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Energetic and Geometric Characteristics of Substituents, Part 3: The Case of NO₂ and NH₂ Groups in Their Mono-Substituted Derivatives of Six-Membered Heterocycles

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Abstract: Substituted heterocyclic arenes play important roles in biochemistry, catalysis, and in the design of functional materials. Exemplary six-membered heteroaromatic molecules, that differ from benzene by inclusion of one heteroatom, are pyridine, phosphorine, arsabenzene, and borabenzene. This theoretical study concerns the influence of the heteroatom present in these molecules on the properties of substituents of two types: electron-donating (ED) NH₂ group and electron-accepting (EA) NO₂ group, attached at the 2-, 3-, or 4-position. The effect is evaluated by the energy of interaction (E_{rel}) between the substituent and the substituted system and electronic properties of the substituents described by the charge of the substituent active region (cSAR) index. In addition, several geometric descriptors of the substituent and heteroaromatic ring, as well as changes in the aromaticity, are considered. The latter are assessed using the Electron Density of Delocalized Bonds (EDDBs) property of delocalized π electrons. The obtained results show that the electronegativity (EN) of the heteroatom has a profound effect on the EA/ED properties of the substituents. This effect is also reflected in the geometry of studied molecules. The E_{rel} parameter indicates that the relative stability of the molecules is highly related to the electronic interactions between the substituent and the heteroarene. This especially applies to the enhancement or weakening of π -resonance due to the EN of the heteroatom. Additionally, in the 2-heteroarene derivatives, specific through-space *ortho* interactions contribute to the heteroatom effects.

Keywords: substituent effect; heterocyclic compounds; substituent energy; aromaticity; EDDB

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1. Introduction

Substituent effects are among the most important intramolecular interactions in organic chemistry and related fields. Traditionally, for a given series of substituted systems, the relations between the properties of the reaction center and the characteristics of the substituents are used for their analysis. The first quantitative approach to the description of the substituent effect was proposed by Hammett [1,2]. Most often, Hammett substituent constants or alike are used to characterize the substituent effect quantitatively [3]. It is also known that the properties of the substituent itself depend both on its position in the transmitting moiety and on the nature of the reaction site. The first case can be represented by the different substituent constants for the *para* and *meta* positions, while the substituent constants σ^+ and σ^- , characterizing the substituent effects in molecules with positively and negatively charged reaction sites, respectively, are an example of the second case. This is known as the reverse substituent effect [4]. For any substituent in any system, it can be quantified using the charge of the substituent active region (cSAR) concept [5,6].

The aim of this study is to determine to what extent the heteroatom in the six-membered aromatic ring affects the stability of the substituted system, as well as the electronic and geometric properties of the strongly electron-attracting and electron-donating substituents, the nitro and amino groups, respectively. The following heteroarenes were

selected as the studied substituted moieties: pyridine, phosphorine, arsabenzene, and borabenzene, shown in Figure 1. The atomic properties of heteroatoms are summarized in Table 1. It should be emphasized that each of these atoms may interact with the substituent differently, especially when it is in the *ortho* position. The nitrogen, phosphorus, and arsenic atoms have an electron pair in the plane of the ring, which can cause specific proximity interactions with the substituent. Boron, on the other hand, has an empty orbital in this plane, which is a Lewis acidic site open to interaction with a Lewis base. Additionally, As is the only atom in this group that has a filled 3d subshell.

Figure 1. Studied mono-heterocyclic analogues of benzene (C_5H_5-E , where $E = B, N, P, As$).

Table 1. Selected characteristics of ring atoms. χ_P , Pauling electronegativity, α , polarizability and η , chemical hardness.

Atom	Covalent Radius [7]/Å	Atomic Radius [8]/Å	χ_P [9]	α [10]/a.u.	η [11]/eV
C	0.76, 0.73, 0.69 *	0.6513	2.55	11.3 ± 0.2	10.00
N	0.71	0.5427	3.04	7.4 ± 0.2	14.53
P	1.07	0.9922	2.19	25 ± 1	9.74
As	1.19	1.2431	2.18	30 ± 1	8.99
B	0.84	0.8141	2.04	20.5 ± 0.1	8.02

* Csp^3 , Csp^2 , and Csp , respectively.

