002)$ ,  $F = 292.4$  (95% confidence level). (C) *meta*- carbon atom occupancy plotted against the *pEDA* descriptor,  $R = 0.602$ . Standard Error of Estimate = 0.0043. Correlation equation:  $C_{meta} \text{ occupancy} = -0.04 (\pm 0.01) * pEDA - 0.004 (\pm 0.001)$ .  $F = 17.0$  (95% confidence level). (D) *para*- carbon atom occupancy plotted against the *pEDA* descriptor,  $R = 0.940$ . Standard Error of Estimate = 0.0097. Correlation equation:  $C_{para} \text{ occupancy} = 0.33 (\pm 0.02) * pEDA - 0.006 (\pm 0.002)$ .  $F = 225.9$  (95% confidence level) The *ortho*- and *meta*- carbon atom occupancies refer the average of two *ortho*- or two *meta*- carbon atom occupancies

*ortho*- and *para*- carbon atoms ( $R = 0.991$ —supplementary materials). The sensitivity of *para*- atom occupancies change to the substituent effect is smaller than in the case of *ortho*- atom which is indicated by the first regression coefficient (0.72) of the regression of  $C(\text{para-})$  versus  $C(\text{ortho-})$ —as shown in supplementary materials. As our aim was to express the entire substituent effect we decided to sum up the  $p_z$  orbital occupancies over all ring carbon atoms instead of selecting, for example, only the *para*- and/or *ortho*- occupancies.

The influence of the substituent effect on particular benzene ring carbon atoms is presented in details in Table 3. One can see that the *ipso*- carbon atom occupancies change almost randomly with the change of the *pEDA* descriptor. On the other hand, the substituent influence on the *ortho*- and *para*- carbon atoms reflects changes of the *pEDA* descriptor and is always in agreement with the *pEDA* descriptor sign. With one exception, the *ortho*- effect is greater than the *para*-effect, whereas the *meta*- effect is often smaller than the *ortho*- and *para*- effects and exhibits the opposite sign. This is in good qualitative agreement with fundamental knowledge on reactivity of the monosubstituted benzene ring molecules.<sup>[84]</sup> For substituents strongly activating benzene ring for electrophilic substitution, such as the amino or hydroxy groups, increase in occupancy of the  $\pi$  orbitals in the *ortho*- and *para*- positions is observed, whereas for the *meta*- position the effect is weak and is opposite in sign i.e., the  $\pi$  orbital occupancy decreases. However, substituents weakly activating electrophilic substitution, such as  $-\text{CH}_3$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,

and  $-\text{Br}$ , increase slightly the occupancy of the  $\pi$  orbitals in the *ortho*- and *para*- positions. The effect for  $-\text{Cl}$  and  $-\text{Br}$  is especially weak. In contrast, the substituents deactivating the benzene ring for the electrophilic substitution, such as  $-\text{NO}_2$  or  $-\text{CN}$ , decrease occupancy of the  $\pi$  orbitals in the *ortho*- and *para*- positions and produce almost negligible change in the *meta*- position (Table 3). Unlike for the  $\pi$  electron system, the substituent effect on  $\sigma$  occupancy is practically not transmitted to the atoms other than *ipso*-. At the *ortho*- atoms, the effect can be detected sometimes, e.g., for the  $-\text{NO}_2$  and  $-\text{NH}_2$  groups, whereas for the most substituents it is negligible (Table 3). In the case of the *meta*- and *para*- carbon atoms it is even weaker by one order of magnitude. The sign of the  $\sigma$  effect does alter in series of *ipso*-, *ortho*-, *meta*-, and *para*-.

