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Heteroatom Incorporation Effect in σ- and π-Electron Systems: The sEDA(II) and pEDA(II) Descriptors

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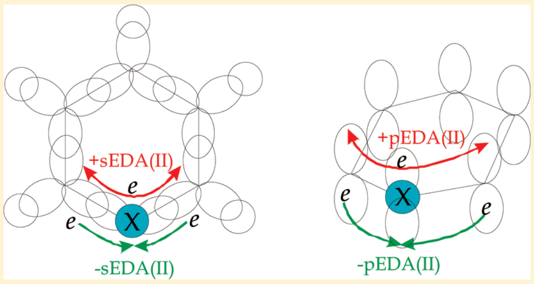
S Supporting Information

ABSTRACT: The effect of heteroatom or heteroatomic group incorporation into unsaturated five- and six-membered cyclic systems was studied by means of DFT/B3LYP/aug-cc-pVDZ calculations. Two descriptors of the incorporation effect, sEDA(II) and pEDA(II), reflecting the influence of the incorporated atom or group on the population of the σ and π valence electrons, were constructed on the basis of natural bond orbital analysis. The sEDA(II) and pEDA(II) descriptors were shown to be linearly independent; the former correlated very well with electronegativity scales, whereas the latter correlated with $\mathrm{NICS(1)_{ZZ}}$ and $\mathrm{HOMA_{CC}}$ aromaticity indices. The two descriptors seem to be universal tools for analyzing different chemical and physicochemical effects occurring in unsaturated heterocyclic systems.



INTRODUCTION

Substitution of a chemical system by a group or incorporation of a heteroatom are two of a few fundamental modifications used in the search of new properties of a system. The effect of substitution of a cyclic system by a group is relatively well-recognized and can be quantitatively evaluated by an array of parameters. However, the heteroatom incorporation effect has been poorly evaluated quantitatively. Intuitively, the two effects are interrelated. Here, the correctness of this intuition is demonstrated.

The idea of quantifying the substituent effect in terms of substituent constants was introduced by Hammett in the 1930s.[1−3] Since then, the substituent effect has been one of the most frequently used terms in organic chemistry, and many groups have investigated this issue.[4] In general, the structural unit called a "substituent" should be considered as[5]

- a small part of a molecule which can be introduced by a simple chemical operation, particularly when it can directly replace a hydrogen atom
- a small and less important part of a molecule which influences the properties of this molecule in the quantitative sense but does not alter its general chemical character

The original Hammett equation elucidates the contribution of inductive and resonance effects to free energy changes on going from one side to the other of an equilibrium from the ground state to the transition state of the reaction.[5,6] Values of σ were defined from the ionization constants of benzoic acid as follows:

$$\sigma_X = \log K_X - \log K_H$$

where K_H stands for the ionization constant of benzoic acid in water at 25 °C and K_X stands for the corresponding constant for meta- or para-substituted benzoic acid.[1]

Even though elucidating Hammett constants was a milestone, this did not give a full picture of the substituent effect. Taking into consideration the complexity of this issue, it was proposed that the electronic effect of substituents is composed of two main parts: a field/inductive component and a resonance component.[7] Thus, σ_m and σ_p were expressed as

$$\sigma_m = \sigma_F + \alpha\sigma_R \text{ and } \sigma_p = \sigma_F + \sigma_R$$

where σ_F stands for the field/inductive effect, σ_R stands for the resonance effect, and α is the transmission coefficient. With this reasoning, the field or field/inductive effect (F) describes electrostatic interactions through space (the predominant field effect) and through the intervening σ bonds (inductive).[8] It should be noted that some authors attribute greater importance to the through-space mode of transmission of this effect.[9] Generally, pole−pole, pole−dipole, and dipole−dipole interactions are distinguished for F. Furthermore, substituents exhibit a profound influence on the molecular properties of the attached molecular units and the resonance contribution of such is quantified as the resonance constant (σ_R).[10]

However, it appears that the validity of this dual substituent parametric (DSP) equation, introduced by Taft et al.[6,11] to derive σ_R, is limited.[12] Underlying this assertion is the fact that the acceptor substituents are not properly expressed by σ_R.[12] Therefore, Exner and Böhm suggested two different resonance scales for both acceptors and donors.[13] However, at the end of

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the day, there was still a need to establish a better description of the substituent effect. In the most developed form of the empirical theory, four constants were assumed to reflect four different interaction mechanisms between a substituent and a core molecule.[6,11] These four factors are called field (σ_F), resonance (σ_R), polarization (σ_α), and electronegativity (σ_χ) and are postulated to be related to an observed quantity by a quadrilinear relationship:

$$y = y_0 + \rho_F\sigma_F + \rho_R\sigma_R + \rho_\alpha\sigma_\alpha + \rho_\chi\sigma_\chi + \varepsilon$$

where y, y_0, ρ, and ε stand for the observed quantity in the substituted and unsubstituted compounds, the proportionality constant, and the error fitting random variable, respectively. However, in most cases, the relationship can be simplified to a bilinear function of the electronegativity and resonance variables, as for example the polarization effect appears to be relatively small, except for large hydrocarbon substituents.[14,15]

The electronegativity parameter (EN) is a response to concerns regarding the insufficiency of the field/inductive component in describing nonresonance contributions to the substituent effect. With this reasoning, the EN factor is considered to be responsible for short-range perturbation of the σ-electron structure of the substituted molecule.[16] According to Pauling, electronegativity is "the power of an atom in a molecule to attract electrons to itself".[17] Despite the fact that, over the decades, many different ideas came into being (Mulliken utilized the combination of ground state ionization energies and electron affinities,[18,19] Allred and Rochow represented electronegativity as the electrostatic force exerted by the atom's effective nuclear charge upon an electron at its covalent radius,[20] Iczkowski and Margrave proposed including higher ionization potentials into EN,[21] Weinhold and Landis recently introduced a concept of "natural π-electronegativity" ($\chi_A{}^\pi$), which is associated with the polarity of π bonding and is parallel to the definition of "natural" electronegativity related to σ bonds ($\chi_A{}^\sigma$),[22,23] and many others[16,24]), the scale developed by Pauling as a result of his quite successful approach based on thermochemical data still remains, of course in an updated form, a standard against which others are measured.[25]

Different EN scales created for mere atoms were found to be insufficient, since a desire for group electronegativity had occurred. In fact, groups have a far better ability to donate or accept charges than mere atoms, and therefore, they can be considered as reservoirs of enhanced charge capacity.[26] Inamoto and Masuda proposed an empirical approach to group electronegativity.[27] Then, Reynolds utilized a purely theoretical approach using the values of atomic electron population on the hydrogen atom in HG compounds (where G is the group being considered) which were obtained from ab initio calculations using Mulliken population analysis.[24] Reynolds, along with Marriot, proposed dividing EN into σ_F, which measures field effects, and σ_χ for the through-bond inductive effect.[16,28] Also, other researchers have had a great contribution in the development of different group EN scales, such as Mullay with his bond orbital EN formulation,[29] Boyd and Edgecombe with the application of AIM topological electron partitioning,[30,31] and many others. In recent days, there have also been a few attempts to define EN using density functional theory.[16] Finally, in a series of papers, Exner and his group focused on the field-inductive effect, reasoning that "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.[16]

Here, it is worth mentioning that theoretical models can provide interesting alternatives to evaluate intrinsic electronic substituent effects. These methods, such as the response functions defined as a global or local reactivity indices, the variations of a reactivity index for a set of functional groups attached to a common molecular frame, or, finally, the global electrophilicity index (ω), can be applied.[15,32]

A brief review of different parameters of the substituent effect can be found in our recent study introducing the sEDA and pEDA descriptors of the substituent effect. The acronyms sEDA and pEDA are derived from σ and π electron donor–acceptor effect. sEDA and pEDA show to what extent the σ and π electrons are donated to or withdrawn from a substituted system by a substituent. The descriptors were constructed using DFT calculations followed by natural bond orbital analysis.[33−35]