Nitrogen heteroarenes are extremely important in biochemistry, and they also occur in nucleic acid bases (pyrimidine and imidazole fragments) [12]. Many derivatives of N-heterocycles have found application in medicinal chemistry. For example, various quinoline derivatives are used in the treatment of malaria [13]; Imatinib, which contains pyridine and pyrimidine fragments, is used as a protein-targeted anticancer drug. Another important anticancer drug, Bortezomib, contains a substituted pyrazine ring [14]. Knowing the properties of substituents is an important aspect considered while designing such compounds. Nitro-, amino-, and chloro-derivatives of pyridine, as well as of N-heterocycles with more endocyclic N atoms, i.e., pyrimidine, pyrazine, and triazine, were the subject of Part 2 in this article series [15]. Phosphorine and arsabenzene were synthesized and characterized, for the first time, 50 years ago [16]. Since their discovery, they have been the subject of much experimental and theoretical research [17–21]. These heterocycles (C_5H_5E , $E =$ element of group 15), like pyridine, can bind to metals via a lone pair at E (η^1 complexes) and/or via a π -electron sextet (η^6 complexes). Of course, the type of complex formed depends on the substituents attached to the ring. However, in the case of unsubstituted phosphabenzene and arsabenzene, the η^6 complexes predominate [22–24]. Phosphorine-based complexes and their use in homogeneous catalysis were summarized in a review by Le Floch [25]. Interestingly, it has been suggested that polycyclic aromatic hydrocarbons (PAHs) containing an endocyclic N atom (PANHs) may be responsible for the characteristic 6.22 μm feature in the emission spectra of some galaxies [26,27]. For this reason, astrophysicists predict that about 1 percent of the nitrogen in our Universe may exist in form of PANHs in an interstellar medium of galaxies. Similarly, the existence of P-containing PAHs in the interstellar medium (PAPHs) has been proposed and plausible mechanisms of their formation have been investigated [28]. However, such PAPHs have not yet been detected [29].

Borabenzene has not been separated in a pure form. However, several of its donor–acceptor complexes, in which a Lewis basic site of a ligand donates electrons on the empty orbital of the boron atom, have been synthesized. Already in 1985, the borabenzene–

pyridine complex was obtained and characterized using the XRD method [30]. This complex has also been studied by ab initio quantum chemistry methods, with emphasis on the B–N interaction, as well as IR and UV-vis spectra [31]. More recently, complexes of borabenzene with the N-heterocyclic carbenes Ime4 [32] and ImeS [33] were prepared, and their chemical reactivity was investigated [34]. Another example is the 1,3,5-tris (η^6 -borabenzene- η^5 -cyclopentadienylcobalt) benzene, which was deposited on a Cu(111) surface and studied using STM measurements and DFT calculations, revealing its possible application in molecular spintronics [35]. Additionally, the results of ab initio calculations showed that replacing carbon atoms in PAHs by bonded B and N atoms may modify PAHs' optical properties, leading to interesting nonlinear optical behavior of such compounds [36].

According to the Hückel rule, cyclic compounds are aromatic when they are planar and have $4n + 2$ delocalized π electrons (where n is a positive integer). All studied heterocycles (Figure 1), following this rule, have six delocalized π electrons in the ring, just like benzene. However, the presence of a heteroatom in the ring has different consequences [37]. As shown in Table 2, energetic (Aromatic Stabilization Energy, ASE), electronic (electron density in the ring critical point, ρ_{RCP} , and Electron Density of Delocalized Bonds, EDDb), [38,39] magnetic (Nucleus-Independent Chemical Shift, NICS) [40], and geometric (Bird, I_6 , and Harmonic Oscillator Model of Aromaticity, HOMA) [41,42] aromaticity indices do not speak exactly the one voice. Phosphorus and arsenic analogs of pyridine exhibit lower aromaticity than benzene and pyridine. However, for these two subgroups, there is significant inconsistency between the different aromaticity indices. For example, the ρ_{RCP} , the HOMA, and one of the ASE [43] descriptors suggest higher aromaticity of the pyridine ring than that of benzene. On the other hand, the Bird index indicates that phosphorine is less aromatic than arsabenzene. Therefore, it is also interesting to investigate the effect of the substituent and its position on the aromaticity of the ring.