#### Computational validation of the *pEDA* descriptor

As for the  $\text{sEDA}(\text{CH}_4)$  descriptor we checked whether an increase of a number of basis functions (cc-pVTZ), change of the method from DFT B3LYP to perturbative MP2, and inclusion of water environment (simulated by the IEF-PCM method) result in a qualitative alteration of the descriptor or not. Correlations presented in Fig. S3 ( $R = 0.999$ ,  $0.998$ , and  $0.996$ , respectively) do prove that the above-mentioned changes do not alter the *pEDA* descriptor in a qualitative manner. This means that the convenient B3LYP/6-31G\*\* level is sufficiently adequate to allow a study of the substituent's influence on  $\sigma$ - and  $\pi$ -electron system,

**Table 3.** The relative  $\sigma$  and  $\pi$  occupancies of the *ipso*-, *ortho*-, *meta*-, and *para*-carbon atoms in benzene derivatives calculated at the B3LYP/6-31G\*\* level ordered according to *sEDA* and *pEDA* descriptors

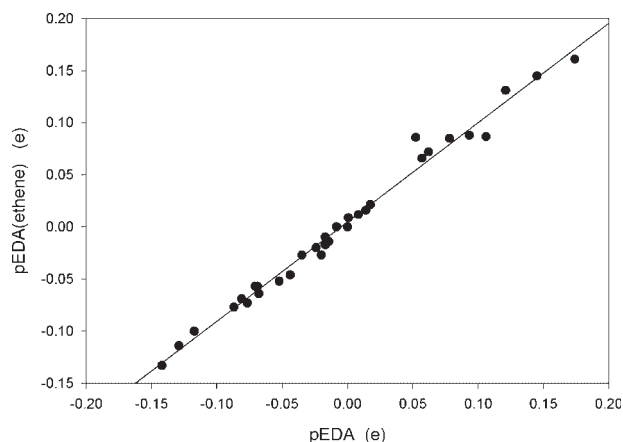
Substituent	<i>sEDA</i>	<i>ipso</i> -	<i>ortho</i> -	<i>meta</i> -	<i>para</i> -	Substituent	<i>pEDA</i>	<i>ipso</i> -	<i>ortho</i> -	<i>meta</i> -	<i>para</i> -
-Li	0.460	0.451	0.006	0.002	-0.007	-NMe <sub>2</sub>	0.174	-0.020	0.080	-0.010	0.053
-BeH	0.396	0.398	-0.007	0.005	0.002	-NH <sub>2</sub>	0.145	-0.030	0.073	-0.011	0.052
-SiMe <sub>3</sub>	0.230	0.249	-0.009	-0.001	0.000	-OH	0.121	-0.026	0.065	-0.012	0.040
-BF <sub>2</sub>	0.193	0.190	-0.006	0.005	0.006	-MeS	0.106	0.045	0.028	-0.007	0.019
-SiH <sub>3</sub>	0.184	0.194	-0.006	0.000	0.002	-SH	0.093	0.047	0.024	-0.009	0.016
-BH <sub>2</sub>	0.173	0.166	-0.007	0.007	0.007	-F	0.078	-0.004	0.041	-0.010	0.022
-MeSO <sub>2</sub>	0.016	-0.023	0.017	-0.001	0.007	-Cl	0.062	0.068	0.004	-0.008	0.003
-H	0.000	0.000	0.000	0.000	0.000	-Br	0.057	0.069	0.001	-0.008	0.001
-MeSO	-0.024	-0.005	0.004	-0.026	0.025	-Ac	0.052	0.019	0.016	-0.005	0.011
-CFO	-0.088	-0.102	-0.001	0.004	0.008	-MeSO	0.018	0.068	-0.013	-0.007	-0.010
-CHO	-0.102	-0.110	-0.002	0.003	0.006	-Me	0.014	-0.016	0.012	-0.003	0.011
-COOH	-0.110	-0.118	0.000	0.002	0.006	-tBu	0.008	-0.018	0.011	-0.001	0.008
-COCH <sub>3</sub>	-0.119	-1.221	-0.031	0.001	0.005	-Ph	0.001	-0.003	0.003	-0.002	0.003
-COCN	-0.119	-0.139	0.001	0.005	0.009	-H	0.000	0.000	0.000	0.000	0.000
-CF <sub>3</sub>	-0.130	-0.125	-0.004	-0.001	0.005	-CH=CH <sub>2</sub>	-0.008	0.003	-0.004	-0.002	0.000
-MeS	-0.134	-0.096	-0.009	-0.007	-0.005	-SiMe <sub>3</sub>	-0.015	0.015	-0.011	0.000	-0.007
-CONH <sub>2</sub>	-0.140	-0.126	-0.008	-0.001	0.003	-SiH <sub>3</sub>	-0.017	0.036	-0.017	-0.002	-0.014
-SH	-0.149	-0.116	-0.485	-0.006	-0.004	-MeSO <sub>2</sub>	-0.017	0.103	-0.039	-0.007	-0.029
-CN	-0.159	-0.136	-0.018	0.004	0.006	-Li	-0.020	-0.093	0.014	0.013	0.019
-Br	-0.197	-0.210	0.012	-0.006	0.000	-CF <sub>3</sub>	-0.024	0.055	-0.023	-0.006	-0.019
-CH=CH <sub>2</sub>	-0.213	-0.168	-0.020	-0.002	-0.002	-CN	-0.035	0.069	-0.030	-0.008	-0.028
-Me	-0.229	-0.192	-0.013	-0.004	-0.003	-CONH <sub>2</sub>	-0.044	0.032	-0.028	0.000	-0.019
-Ph	-0.232	-0.003	-0.009	-0.097	-0.017	-BeH	-0.052	0.010	-0.022	0.001	-0.020
-tBu	-0.240	-0.199	-0.012	-0.007	-0.002	-COOH	-0.068	0.055	-0.047	0.000	-0.030
-Cl	-0.264	-0.273	0.009	-0.005	0.000	-NO <sub>2</sub>	-0.069	0.073	-0.046	-0.006	-0.038
-NO	-0.264	-0.321	0.020	0.004	0.008	-COCH <sub>3</sub>	-0.071	0.036	-0.040	0.000	-0.028
-NO <sub>2</sub>	-0.320	-0.372	0.021	0.001	0.009	-BF <sub>2</sub>	-0.077	0.052	-0.048	0.001	-0.034
-NH <sub>2</sub>	-0.451	-0.382	-0.022	-0.007	-0.012	-CFO	-0.081	0.068	-0.052	-0.003	-0.040
-NMe <sub>2</sub>	-0.475	-0.400	-0.022	-0.010	-0.013	-CHO	-0.087	0.040	-0.045	-0.002	-0.034
-Ac	-0.546	-0.560	0.013	-0.005	-0.002	-COCN	-0.117	0.056	-0.055	-0.007	-0.050
-OH	-0.561	-0.547	0.003	-0.006	-0.008	-NO	-0.129	0.035	-0.057	-0.002	-0.046
-F	-0.621	-0.668	0.028	-0.004	-0.002	-BH <sub>2</sub>	-0.142	0.030	-0.068	0.006	-0.046