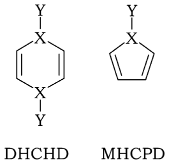
The sEDA descriptor correlates well with the Boyd and Boyd/Boyd−Edgecombe χ electronegativity parameter, as does the pEDA descriptor with the Taft−Topsom σ_R resonance constant.[16] The sEDA descriptor was demonstrated to describe equally well the σ electron changes in methane derivatives and in ethane, benzene and triazole systems, whereas pEDA was shown to be adequate for monitoring the π electron changes in derivatives of the last three π electron systems. So far, the sEDA and pEDA descriptors were used in analysis of substituent effects on the energetic landscape of an optical molecular switch,[36] to analyze aromaticity in fulvene derivatives and their complexes,[37−41] substituted hydroxyquinolines,[42,43] 1-deazapurine derivatives,[44] azoles and phospholes,[45−47] and disubstituted diacetylenes.[48]

Although the substituent effect is of importance for chemistry, which cannot be overemphasized, it does not cover structural modifications in which an atom or group is incorporated into a ring or more developed chemical systems. The substituent effect descriptors cannot be used to evaluate the effect produced by an atom or group inside the core molecule. There are three inherent differences between the substituent and the atom or group incorporation effects. First, halogens and pseudohalogens, or more generally substituents that (as a group) exhibit valency equal to 1, cannot be considered as capable of being incorporated into a ring. As such, they can be considered only by the substituent effect ("first order") descriptors. Second, even if the substituents bonded to two C atoms and one H atom (or a group X), such as >N−X, >P−X, >B−X, etc., can be considered as both substituents and incorporated atoms or groups, they act a bit differently in these two situations. Indeed, as a heteroatom (or group) incorporated into a ring, they are rigid and necessarily embedded into the ring π electron structure. In contrast, as an external group, they may rotate more or less freely and may interact with the π electron system only in some selected positions. As an example, one may consider a (ring-C)−NHMe substituent, the free electron pair of which interacts with the benzene π electron structure if and only if it is more or less perpendicular to the ring plane. Third, like the substituent, a heteroatom is a "small part" of a larger chemical system which can be formally introduced by a "simple chemical operation". However, unlike a substituent, an incorporated heteroatom does alter the general chemical character of a considered system. Therefore, we see the need to introduce "second order" descriptors specifically evaluating the effect of the heteroatom or group incorporated into a ring or more developed molecular fragment.

To construct the descriptors of the heteroatom incorporation effect, we adopted the natural atomic orbitals (NAOs) of the natural bond orbitals (NBO) method applied earlier by us to construct the sEDA and pEDA substituent effect descriptors[16] (denoted sEDA(I) and pEDA(I) from now on). This approach has been flexible enough to also study the heteroatom incorporation effect on the σ and π electrons in the valence orbitals of the core molecule. In classical terminology, the heteroatom incorporation effect on the σ and π electrons corresponds to the incorporated heteroatomic group electronegativity and resonance factor.

The constructed "second order" descriptors, sEDA(II) and pEDA(II), of the heteroatom incorporation effect were modeled by considering the X heteroatom incorporated into five- and six-membered rings (Scheme 1). The heteroatom was further substituted or not by a Y group modifying its electron donor–acceptor properties. The σ and π electron shift between the X heteroatom (or heteroatomic group X–Y) and a core molecule, assumed to reflect important components of various physicochemical properties of heterocycles, was evaluated by the NBO approach. This very methodology allowed us to find a change in the occupancies of the σ and π orbitals, which hereafter is referred to as *the heteroatom incorporation effect* or, more simply, *the incorporation effect*.

Scheme 1. DHCHD (Diheterocyclohexadiene) and MHCPD (Monoheterocyclopentadiene)



The new sEDA(II) and pEDA(II) descriptors of the heteroatom incorporation effect are expected to be valuable tools in QSAR, 3D QSAR, computational drug design, pharmacophore design, etc. of a series of compounds of suspected pharmacological activity.[49−54] The significance of such studies is continuously increasing. Indeed, for only the applied model substructures, a PubChem structure search provides tens of thousands of entries in which they are present (e.g., topoisomerase I and II inhibitors, FAS inhibitors, antiasthmatic agents, antineoplastic agents, photosensitizing agents, free radical scavengers, serotonin antagonists, hemostatics, and antiviral agents). However, the sEDA(II) and pEDA(II) descriptors can possibly be used in studies of a much larger class of heterocyclic compounds.

■ CALCULATIONS

sEDA(II) and pEDA(II) Calculations. The NBO calculations enabling the determination of the σ and π valence electron populations were performed for molecules oriented such that the axis of atomic orbitals contributing to the π molecular orbitals were in parallel to the z axis. The populations of the s, p_x, and p_y atomic orbitals, contributing to the σ valence orbitals, were summed up, and the same was separately done for the p_z atomic orbitals contributing to the π valence orbitals. Then, the sEDA(II) and pEDA(II) descriptors were calculated according to

$$\mathrm{sEDA(II)} = a\sum_{i=1}^{4}(\sigma_i - \sigma_i^{\mathrm{ref}})$$

$$\mathrm{pEDA(II)} = a\sum_{i=1}^{4}(\pi_i - \pi_i^{\mathrm{ref}})$$

$$\mathrm{(s{+}p)EDA(II)} = \mathrm{sEDA(II)} + \mathrm{pEDA(II)} \qquad (1)$$

where i labels four C atoms in the DHCHD ring, the indexed σ and π stand for populations of the σ and π electrons of the ith atom, and the superscript *ref* denotes the reference benzene molecule. The factor a is equal to $^1/_2$ to selectively show the effect produced by only one heteroatom. The indexing of benzene atoms is redundant for the definition of descriptors in DHCHD molecules, yet it is useful in the construction of the analogous descriptors (in different model molecules such as the five-membered C_4H_4X systems studied below) to emphasize that the corresponding atoms in the studied and reference molecules are considered. In definition of the index for the MHCPD molecules, we used a = 1 and have taken the cyclopentadiene molecule as a reference.

It is important to add that the sEDA(II) and pEDA(II) indices can be correctly defined even for slightly nonplanar systems. This requires a few subsequent orientations of a nonplanar molecule in the XYZ coordinate system such that the subsequent triplets of the ring CCC atoms are positioned in the XY plane. This enables finding the occupancies of the perpendicular orbitals of each ring atom. Moreover, the effect is propagating through σ orbitals vanish quickly and, thus, sEDA(II) is practically determined by the atoms attached directly to the heteroatom.

It should be emphasized that, in our definition of the sEDA(II) descriptor, we omitted all contributions of σ electrons originating from H atoms attached to the ring. Indeed, the sEDA descriptor could also be defined by including the occupancy of all these H atoms. For some incorporated atoms, this makes a difference, whereas for others, the difference is negligible. Such a descriptor would be a bit different. Here, we decided to construct the sEDA(II) descriptor based only on the C atom σ orbitals for two reasons. First, such a definition enables one to simultaneously study both the substituent and heteroatom incorporation effects. If the σ electrons of H atoms are taken into account, they should be necessarily reincluded in a combined study of substituent and heteroatom incorporation effects. Second, the useful parameters should be defined as simply as possible, and for this very reason we also disregarded the Core and Rydberg NAOs.

Quantum Chemical Calculations. All of the essential calculations were performed using the hybrid Becke three-parameter Lee–Yang–Parr DFT B3LYP functional,[55,56] the reliability of calculations of the ground state geometries of which has been widely assessed.[57] The aug-cc-pVDZ Dunning[58,59] basis set was employed. In order to confirm that each of the calculated structures corresponded to the minimum potential energy surface (PES), the vibrational frequencies were calculated at the same level and their positive definity was controlled.[60] Several conformations of each of the analyzed structures were calculated to choose a global minimum energy structure for which further analysis was performed. Moreover, we also selectively performed B3LYP/cc-pVTZ calculations to ensure that the basis set size did not influence the quality of the constructed incorporation effect descriptors.