Table 2. Selected characteristics of ring atoms.

Compound	ASE [37]/kcal·mol ^{−1}	ASE [43]/kcal·mol ^{−1}	ρ_{RCP} [37]	NICS(1) _{zz} [37]/ppm	NICS(1) [44]/ppm	I_6 [37]	I_6 [45]	HOMA [46]	EDDb _p (π) *
C ₆ H ₆	37.36	42.5	0.025	−30.4	−12.8	100	100	0.990	5.305
C ₅ H ₅ N	32.65	45.7	0.027	−30.2	−12.4	90.9	85.7	0.995	5.248
C ₅ H ₅ P	30.21	36.9	0.020	−28.0	−11.4	69.1	74.1	0.913	5.102
C ₅ H ₅ As	29.05	34.9	0.018	−26.8	−11.4	82.1	66.9		5.012
C ₅ H ₅ B								0.9082 [47]	5.044

* Data generated in this work.

2. Materials and Methods

According to previous research [48–50], B3LYP functional [51] with the 6-311++G(d,p) [52] basis set was chosen as a computational method. Calculations were performed in the Gaussian 16, Revision C.01 program [53]. For all systems, frequency calculations were performed after geometry optimization. No imaginary frequencies were found. The geometries obtained in the calculations are in good agreement with the experimental data (X-ray diffraction, microwave spectroscopy) for unsubstituted pyridine [54] and arsabenzene [55]. Some differences in C–C bond lengths (~ 0.015 Å) and C–P–C angles ($\sim 1^\circ$) are observed in phosphorine; however, the uncertainties of experimental parameters are quite large [56]. A comparison of the calculated and experimental geometries is presented in Table S1 (Supplementary Materials).

Substituents were described in terms of the relative energy of the substituent, $E_{rel}(X)$. It is defined as an energetic effect of the homodesmotic reaction shown in Scheme 1.

Scheme 1. Studied mono-heterocyclic analogues of benzene (C_5H_5-E , where $E = B, N, P, As$).

Hence, it can be calculated from Equation (1):

$$E_{\text{rel}}(X) = E(RX) + E(\text{benz}) - E(\text{benz}X) - E(R), \quad (1)$$

where $E(RX)$, $E(\text{benz})$, $E(\text{benz}X)$, and $E(R)$ are the electronic energies of the substituted R-X system, benzene (the reference system), X-substituted benzene, and unsubstituted R heterocycle, respectively. Hereinafter, $E_{\text{rel}}(X)$ is abbreviated as E_{rel} . This parameter evaluates the energetic effect of interactions between the substituent and the substituted system. Negative values correspond to the stabilization of the molecule with respect to the reference system, whereas the positive values indicate destabilizing interactions.

The charge of the substituent active region (cSAR) index [5,6] was used to characterize the electron-accepting/donating properties (EA/ED) of the substituents. For the X substituent, it was calculated according to Equation (2):

$$\text{cSAR}(X) = q(X) + q(C_{\text{ipso}}), \quad (2)$$

where $q(X)$ is a sum of charges of atoms at substituent X, and $q(C_{\text{ipso}})$ is the atomic charge at the *ipso* carbon atom. In line with previous studies [4,57,58], atomic charges were evaluated using the Hirshfeld method [59]. Additionally, it should be noted that Hirshfeld charges have been documented to be almost insensitive to the basis set improvement [60]. The interpretation of the cSAR(X) values is as follows: the electron-donating strength of the X group increases with the increase in cSAR(X), whereas the electron-accepting strength decreases.

Natural population analysis was performed using NBO 6.0 software (Theoretical Chemistry Institute, University of Wisconsin, Madison) [61]. Quantum theory of atoms in molecules (QTAIM) calculations and analyses were performed using AIMAll software [62].