which would be important should one wish to study large substituents and/or molecular systems.

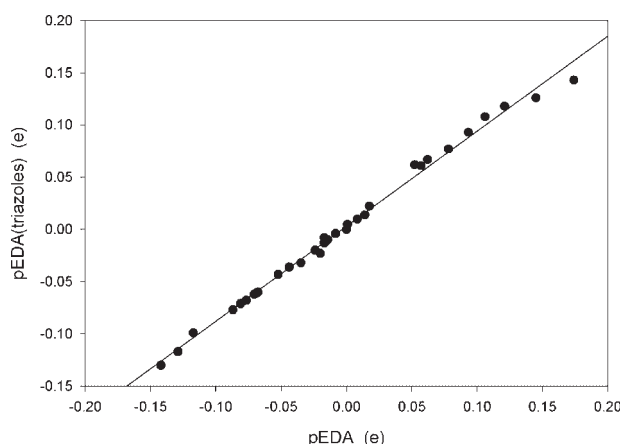
#### Comparison of the *pEDA* descriptors in benzene, ethene, and triazole derivatives

Juxtaposition of the *sEDA* and *pEDA* descriptors (Table 2) demonstrates that they reflect independent substituent effects. On the other hand, comparison of the *sEDA* descriptors for benzene and methane shows (Fig. 2) the two descriptors to define essentially the same effect. The same holds true for the *pEDA* descriptors invented based on the benzene and ethene derivatives (Fig. 3), as well as for C5 substituted 2*H*-1,2,3-triazole derivatives (Fig. 4).