All the calculations were performed using the Gaussian 03[61] and Gaussian 09[62] programs. Natural population analysis (NPA), based on the natural atomic orbitals (NAOs) of the natural bond orbital (NBO) theory,[33−35] (NBO Version 3.1 as implemented in Gaussian 09), was used to reveal the σ and π electron shift between the core molecule and the incorporated heteroatomic group.[63] The atoms in molecules (AIM) analysis[64] was performed using the AIM2000 program.[65]

■ RESULTS AND DISCUSSION

There are three main differences between the substituent effect and the heteroatom incorporation effect: (i) groups exhibiting valency equal to 1 cannot be incorporated into a ring and thus they can be considered by descriptors of the former but not the latter, (ii) the groups of valency 2, that can be both substituted and incorporated, differ in the two situations, because in the former situation they are capable of rotating, whereas in the second they are rigid and forced to participate in the π electron system of the ring, and (iii) the substituent is a "small part" of a larger chemical system which does not alter the general chemical character of the considered system, whereas an incorporated heteroatom does alter the general chemical character of the considered system. Therefore, we developed "second order" descriptors to quantitatively reveal the heteroatom incorporation effect.

The quantitative descriptors of the heteroatom incorporation effect on the remaining part of a molecule are determined based on NBO evaluation of the σ and π electron populations in the valence orbitals of model six-membered 1,4-diheterocyclohexadiene systems (DHCHD, Scheme 1). The descriptors show changes in the electron populations of the reference benzene molecule as the heteroatomic group is changed (see Calculations). They are denoted sEDA(II) and pEDA(II) (the second order σ and π electron donor−acceptor effect descriptors), and they express the incorporation effect on the core molecule σ and π electron systems, respectively. sEDA(II) and pEDA(II) have very clear physical meanings: they show the amount of electrons shifted to or withdrawn from the σ and π valence orbitals of the core molecule by the heteroatomic group. The sEDA(II) and pEDA(II) values for 30 studied heteroatoms and heteroatomic groups are given in Table 1, ordered according to decreasing sEDA(II) values.

The model DHCHD molecules have two advantageous properties for studying the heteroatom incorporation effect. First, they are unsaturated and planar and the effect can naturally be propagated through both the σ and π valence orbitals. Second, a large variety of moieties X can be incorporated into DHCHD and the system remains a closed-shell one. For example, incorporation of both CH and CH_2 as well as N and NH into DHCHD simply leads to benzene, 1,4-cyclohexadiene, pyrazine, and 1,4-dihydropyrazine, respectively. This is important because, for closed-shell systems, the standard (DFT) computations are much more reliable than for open-shell systems. In contrast, in models such as MHCPD (C_4H_4X, Scheme 1), the incorporation of groups such as CH_2, NH, BH, etc. yields closed-shell systems, whereas the insertion of CH, N, B, and analogues yields radicals.

In full analogy to the previously constructed sEDA(I) descriptor of the substituent effect on σ orbitals in monosubstituted compounds,[16] the sEDA(II) values depend primarily on electronegativity of the heteroatom. There are very good correlations between sEDA(II) and Pauling, Skinner, Mann, Allred−Rochow, and "natural"[22,23] electronegativity scales. The correlation coefficient between sEDA(II) and, for example, Pauling's electronegativity, is high ($R = 0.978$, Figure 1a). However, the best correlation ($R = 0.982$) was obtained for the purely theoretical "natural" electronegativity scale also constructed in the frame of NBO theory using NBO calculated ionicities (Figure 1b).[22,23] It should be noted that, to find these correlations, the sEDA(II) values of heteroatomic groups were compared with the atomic electronegativities.

Table 1. sEDA(II), pEDA(II), and (s+p)EDA(II) Descriptors of the X Heteroatom Incorporation Effect into the Diheterocyclohexadiene System Found using B3LYP/aug-cc-pVDZ Calculations[a]

X	sEDA(II)	pEDA(II)	(s+p)EDA(II)
Mg	1.208	−0.039	1.169
Be	1.190	−0.100	1.090
AlH	1.142	−0.079	1.063
Al	1.024	0.364	1.388
GaH	0.997	−0.077	0.920
SiH	0.840	0.181	1.021
SiH_2	0.805	−0.017	0.788
GeH	0.748	0.182	0.930
GeH_2	0.722	−0.007	0.715
BH	0.690	−0.160	0.530
B	0.684	0.261	0.945
As	0.651	0.078	0.729
P	0.609	0.077	0.686
PO	0.600	0.230	0.830
PF	0.595	0.021	0.616
SeO_2	0.427	0.026	0.454
PH	0.368	0.213	0.581
AsH	0.366	0.210	0.576
SO_2	0.308	0.046	0.354
Se[b]	0.247	0.169	0.416
SeO[b]	0.346	0.101	0.447
S[b]	0.141	0.166	0.307
SO[b]	0.248	0.092	0.330
CH	0.000	0.000	0.000
CH_2	−0.053	0.022	−0.031
N	−0.368	−0.120	−0.488
NO	−0.451	0.018	−0.434
NF(np)[b]	−0.439	0.103	−0.336
NF(pl)	−0.495	0.187	−0.308
NH	−0.501	0.178	−0.323
O	−0.726	0.143	−0.583

[a] All values are given in electrons. [b] The molecule is nonplanar.

A closer inspection into the sEDA(II) values given in Table 1 shows that the sEDA(II) descriptor also reflects the electronic state of the heteroatom in the incorporated group. Indeed, the sEDA(II) values of groups with the same heteroatom, for example, Al and AlH, P and PH, and N, NO, and NH are equal to 1.024 and 1.142 e, 0.609 and 0.368 e, and −0.368, −0.451, and −0.501 e, respectively. However, unlike electronegativity, the sEDA(II) descriptor mirrors more subtle changes in the electronic configuration of the incorporated heteroatom in its functional group. The overall effect of the incorporated heteroatomic group on both σ and π electron systems can be expressed by the (s+p)EDA(II) descriptor. For (s+p)EDA(II), the linear correlations with Pauling and "natural" electronegativities are a bit weaker (0.962 and 0.964, respectively).

The effects in organic molecules propagate mainly either through σ or π electronic systems, and as is known from the theory of substituent effects, the descriptors revealing only transmission through the σ electron system (correlating with electronegativity) are not sufficient to thoroughly characterize the effect. There are important features of organic systems, such as aromaticity, which are solely related to the π electron system. Therefore, we introduced the pEDA(II) descriptor, which expresses the incorporated heteroatom influence on the π electron system and is expected to correlate with such features

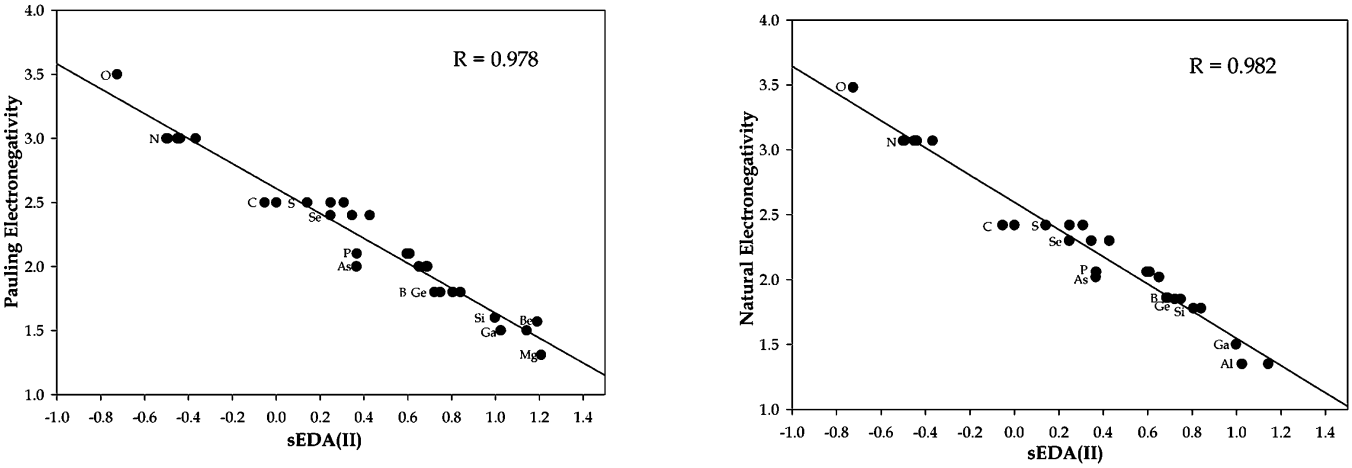


Figure 1. Linear correlations between the Pauling (a) and the "natural" (b) electronegativity scales and the sEDA(II) descriptor of the incorporation effect of a heteroatom or group.