For analysis of non-covalent interactions, a reduced density gradient (RDG) function was used [63]. This function is a modification of electron density (ρ) and its gradient ($\nabla\rho$) (Equation (3)).

$$\text{RDG} = \frac{1}{[2 \cdot (3\pi)^2]^{1/3}} \cdot \frac{|\nabla\rho(r)|}{\rho(r)^{4/3}} \quad (3)$$

Analysis of RDG isosurfaces is frequently used [64,65] to visualize the non-covalent interactions between groups of atoms. Additionally, the character of these interactions can be assessed by looking at the value of $\text{sign}(\lambda_2) \cdot \rho$ (where λ_2 is the second eigenvalue of the Hessian matrix of ρ) at each point of the isosurface. Negative values indicate strong non-covalent interactions such as hydrogen bonding, values around zero indicate weak ones (van der Waals), and positive values indicate non-bonding ones, e.g., the steric repulsion. Algorithms for the calculation of RDG implemented in Multiwfn software were used [66]. Visualization of isosurfaces was done in the VMD program [67].

Aromaticity of substituted heteroarenes was evaluated using the Electron Density of Delocalized Bonds (EDDB) [39]. This descriptor derives from partitioning of the one-electron density matrix in the natural atomic orbital basis into components representing localized bonds (EDLB(r)) and delocalized bonds (EDDB(r)) [38]. EDDB(r) proved to be a good descriptor of local and global aromaticity in several systems, including hydrocarbons [68] and metallacycles [69]. In this study, the component of EDDB(r) coming from π -electron delocalization, EDDB $_{\pi}$ (π), was used. Additionally, the values obtained for the

unsubstituted systems were subtracted from those for the substituted heteroarenes. Such a difference indicates a change in aromaticity due to the substituent effect and is further denoted as ΔEDDB_π (π).

The geometry of substituents and heterocyclic rings was evaluated using the parameters presented in Figure 2.

Figure 2. Various geometric parameters describing the substituent (a) and the substituted system (b).

3. Results

The discussion of the results is presented in four parts. The first is devoted to the energetic and electronic characteristics of substituents. The second part deals with proximity effects. Then, changes in the structural properties of the substituents and the substituted ring are discussed. The last part concerns the influence of substituents on π -electron delocalization. For all studied systems, the obtained values of the considered descriptors of the substituent effect are collected in Table S2 (Supplementary Materials).

3.1. Energetic and Electronic Substituent Effects

The energy of a substituent (E_{rel}), Scheme 1, characterizes interactions of a substituent with a given substituted molecule. As mentioned above, its value indicates whether and to what extent these interactions are stabilizing or destabilizing. In order to allow comparisons with well-known systems for substituent effects, its values were calculated relative to benzene as the reference system. E_{rel} can be considered as a global substituent effect descriptor, i.e., an indication of the energetic consequence of all intramolecular interactions induced by substitution. The local descriptor, cSAR, indicates changes induced in the electronic structure of a chosen molecular fragment, e.g., a substituent or a substituted ring.

It should be emphasized that in 2-, 3-, and 4-derivatives, different types of interactions occur (Figure 3). For the 2- position (*ortho* interaction), through-bond and through-space proximity interactions between O (in NO_2) or H (in NH_2) and the endocyclic heteroatom are expected. In 3-derivatives, the proximity interaction with the heteroatom is replaced by an interaction with the C-H group, thus representing a situation similar to the substituted benzene reference system. Therefore, it can be assumed that in these cases the energetic substituent effect is only a consequence of inductive and resonance interactions with the heteroatom in the *meta* position. Regarding 4-derivatives, a similar assumption can be made, but in this case, the *para* interaction occurs.

Figure 3. Possible interactions of the substituent ($\text{Y} = \text{H}$ or O) with the substituted system. Through-bond electronic interactions are marked in blue; through-space proximity interactions in red.

As shown in Figure 4, the NO₂ and NH₂ groups show a significantly different, in most cases opposite, energetic substituent effect. The nitro derivatives in all cases but one have positive E_{rel} values, which indicates lower stability with respect to nitrobenzene.