The correlation with the *pEDA* (ethenes) descriptor (Fig. 3) and for the C5-substituted 1,2,3-2*H*-triazoles requires no comment. The triazole  $\pi$ -electron system is strongly perturbed by the presence of the three triazole nitrogen atoms and, in case of strongly charged substituents, there is a 'through space' interaction between the charged substituent in C5 position and the N1 atom lone electron pair which causes deviations from the linear relationship. In case of ethene derivatives there is no



**Figure 3.** Linear correlation between the *pEDA* descriptors for benzene and ethene derivatives  $R = 0.993$ . Standard Error of Estimate = 0.0088. Correlation equation:  $pEDA(\text{ethene}) = 0.95 (\pm 0.02) * pEDA + 0.005 (\pm 0.002)$ .  $F = 2278.8$  (95% confidence level)

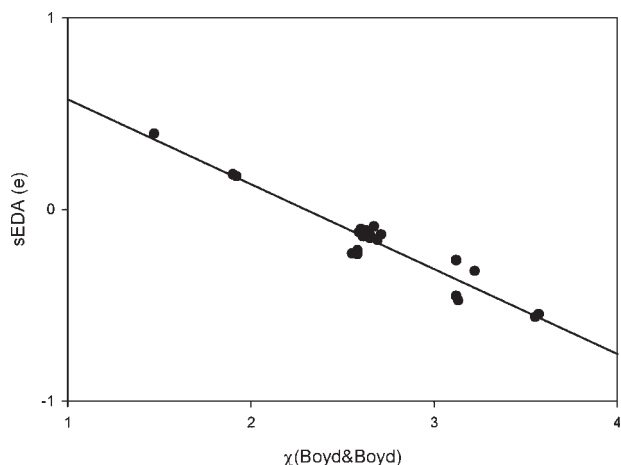


**Figure 4.** Linear correlation between the *pEDA* descriptors for benzene 2H-1,2,3-triazole derivatives and the *pEDA* in benzene derivatives  $R=0.997$ . Standard Error of Estimate = 0.0056. Correlation equation:  $pEDA(\text{triazoles}) = 0.91 (\pm 0.01) * sEDA + 0.003 (\pm 0.001)$ .  $F = 5132.1$  (95% confidence level)

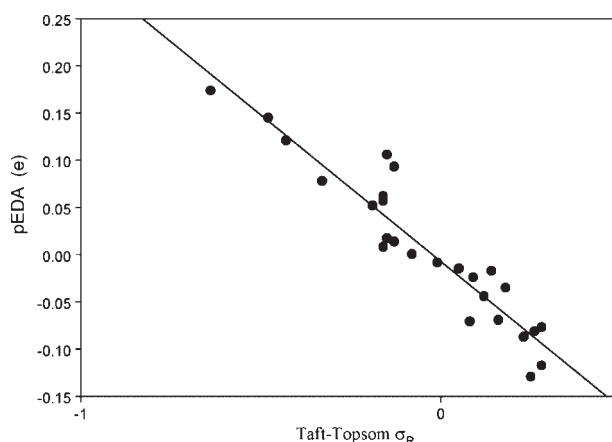
possibility for such interactions and no deviations are observed. Finally, let us mention that the correlation between the *sEDA* descriptors in benzene and triazoles is also good, yet we do not discuss it in this paper because substituent influence on the triazole  $\sigma$ -electron system is mainly restricted to the C5 triazole atom and no specific perturbations are worth our attention here.

#### Comparison of the *sEDA* and *pEDA* descriptors with selected known scales

It is known that each of the EN scales has its own specificity, being the result of its definition and physicochemical characteristics. Frequently, different EN scales intercorrelate only to some degree.<sup>[47,48]</sup> An exemplary correlation between the *sEDA* descriptor and the known EN scales of Boyd&Boyd/Boyd-Edgecombe<sup>[41,42]</sup> is presented in Fig. 5. Although the correlation exhibits some scattering of the points around the regression line, it is definitely significant since for 21 points



**Figure 5.** Correlation between the Boyd&Boyd/Boyd-Edgecombe electronegativity scale and the *sEDA* descriptor,  $R = 0.961$ . Standard Error of Estimate = 0.0660. Correlation equation:  $\chi(\text{Boyd\&Boyd}) = -0.44 (\pm 0.03) * sEDA + 1.02 (\pm 0.08)$ .  $F = 231.3$  (95% confidence level)