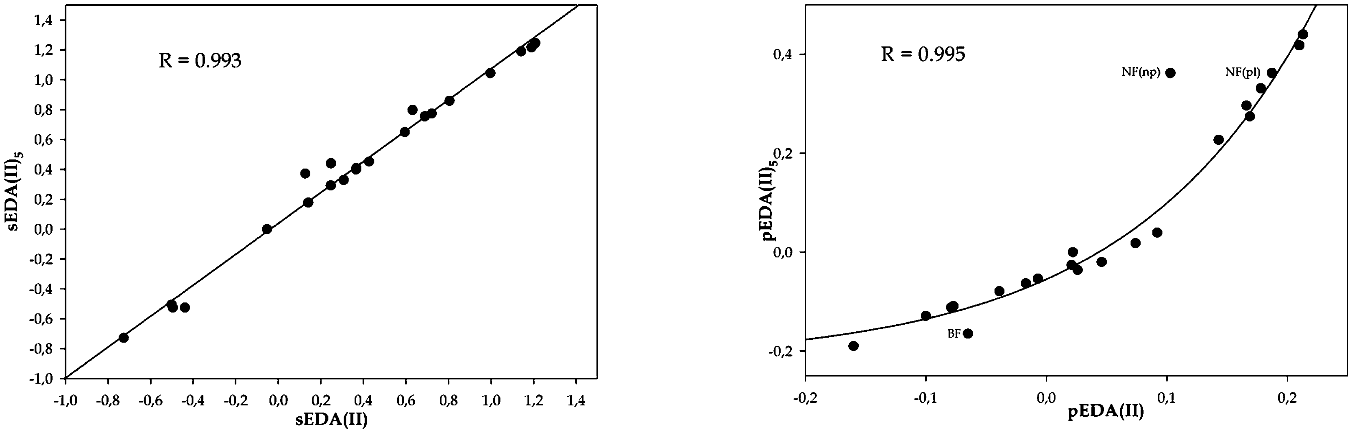


Figure 2. Linear correlation between the sEDA(II) and sEDA(II)$_5$ descriptors (a) and exponential function correlation between the pEDA(II) and pEDA(II)$_5$ descriptors (b) of the incorporation effect of a heteroatom or group in the studied five- and six-membered rings.

of organic systems that are connected mostly with the π electron system, such as aromaticity.

It can be observed that there is absolutely no correlation between the pEDA(II) descriptor (illustrating the heteroatom influence on the DHCHD π electron system) and Pauling or "natural" electronegativities (Table 1). Thus, the factors connected to the π electronic structure of the molecule are linearly independent of both sEDA(II) and electronegativity. Indeed, the juxtaposition of the analyzed sEDA(II) and pEDA(II) descriptors (Table 1) shows that they are definitely different and do not correlate with each other. For example, for B and BH, the sEDA(II) values are very close (0.684 and 0.690 e, respectively) whereas the pEDA(II) values are different and have opposite signs (0.261 and −0.160 e, respectively). On the other hand, the two descriptors are very similar for AsH and PH (sEDA(II), 0.366 and 0.368 e, respectively; pEDA(II), 0.210 and 0.213 e, respectively). Finally, for GeH and NH, the sEDA(II) values differ drastically (0.748 and −0.501 e, respectively), whereas the pEDA(II) values are very close (0.182 and 0.178 e, respectively). This is not surprising, because the similar substituent effect parameters describing the influence on σ orbitals and correlating with electronegativity do not correlate with the parameters revealing the resonance effect which propagates through the π electron system. This is a consequence of the different orientation of the σ and π orbitals and the way the effects decay.

The pEDA(II) descriptor of the heteroatom incorporation effect on the π electron system (Table 1) was introduced in full analogy to the pEDA(I) descriptor.[16] Demonstration of its usefulness requires presenting correlations with some π electron properties of model systems. Unfortunately, a number of examined DHCHD molecules are not aromatic and some widely used aromaticity indices yield rather erratic characteristics. Therefore, we included in our studies five-membered monoheterocyclopentadiene molecules (MHCPD, C_4H_4X; Scheme 1).

For MHCPD molecules, we constructed sEDA(II)$_5$ and pEDA(II)$_5$ descriptors using eq 1, in which the factor of $a = {}^1/_2$ was replaced by $a = 1$ and the reference molecule was changed to cyclopentadiene. The sEDA(II) and sEDA(II)$_5$ descriptors correlated linearly (R = 0.993, Figure 2a). Surprisingly, there was a very significant yet nonlinear correlation between the pEDA(II) and pEDA(II)$_5$ descriptors (Figure 2b). The nonlinearity could be well fitted by either a rational or exponential function with correlation coefficients exceeding 0.99 (Figure 2b). It is important to understand where the nonlinearity comes from.

First, let us comment on the behavior of the sEDA(II) and sEDA(II)$_5$ descriptors. Like the substituent effect on σ electron

Table 2. $sEDA(II)_5$ and $pEDA(II)_5$ Descriptors of the Heteroatom Incorporation Effect in MHCPD (C_4H_4X) Molecules and Different NICS Indices Found Using B3LYP/aug-cc-pVDZ Calculations[a]

X	$sEDA(II)_5$	$pEDA(II)_5$	NICS(0)	$NICS(0)_{ZZ}$	$NICS(1)_{ZZ}$	$HOMA_{CC}$
Mg	1.245	−0.079	1.531	18.018	5.178	−0.576
Be	1.216	−0.129	6.587	31.195	15.588	−0.817
AlH	1.190	−0.112	7.719	32.122	14.455	−0.381
GaH	1.044	−0.109	8.314	36.023	14.313	−0.432
SiH_2	0.858	−0.063	1.278	20.617	−0.139	−0.045
GeH_2	0.774	−0.054	0.412	22.468	−0.195	−0.067
BH	0.755	−0.190	20.880	65.731	38.101	−0.761
BF	0.797	−0.165	14.532	−49.830	26.564	−0.748
PF[b]	0.649	−0.026	np	np	np	0.087
SeO_2	0.452	−0.036	−0.640	18.399	0.956	−0.311
SeO[b]	0.440	0.039	np	np	np	0.021
PH[b]	0.408	0.440	np	np	np	0.877
AsH	0.398	0.418	np	np	np	0.836
SO[b]	0.372	0.018	np	np	np	0.181
SO_2	0.328	−0.020	−0.107	17.382	1.246	−0.275
Se	0.292	0.274	−11.617	−4.353	−25.632	0.731
S	0.177	0.296	−12.130	−8.521	−28.632	0.795
CH_2	0.000	0.000	−2.586	11.414	−13.025	0.208
NH	−0.506	0.331	−13.120	−11.952	−31.484	0.855
NF	−0.527	0.362	−15.916	−11.799	−29.037	0.881
O	−0.729	0.227	−11.474	−8.494	−27.708	0.684

[a] All values are in electrons. The $HOMA_{CC}$ index is based solely on the conjugated C1═C2, C2−C3, and C3═C4 bonds in MHCPD molecules.
[b] The molecule is nonplanar (np).