Figure 4. Obtained E_{rel} values (in kcal/mol) for heteroarenes substituted in the 2-, 3-, or 4-positions by the nitro (left) or the amino (right) groups. The shown abbreviations for molecule names are used hereafter.

In the case of nitro derivatives of pyridine, E_{rel} grows in the sequence 2- > 3- > 4-nitropyridine (the abbreviations shown in Figure 4 are further used). This indicates that the resonance-driven para interaction between NO₂ and N_{endo} results in a substantial destabilization. Since the *meta* resonance effect is negligible [3], the E_{rel} of 2.63 kcal/mol in N-3-NO₂ can be associated with a decrease in aromaticity due to substitution, which is discussed in Section 3.4. Although the *ortho* interaction is associated with the intuitively repulsive NO $\cdots$ N_{endo} contact, E_{rel} has the lowest value. Moreover, it has recently been shown by analyzing the RDG function that this interaction is not purely repulsive and has an attractive contribution from van der Waals interaction [15]. Thus, the highest stability of N-2-NO₂ can result from the strongest inductive effect due to the close distance between NO₂ and N_{endo} and the proximity interaction. However, it should be remembered that all the E_{rel} values for NO₂-substituted N-heterocycles are positive. Thus, exchanging one of the CH groups for N in nitrobenzene leads to destabilization.

Amino derivatives of pyridine are additionally stabilized compared with aniline (Figure 4). The stability sequence is N-2-NH₂ > N-4-NH₂ > N-3-NH₂. The *meta* interaction leads to a negligible energetic effect, while the *para* interaction has roughly the same absolute value as for N-4-NO₂. However, with an opposite sign—in this case, stabilization occurs. The *ortho* interaction in N-2-NH₂ leads to the most stabilizing interactions between the substituent and the pyridine ring. A possible cause is the enhancement (with respect to aniline) of inductive and resonance effects by introducing the N atom in the *ortho* position. Another possible explanation could be the presence of the N $\cdots$ HN proximity interaction. This interaction, however, has been recently proven to be extremely weak and has not been detected by means of RDG and AIM analyses in any six-membered N-heteroarene [15].

Borabenzene derivatives are interesting cases, as the boron atom is the least electronegative in the studied series (Table 1). Additionally, an empty 2p orbital of B in the ring plane allows the formation of a donor–acceptor interaction with electron-rich atoms (Lewis basic sites) of the *ortho* substituent. Nitro substitution in the 2-position is associated with a small positive energetic effect (1.12 kcal/mol), in the 3-position with a negligible effect (0.13 kcal/mol), and in the 4-position with a moderately negative effect (−2.07 kcal/mol). However, the amino substitution in the 2- and 4-positions leads to a large destabilizing effect (5.00 and 5.38 kcal/mol, respectively). This is due to changes in the electron-donating

power of the amino group, shown in Figures 5 and 6, which are discussed below. On the other hand, interactions between the substituent and the substituted system in 3-B-NH₂ are slightly more favorable than in aniline (−0.40 kcal/mol).

Figure 5. Obtained cSAR(X) values for heteroarenes substituted in the 2-, 3-, or 4-positions by the nitro (left) or amino (right) groups; data for nitrobenzene and aniline included.

Figure 6. Resonance structures for E-4-NO₂ and NH₂ systems, E = B, As, P, N.

Phosphorine and arsabenzene contain group 15 heteroatoms of similar electronegativity but differing in other atomic properties (see Table 1). The trends in E_{rel} values are similar for these heterocycles. For both amino and nitro substitution, E_{rel} decreases in the order of 2-, 3-, 4-, meaning that the ortho derivatives are the least stable and the para ones are the most. The difference between NO₂ and NH₂ systems lies in the signs of E_{rel} . In all NO₂ derivatives, the interaction between the substituent and the heteroarene is less, while in all NH₂ derivatives it is more energetically favorable than in their corresponding benzene derivatives.

Electron-accepting and electron-donating properties of the NO₂ and NH₂ groups, respectively, can be assessed using the cSAR(X) approach (Figure 5). It can be noticed immediately that in *meta* derivatives the variability in cSAR(X) is small, and the values are close to the values for nitrobenzene and aniline. Although the differences are small, in all cases the values for the NO₂ group in heterocycles are slightly higher than in benzene.