**Figure 6.** Linear correlation between the Taft-Topsom  $\sigma_R$  resonance constant and the *pEDA* descriptor,  $R=0.943$ . Standard Error of Estimate = 0.0276. Correlation equation:  $\sigma_R(\text{Taft and Topsom}) = -0.31 (\pm 0.02) * pEDA - 0.007 (\pm 0.006)$ .  $F = 194.1$  (95% confidence level)

the correlation coefficient is equal to 0.961. A similar linear correlation with the Marriott *et al.*<sup>[39]</sup> substituent EN scale (Fig. S3, supplementary information) also shows quite fair linear correlation between the parameters with  $R = 0.943$  for 21 data points. Let us mention that a linear correlation between the Boyd&Boyd/Boyd-Edgecombe<sup>[41,42]</sup> and Marriott *et al.*<sup>[39]</sup> scales is a bit poorer ( $R = 0.930$ ) than the two correlations with the introduced *sEDA* descriptor.

Moreover, another satisfactory linear correlation is the one between the well-known Taft-Topsom  $\sigma_R$  resonance constant and the *pEDA* descriptor, with  $R = 0.943$  (Fig. 6). This indicates that the proposed *pEDA* descriptor of the substituent influence on the  $\pi$  electron structure measures the same property as the classical resonance constant  $\sigma_R$  of Taft and Topsom. A linear correlation with the other resonance scale, the Swain-Lupton *R*-resonance constant,<sup>[14]</sup> is acceptable ( $R = 0.916$ ) (Fig. S4, supplementary information) taking into account that the correlation between  $\sigma_R^-$  and *R* has correlation coefficient equals 0.886.

The comparisons of the *sEDA* and *pEDA* descriptors proposed here with the selected well-known substituent effect parameters of Boyd&Boyd/Boyd-Edgecombe,<sup>[41,42]</sup> Marriott *et al.*,<sup>[39]</sup> Taft and Topsom,<sup>[18]</sup> and Swain and Lupton<sup>[14]</sup> confirm that the *sEDA* and *pEDA* descriptors are useful for study of the substituent influence on the  $\sigma$  and  $\pi$  electron structure of substituted molecules. The proposed descriptors have a perfectly clear physical meaning, as they show the  $\sigma$  and  $\pi$  electron shift and its direction between the substituent and the core molecule. Moreover, since a standard B3LYP/6-31G\*\* and NPA methods have been used, the *sEDA* and *pEDA* descriptors can be routinely calculated for a majority of medium-sized molecules in a reasonable time. Finally, the substituent's influence on  $\sigma$  and  $\pi$  electron structure of a core molecule may be calculated in a single routine.

## CONCLUSIONS

The two descriptors, *sEDA* and *pEDA*, measuring the  $\sigma$ - and  $\pi$ -electron substituent effects, were constructed based on NPA performed for the B3LYP/6-31G\*\* optimized 32 monosubstituted benzene derivatives. They are defined as sums of  $\sigma$ - or  $\pi$ -orbital occupancies of six carbon atoms in the substituted benzene ring



relative to unsubstituted benzene molecule. The sEDA and pEDA descriptors have a clear physical meaning: they show to what extent the  $\sigma$  and  $\pi$  electrons are donated or withdrawn by a substituent from the substituted system. The sEDA and pEDA descriptors were successfully tested not to be mutually correlated and to be independent of the theoretical method, basis set, and solvent presence. Furthermore, the sEDA and pEDA descriptors were shown to be adequate to analyze such different systems as substituted methanes, ethenes, and triazoles. The transmission of the  $\sigma$ -substituent effect in substituted benzene and methane is profoundly similar. The same is true for transmission of  $\pi$ -substituent effect in substituted benzene, ethane, and triazoles. Comparisons of the sEDA and pEDA descriptors with the selected well-known substituent effect descriptors show that the sEDA descriptor correlates fairly well with the Boyd & Boyd/Boyd–Edgecombe and Marriott *et al.* EN scales, while the pEDA descriptor correlates definitely well with the Taft and Topsom and fairly well with Swain and Lupton resonance effect scales. Thus, the sEDA and pEDA descriptors illustrate in a simple and clear way the characteristics of the two  $\sigma$ - and  $\pi$ -electron components of the substituent effect.

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