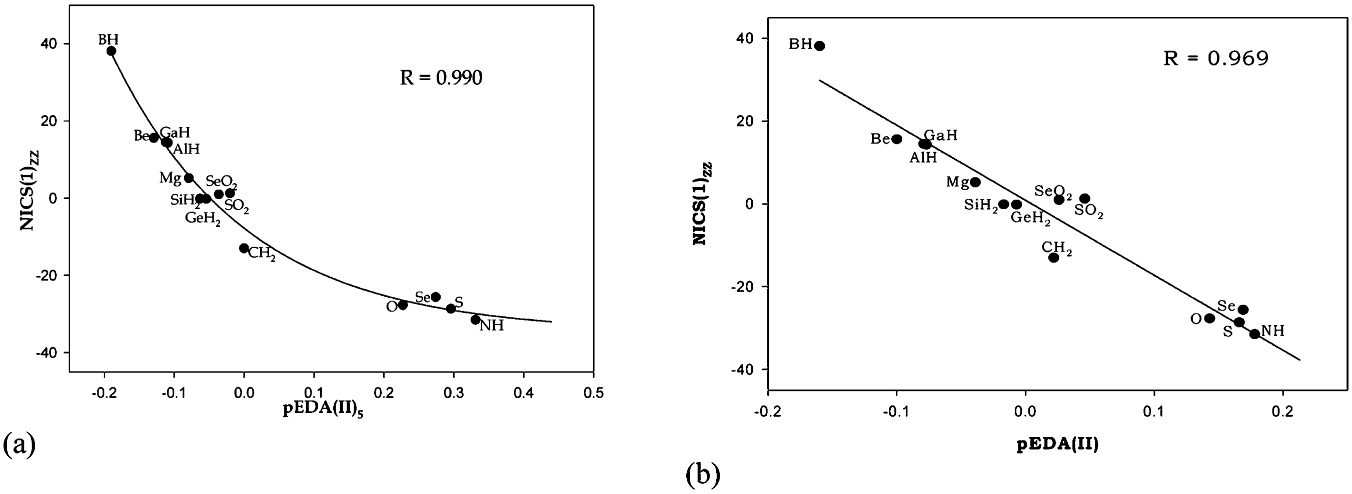


Figure 3. Exponential decay between the $pEDA(II)_5$ and the $NICS(1)_{ZZ}$ aromaticity index of the MHCPD molecules (a) and linear correlation between pEDA(II) descriptor constructed on the basis of DHCHD molecules and the $NICS(1)_{ZZ}$ aromaticity index in MHCPD molecules calculated at the B3LYP/aug-cc-pVDZ level (b).

valence orbitals,[16] the effect of heteroatom incorporation on these orbitals decreases rapidly. In practice, it vanishes at the second atom from the place of substitution or incorporation. In contrast, the substituent and heteroatom effects on the π electron valence orbitals are extended over all the π electron orbitals.[16] In the six-membered DHCHD systems, all four ring carbon atoms are equivalent and have the same σ and π electron populations. Because of the rapid decrease in the effect on the σ valence orbitals, only the closest heteroatom contributes to the σ electron populations of two C atoms and both the sEDA(II) and $sEDA(II)_5$ descriptors reflect changes in the σ electron populations at the two C atoms attached to the heteroatom. The correlation between the sEDA(II) and $sEDA(II)_5$ descriptors is linear because the two descriptors measure exactly the same effect in the two systems. However, this is not the same for the pEDA(II) and $pEDA(II)_5$ descriptors. In the DHCHD systems, the π electron populations have contributions from both close and distant heteroatoms. A mutual interaction of the two heteroatoms may also play a role. On the other hand, in the MHCPD systems, only one heteroatom acts on the four C atoms. The change in the π electron population in the pair of C atoms close to the heteroatom is different from that in the second pair of C atoms, as are their contributions to the $pEDA(II)_5$ descriptor. This gives rise to nonlinearity between the indices, which increases with the π electron donating capabilities of the incorporated heteroatomic group (Figure 2b).

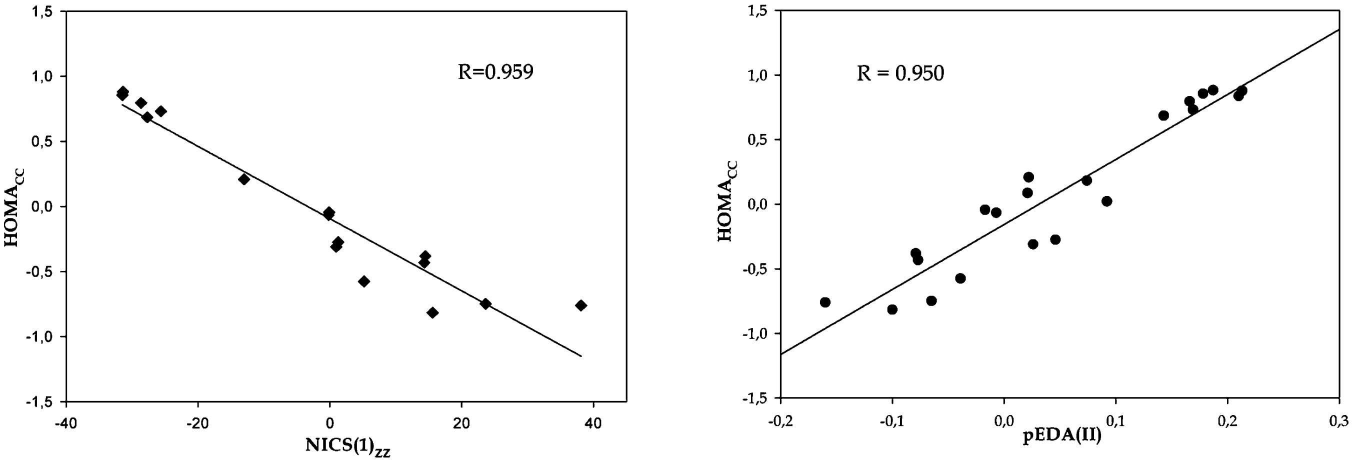


Figure 4. Linear correlation between the NICS(1)$_{ZZ}$ aromaticity index and the HOMA$_{CC}$ index truncated to CC bonds in the MHCPD system (a) and the linear correlation between the pEDA(II) descriptor and the HOMA$_{CC}$ index (b) calculated at the B3LYP/aug-cc-pVDZ level.

The aromaticity of the π electron system of MHCPD molecules can be well described by a series of NICS (nucleus independent chemical shift) indices (Table 2).[66−71] There is a debate about whether to use the simplest NICS(0) index, easily available from calculations, yet biased by contributions from σ valence electrons, or NICS$_{\pi ZZ}$, a more sophisticated index, which although free from superfluous contributions of σ valence electrons, requires estimation.[68] In our study, we chose a compromise solution by using the NICS(1)$_{ZZ}$ index, which includes the contribution from only those electrons which are delocalized 1 Å out of the ring plane. This index is defined as the ZZ component of the NICS(1) tensor.[68] We found that the correlation of the pEDA(II)$_5$ descriptor with the corresponding NICS(1)$_{ZZ}$ values was very strong and nonlinear (Figure 3a). The best fit was either of a rational or exponential decay shape (R = 0.990, Figure 3a). The correlations show that the greater the π electron withdrawing effect of the incorporated heteroatomic group, the less aromatic the system, and conversely, the greater the donating heteroatom incorporation effect, the more aromatic the system. Indeed, the two correlated parameters describe the π-electron properties of the analyzed system, yet NICS(1)$_{ZZ}$ describes aromaticity, whereas pEDA(II)$_5$ evaluates the heteroatom incorporation effect on the MHCPD π electron system.

Taking into account the discussion of nonlinearity between the pEDA(II) and pEDA(II)$_5$ descriptors, one may suppose that the nonlinearity also observed in Figure 3a can be descriptor definition dependent. Therefore, we checked the correlation between NICS(1)$_{ZZ}$ and the pEDA(II) descriptor and we found that it was indeed statistically important and linear (R = 0.969, Figure 3b). Thus, DHCHD is the correctly chosen model system and pEDA(II) is the correctly chosen descriptor of the heteroatom incorporation effect. From one side, we constructed the pEDA(II)$_5$ descriptor correlating very well yet nonlinearly with NICS(1)$_{ZZ}$ obtained for the same MHCPD molecules, and from the other side, we constructed the pEDA(II) descriptor (based on a different type of molecule, DHCHD), which had a weaker correlation with NICS(1)$_{ZZ}$ but appeared to be more universal by yielding a linear dependence.

For aromatic heterocyclic molecules, the widely used HOMA aromaticity index[72,73] has an important drawback, because it must be additionally parametrized for heteroatoms and most of the possible heteroatoms are difficult to parametrize because of a very small or even absent number of experimental molecules that can be used for such a parametrization. However, here we adopted a trick very recently applied to calculate the HOMA index of conjugated paths in monosubstituted naphthoquinones.[74] We assumed that the HOMA index of the conjugated path in MHCPD molecules, i.e., the HOMA$_{CC}$ index based solely on the conjugated C1═C2, C2−C3, and C3═C4 bonds, reflects the π electron properties of the MHCPD molecule, although it does not contain the distances taken directly to the heteroatom. Such a HOMA$_{CC}$ index truncated to the carbon atoms of the studied heterocyclic system can be easily defined, thanks to the additive properties of the HOMA index of heterocyclic compounds with respect to the bonds constituting the molecule.[72,73] For the five-membered MHCPD molecules studied here, it can be written in a simpler form:

$$\begin{aligned}\mathrm{HOMA} &= 1 - \frac{\alpha(\mathrm{CC})}{5}\sum_{\mathrm{CC}} |R(\mathrm{CC})_{\mathrm{opt}} - R(\mathrm{CC})_i|^2 \\ &\quad - \frac{\alpha(\mathrm{CX})}{5}\sum_{\mathrm{CX}} |R(\mathrm{CX})_{\mathrm{opt}} - R(\mathrm{CX})_i|^2 \\ \mathrm{HOMA} &= 1 - \mathrm{HOMA}_{\mathrm{CC}} - \mathrm{HOMA}_{\mathrm{CX}} \\ \mathrm{HOMA}_{\mathrm{CC}} &= 1 - \mathrm{HOMA} - \mathrm{HOMA}_{\mathrm{CX}} \qquad (2)\end{aligned}$$

where α and R are empirical parameters found for given types of bonds.

The values of the HOMA$_{CC}$ index truncated to the CC bonds in the MHCPD molecule are given in Table 2, and the linear correlations between the NICS(1)$_{ZZ}$ and HOMA$_{CC}$ indices as well as between the pEDA(II) descriptor and the HOMA$_{CC}$ index are presented in Figure 4. The two correlations are practically of the same grade with $R \approx 0.95$, which is surprising when taking into account the fact that the HOMA$_{CC}$ index was reduced to an extremely simple form. Thus, both the HOMA$_{CC}$ index and the pEDA(II) descriptor (calculated for six-membered DHCHD structures) correctly express the π electron properties of the unsaturated heterocyclic five-membered MHCPD compounds.

As mentioned before, Weinhold and Landis recently introduced concept of “natural π-electronegativity” ($\chi_A{}^{\pi}$) which is associated with the polarity of π bonding and is parallel to the definition of “natural” electronegativity related to σ bonds ($\chi_A{}^{\sigma}$).[22,23] They considered a series of heteroatoms in H_2C═X molecules and determined π bond ionicity, which is

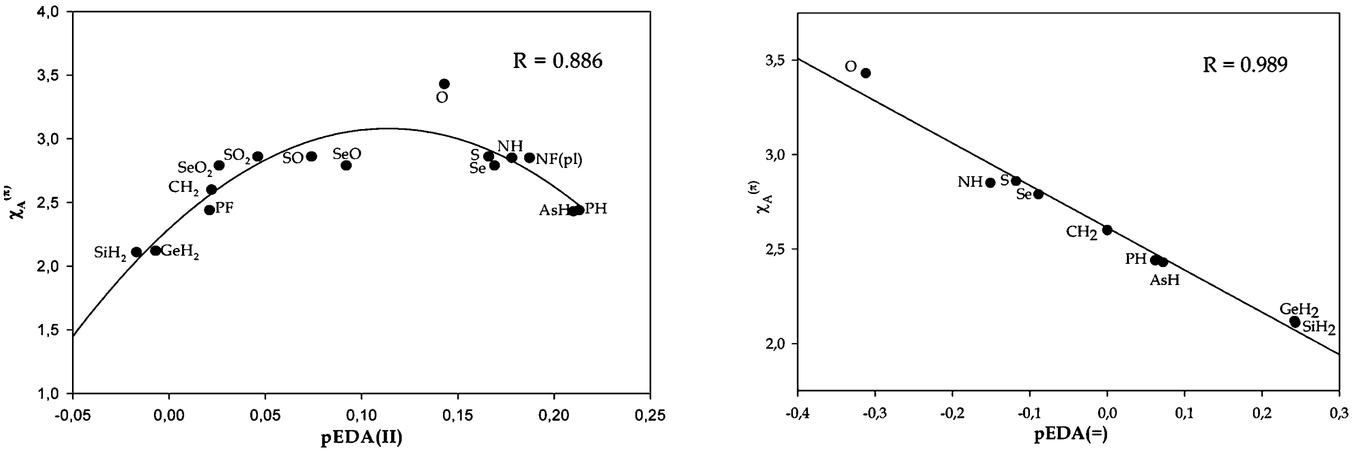


Figure 5. Quadratic correlation between the pEDA(II) descriptor and π type "natural" electronegativity[64] (a) and a linear correlation between the pEDA(=) descriptor calculated at the B3LYP/aug-cc-pVDZ level and π type "natural" electronegativity[22,23] in $H_2C{=}X$ molecules (b).

connected with the natural π electronegativity through an equation fully analogous to that defining "natural (σ) electronegativity". They demonstrated that χ_A^{π} exhibited trends similar to those for χ_A^{σ}, yet the range of changes of the former was found to be significantly smaller than that of the latter. This is due to the fact that π(AB) bonds are usually less polarized than σ(AB) bonds. The idea of "natural" π electronegativity seems to be so closely connected to the concept of the pEDA(I) and pEDA(II) descriptors that we expected to find a good correlation between χ_A^{π} and the pEDA(II) descriptor. Unexpectedly, we found only a weak quadratic correlation between these two parameters ($R = 0.886$, Figure 5a).

To understand the differences in natural π electronegativity defined through π bond ionicity[22,23] and our pEDA(II) descriptor, we determined a new pEDA(=) descriptor based on the occupancies of the π orbital of the C atom in a series of $H_2C{=}X$ molecules (used to construct χ_A^{π}) and presented χ_A^{π} as a function of the pEDA(=) descriptor (Figure 5b). It appeared that there was a strong linear correlation between them ($R = 0.989$). Thus, the difference between χ_A^{π} and pEDA(II) is substantial and these parameters describe different properties, whereas the similarity between χ_A^{π} and pEDA(=) is substantial as well and these parameters describe the same properties of organic systems. The key difference between χ_A^{π} and pEDA(II) or the pEDA(=) and pEDA(II) descriptors is in the way the heteroatom is attached to the core molecule; in the case of χ_A^{π} and pEDA(=), there is only a double bond between one C and one X atom, whereas in case of the pEDA(II) descriptor, the heteroatoms are incorporated into a ring system and two C atoms are connected to one X atom through bonds that form an intramolecular angle close to 120°. In these two cases, the hybridization of X is sp^2; in the former case, the p_z orbital of X is engaged by only one C atom, while in the second case it interacts with two p_z orbitals of two neighboring C atoms. It is easy to find the chemical interpretation of the χ_A^{π} and pEDA(=) parameters. They express the influence of the substituent attached by a double bond to the core (ring) molecule. Moreover, it is obvious that the new sEDA(=) descriptor can also be correctly defined in full analogy to the previously constructed sEDA(I) and sEDA(II) descriptors. It expresses the effect of the substituent connected to the core molecule by a double bond, which correlates to the σ electronegativity parameters. At the end of this paragraph, it should be mentioned that we are about to finish a study on the sEDA(=) and pEDA(=) descriptors built based on the same DHCHD molecules, where the heteroatomic group X is simply the $>C{=}Y$ group, where Y = CZ_2, SiZ_2, GeZ_2, NZ, PZ, AsZ, BZ, AlZ, GaZ, Z are substituents bonded by a single bond.

A few years ago, the AIM (atoms in molecules) electron density parameters in ring critical points (RCP) were shown to correlate well with the aromaticity of heterobenzenes.[75−77] Therefore, we checked whether or not there were similar correlations between the AIM parameters in the RCP of MHCPD molecules and the descriptors of the heteroatom incorporation effect. It appeared that the sEDA(II) descriptor correlated well with electron density and the other parameters, with the strongest correlation ($R = 0.930$) with the Laplacian of the electron density ($\nabla^2\rho$(RCP)), whereas the pEDA(II) descriptors exhibited no significant correlations with the AIM parameters. However, similar correlations with the (s+p)EDA-(II) descriptor of the overall heteroatom incorporation effect were even stronger. These findings show yet another aspect that can possibly be studied using newly developed descriptors of the heteroatom incorporation effect.

To better understand the position of the newly constructed sEDA(II) and pEDA(II) descriptors in the stream of research on substituent effects, we also checked the internal, geometrical ring parameters found by Domenicano et al. to be adequate in the description of the monosubstitution of the benzene ring. They showed that the ipso C6C1C2 angle in C1-substituted benzenes remarkably increases when going from less electronegative to more electronegative substituents. Moreover, a fairly good linear correlation exists between the ring C6C1C2 and C1C2C3 angles.[78] Therefore, we decided to test similar relations between sEDA(II) and pEDA(II) and the appropriate angles in our five- and six-membered heterocyclic systems. We found the following: (i) there was no correlation between either sEDA(II) or pEDA(II) and the CXC angle; (ii) there was a perfect linear correlation between the CXC and XCC angles in DHCHD molecules; (iii) there was no correlation between either sEDA(II)_5 or pEDA(II)_5 and the CXC or XCC angles; (iv) there was no correlation between the CXC and XCC angles in MHCPD molecules; (v) unexpectedly, there was a linear correlation between sEDA(II)_5 and the C1C2C3 angle in MHCPD molecules ($R = 0.89$) and a weaker linear or a quadratic correlation between the XCC and C1C2C3 angles in MHCPD. Thus, even good parameters describing the substituent effect do not necessarily fit the atom or group incorporation effect. There are some regularities in the behavior of angles in six- and five-membered heterocycles with variation of the incorporated atom or group. However, a search for a closer relationship between some geometrical parameters and the sEDA(II) and pEDA(II) descriptors of the heteroatom incorporation effect requires further investigation beyond this study.

It is worth noting that in addition to the main problem of the heteroatom or group incorporation effect on the σ- and π-electronic systems in heterocyclic compounds, there are a few issues that are closely related but need further studies. One of them is the incorporation effect observed for radical heteroatoms or heteroatomic groups. We found that there is a deviation from the observed correlations for the pEDA(II) descriptors produced by such systems. Nevertheless, a systematic analysis of this problem would need a modification of the methodology applied to one more appropriate for open-shell systems. The other problem that goes beyond the scope of this paper is related to chemical modifications of the heteroatomic group by attaching to it another moiety with well-defined EDA properties. For example, incorporation of an N−H group into the studied models enables considering the N−R groups which modify the incorporation effect. Such modifications can theoretically occur in four different ways, because both the σ and π effects are independent and may either donate or withdraw. Finally, it should be noted that the possible interrelations between the sEDA(II) and pEDA(II) with many other σ and π electron parameters were not exhausted in this study but they are worth exploring to better understand the position of our newly developed descriptors in the multitude of molecular scales, descriptors, and parameters.

CONCLUSIONS

The effect of the incorporation of a heteroatom or heteroatomic group into unsaturated five- and six-membered cyclic systems was studied by means of DFT/B3LYP/aug-cc-pVDZ calculations followed by natural bond orbital analysis. On the basis of the NBO approach, two descriptors of the heteroatom incorporation effect, sEDA(II) and pEDA(II), were constructed to measure changes in the electron population of the σ and π valence orbitals upon heteroatom incorporation into an unsaturated cyclic system.

More specifically, the descriptors reflect the influence of a heteroatom or its group on the σ and π electronic systems by showing the extent to which the σ and π electrons are donated or withdrawn by the incorporated atom or group to or from the cyclic system.

We constructed two pairs of sEDA(II) and pEDA(II) descriptors: one based on diheterocyclohexadiene (DHCHD), sEDA(II) and pEDA(II), and the other based on monoheterocyclopentadiene (MHCPD, C_4H_4X) molecules, sEDA(II)_5 and pEDA(II)_5. They differed in particular applications but, generally, revealed the same phenomenon of shifting electrons between the incorporated heteroatom and the core molecule.

The sEDA(II) and pEDA(II) descriptors were shown to be linearly independent. The sEDA(II) descriptor correlated very well with the Pauling, "natural", and other electronegativity scales. However, unlike the electronegativity scales, the sEDA(II) descriptor mirrored more subtle changes in the electronic configuration of the incorporated atom or group. On the other hand, very good correlations between the pEDA(II)_5 and pEDA(II) descriptors and the NICS(1)_{zz} aromaticity index of MHCPD molecules were found. There was, however, a difference in the performance of the two pEDA descriptors as a consequence of some differences of their definitions. As a result, the correlations with pEDA(II)_5 were nonlinear, whereas those with pEDA(II) remained linear despite the fact that the pEDA(II) descriptor was constructed on the basis of six-membered unsaturated DHCHD molecules and applied to monitor the π electron properties of five-membered MHCPD systems.

In addition to relationships between sEDA(II) and Pauling and "natural" electronegativity, as well as pEDA(II) and the NICS(1)_{ZZ} index, we demonstrated interrelations between pEDA(II) and the HOMA_{CC} index constructed for MHCPD heterocyclic molecules as an index for the conjugated C═C−C═C path and the π "natural" electronegativity concept. Additionally, we showed that the AIM properties of the ring critical point in MHCPD molecules was in good correlation with our (s+p)EDA(II) descriptor of the overall incorporation EDA effect. Finally, the eventual correlations of internal angles in MHCPD systems and our parameters were considered.

In conclusion, in a simple and clear way, the sEDA(II) and pEDA(II) descriptors illustrate the characteristics of the two σ and π electron components of the heteroatom or heteroatomic group incorporation effect. Thus, the two descriptors seem to be appropriate for analyzing different physicochemical effects occurring in unsaturated heterocyclic systems, which makes them quite unique and universal tools.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables giving *XYZ* coordinates and Gibbs free energy values for all studied molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96−103.
(2) Hammett, L. P. *Physical Organic Chemistry: Reaction Rates, Equilibria, and Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1970.
(3) Johnson, C. D. *The Hammett Equation, Cambridge Texts in Chemistry and Biochemistry*; Cambridge University Press: Cambridge, U.K., 1973.
(4) Krygowski, T. M.; Stępień, B. T.; Cyrański, M. K. *Int. J. Mol. Sci.* **2005**, *6*, 45−51.
(5) Exner, O.; Krygowski, T. M. *Chem. Soc. Rev.* **1996**, *25*, 71−75.
(6) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1−83.
(7) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119−251.
(8) Hansch, C.; Leo, A.; Taft, W. *Chem. Rev.* **1991**, *91*, 165−195.
(9) Wiberg, K. B. *J. Org. Chem.* **2002**, *67*, 1613−1617.
(10) Krygowski, T. M.; Stępień, B. T. *Chem. Rev.* **2005**, *105*, 3482−3512.
(11) Taft, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 1045−1049.
(12) Sayyed, F. B.; Suresh, C. H. *Tetrahedron Lett.* **2009**, *50*, 7351−7354.

(13) Exner, O.; Böhm, S. *J. Phys. Chem. Org.* **2007**, *20*, 454−462.

(14) Exner, O.; Böhm, S. *J. Phys. Org. Chem.* **2006**, *19*, 393−401.

(15) Domingo, L. R.; Perez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 6060−6062.

(16) Oziminski, W. P.; Dobrowolski, J. C. *J. Phys. Org. Chem.* **2009**, *22*, 769−778.

(17) Pauling, L. *The Nature of the Chemical Bond*, 2nd ed.; Cornell University Press: Ithaca, NY, 1948; p 58.

(18) Mulliken, R. S. *J. Chem. Phys.* **1934**, *2*, 782−793.

(19) Mulliken, R. S. *J. Chem. Phys.* **1935**, *3*, 573−585.

(20) Allred, A. L.; Rochow, E. G. *J. Inorg. Nucl. Chem.* **1958**, *5*, 264−268.

(21) Iczkowski, R. P.; Margrave, J. L. *J. Am. Chem. Soc.* **1961**, *83*, 3547−3351.

(22) Weinhold, F.; Landis, C. R. *Valency and Bonding, A Natural Bond Orbital Donor−Acceptor Perspective*; Cambridge University Press: New York, 2005.

(23) Glendening, E. D.; Landis, C. L.; Weinhold, F. *WIREs Comput. Mol. Sci.* **2012**, *2*, 1−42, DOI: 10.1002/wcms.51.

(24) Mullay, J. Estimation of Atomic and Group Electronegativities. *Structure and Bonding*; Springer-Verlag: Berlin, Heidelberg, 1987.

(25) Politzer, P.; Shields, Z. P.-I.; Bulat, F. A.; Murray, J. S. *J. Chem. Theory Comput.* **2011**, *7*, 377−384.

(26) Garner-O'Neale, L. D.; Bonamy, A. F.; Meek, T.; Patrick, B. G. *J. Mol. Struct. (THEOCHEM)* **2003**, *639*, 151−156.

(27) Reynolds, W. F.; Taft, R. W.; Topson, R. D. *Tetrahedron Lett.* **1982**, 1055−1058.

(28) Marriott, S.; Reynolds, W. F.; Taft, R. W.; Topsom, R. D. *J. Org. Chem.* **1984**, *49*, 959−965.

(29) Mullay, J. *J. Am. Chem. Soc.* **1985**, *107*, 07271−7275.

(30) Boyd, R. J.; Edgecombe, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 4182−4186.

(31) Boyd, R. J.; Boyd, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 1652−1655.

(32) Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.

(33) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry-Structure and Mechanisms*, 5th ed.; Springer Science+Business Media: Berlin, 2007.

(34) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.

(35) Wojciechowski, P. M. *Wiad. Chem.* **2005**, *59*, 193−212.

(36) Rode, M. F.; Sobolewski, A. L. *J. Phys. Chem. A* **2010**, *114*, 11879−11889.

(37) Oziminski, W. P.; Krygowski, T. M.; Fowler, P. W.; Soncini, A. *Org. Lett.* **2010**, *12*, 4880−4883.

(38) Krygowski, T. M.; Oziminski, W. P.; Palusiak, M.; Fowler, P. W.; McKenzie, A. D. *Phys. Chem. Chem. Phys.* **2010**, *12*, 10740−10745.

(39) Krygowski, T. M.; Oziminski, W. P.; Cyrański, M. K. *J. Mol. Model.* DOI 10.1007/s00894-011-1264-4.

(40) Oziminski, W. P.; Krygowski, T. M. *J. Mol. Model.* **2011**, *17*, 565−572.

(41) Oziminski, W. P.; Krygowski, T. M. *Chem. Phys. Lett.* **2011**, *510*, 53−56.

(42) Karpińska, G.; Mazurek, A. P.; Dobrowolski, J. Cz. *J. Mol. Struct. (THEOCHEM)* **2010**, *961*, 101−106.

(43) Karpińska, G.; Mazurek, A. P.; Dobrowolski, J. Cz. *Comput. Theor. Chem.* **2011**, *972*, 48−56.

(44) Jarończyk, M.; Dobrowolski, J. Cz. *Comput. Theor. Chem.* **2011**, *974*, 9−15.

(45) Krygowski, T. M.; Oziminski, W. P.; Ramsden, C. A. *J. Mol. Model.* **2011**, *17*, 1427−1433.

(46) Oziminski, W. P.; Krygowski, T. M. *Tetrahedron* **2011**, *67*, 6316−6321.

(47) Oziminski, W. P. *Comput. Theor. Chem* **2012**, *980*, 92−100.

(48) Roman, M.; Dobrowolski, J. Cz.; Baranska, M. *J. Chem. Inform. Model.* **2011**, *51*, 283−295.

(49) Hua, M. X.; Shi, Z.; Tan, C.; Jiang, Y.; Go, M. L.; Low, B. C.; Chen, Y. Z. *Pharm. Res.* **2010**, *27*, 739−749.

(50) Young, D. C. *J. Am. Chem. Soc.* **2009**, *131*, 8334.

(51) Campegna-Slater, V.; Arrowsmith, A. G.; Zhao, Y.; Schapira, M. *J. Chem. Inf. Model.* **2010**, *50*, 358−367.

(52) Swann, S. L.; Brown, S. P.; Muchmore, S. W.; Patel, H.; Merta, P.; Locklear, J.; Hajduk, J. *J. Med. Chem.* **2011**, *54*, 1223−1232.

(53) Herold, F.; Chodkowski, A.; Izbicki, Ł.; Turło, J.; Dawidowski, M.; Kleps, J.; Nowak, G.; Stachowicz, K.; Dybała, M.; Siwek, A.; Mazurek, A. P.; Mazurek, A.; Pluciński, F. *Eur. J. Med. Chem.* **2011**, *46*, 142−149.

(54) Słowiński, T.; Stefanowicz, J.; Dawidowski, M.; Kleps, J.; Czuwar, S.; Andres-Mach, M.; Łuszczki, J. J.; Nowak, G.; Stachowicz, K.; Szewczyk, B.; Sławińska, A.; Mazurek, A. P.; Mazurek, A.; Pluciński, F.; Wolska, I.; Herold, F. *Eur. J. Med. Chem.* **2011**, *46*, 4474−4488.

(55) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5662.

(56) Burke, K.; Perdew, J. P.; Wang, Y. In *Electronic Density Functional Theory: Recent Progress and New Directions*; Dobson, J. F., Vignale, G., Das, M. P., Eds.; Plenum: Oxford, U.K., 1998.

(57) Janoschek, R. *Pure Appl. Chem.* **2001**, *73*, 1521−1553.

(58) Dunning, T. H. Jr. *J. Chem. Phys.* **1989**, *90*, 1007−1023.

(59) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796−6806.

(60) Foresman, J. B.; Frisch, A. E. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc.: Pittsburgh, PA, 1996.

(61) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian, Inc., Wallingford, CT, 2004.

(62) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.1*; Gaussian, Inc., Wallingford, CT, 2009.

(63) Krygowski, T. M.; Cyranski, M. K. *Chem. Rev.* **2001**, *101*, 1385−1420.

(64) Popelier, P. L. A. *Atoms in Molecules: An Introduction*; Prentice-Hall: Harlow, England, 2000.

(65) Biegler-König, F.; Schönbohm, J. (advices by Bader, R. F. W.) *AIM2000: A Program to Analyse and Visualize Atoms in Molecules, Version 2*; Büro für Innovative Software, C. Streibel Biegler-König Fröbelstrasse 68 33604 Bielefeld, Germany, 2002.

(66) Schleyer, P. v. R.; Freeman, P. K.; Jiao, H.; Goldfuß, B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 337−340.

(67) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao., H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.

(68) Fallah-Bagher-Shaidaei, H.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Org. Lett.* **2006**, *8*, 863−866.
(69) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842−3888.
(70) Nyulaszi, L.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6872−6875.
(71) Cyranski, M. K.; Krygowski, T. M.; Katritzky, A. R.; Schleyer, P. v. R. *J. Org. Chem.* **2002**, *67*, 1333−1338.
(72) Krygowski, T. M. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 70−78.
(73) Cyranski, M. K. *Chem. Rev.* **2005**, *105*, 3773−3811.
(74) Shahamirian, M.; Cyranski, M. K.; Krygowski, T. M. *J. Phys. Chem. A* **2011**, *115*, 12688−12694.
(75) Palusiak, M.; Krygowski, T. M. *Chem. Eur. J.* **2007**, *13*, 7996−8006.
(76) Ebrahimi, A. A.; Ghiasi, R.; Foroutan-Nejad, C. *J. Mol. Struct. (THEOCHEM)* **2010**, *941*, 47−52.
(77) Mohajeri, A.; Ashrafi, A. *Chem. Phys. Lett.* **2008**, *458*, 378−38378.
(78) Campanelli, A. R.; Domenicano, A.; Ramondo, F. *J. Phys. Chem. A* **2003**, *107*, 6429−6440.