A similar trend occurs in the case of NH_2 derivatives. Thus, the $\text{cSAR}(\text{X})$ indicates that in the *meta* derivatives of all heterocycles, the NH_2 group is slightly more electron-donating than in aniline, and NO_2 is slightly less electron-withdrawing than in nitrobenzene.

In *ortho* and *para* systems, where the resonance effect of substituent on heteroatom occurs, the changes in $\text{cSAR}(\text{X})$ and E_{rel} in N and B heteroarenes are highly related to the electronegativity of these atoms. This can be illustrated by the resonance structures of the NH_2 and NO_2 -substituted heteroarenes (Figure 6). The E heteroatoms that are more electronegative than C, i.e., N, will more likely accept electrons donated by the substituent, increasing the negative charge of E (Figure 6, structures (5)–(8)). Hence, when such a heteroatom is in the *ortho* or *para* position, the electron-donating properties of the NH_2 group may be enhanced and the resonance effect strengthened, which, as can be seen from the negative E_{rel} values (Figure 4), also stabilizes the molecule. On the other hand, the electronegative N_{endo} atom is not prone to increase its positive charge (Figure 6, structures (1)–(4)). Hence, the withdrawal of electrons by resonance in nitro derivatives is weakened, and positive values of E_{rel} are observed (Figure 4).

Conversely, when the E heteroatom is less electronegative than C, i.e., B, the resonance effect of the electron-accepting group is enhanced while that of the electron-donating group is weakened. This is well illustrated by the energetic and electronic descriptors of the substituent effect in the B-2- NH_2 and B-4- NH_2 systems. The E_{rel} values reveal the strongest destabilizing intramolecular interactions (among the studied systems), which result in the greatest weakening of the electron-donating power of the amino group. The latter is documented by the lowest $\text{cSAR}(\text{NH}_2)$ values (Figure 5).

In As and P heteroarenes, for $\text{X} = \text{NO}_2$ there is a strong enhancement of the EA properties for the 2-substitution. Regarding the 4-derivatives, the NO_2 is more EA than in the 3-derivatives, but only slightly. In the case of $\text{X} = \text{NH}_2$, the amino group in the 2-derivatives is the least electron-donating, and in the 4-derivatives has slightly more ED ability than in the 3-derivatives.

Therefore, the electronegativity of the heteroatom in the arene ring highly influences the interactions within the substituted system. Depending on the type of substituent—electron-withdrawing (NO_2) or electron-donating (NH_2)—interactions can be enhanced or weakened with respect to benzene derivatives. This is reflected in both the energetic (E_{rel} , Figure 4) and electronic (cSAR , Figure 5) properties of the substituents. In general, in the substituted *ortho* and *para* nitro and amino series, the order of changes in the energetic and electronic properties of the substituent follows the changes in electronegativity of the heteroatoms (Table 1), as shown in Figure 7. Moreover, $\text{cSAR}(\text{X})$ and E_{rel} are well correlated for the series: *para* NO_2 and NH_2 and *ortho* NH_2 ($R^2 > 0.98$). In *para* systems, the proximity effects are similar to those in benzene derivatives (i.e., with C-H groups), and the resonance between heteroatom and substituent is strong. Consequently, the energetic effect of the intramolecular interactions is almost entirely due to the enhancement or weakening of the resonance effect by the heteroatom, which causes changes in the electron-accepting/donating ability of the substituent. The strongest resonance effects, as expected, occur for B-4- NO_2 and N-4- NH_2 derivatives. The slopes of the linear relation between $\text{cSAR}(\text{X})$ and E_{rel} are 0.0191 and -0.0131 for nitro and amino systems, respectively. Their signs are consistent with those of Hammett's substituent constants ($\sigma_p = 0.78$ and -0.66) [3]. In *ortho* systems, the resonance effect is also strong, but different proximity effects also occur. The fact that the *ortho* series of NH_2 is well correlated while that of NO_2 is not can be explained by proximity effects. They are more significant for the bulky NO_2 group than for the small NH_2 group, which is also noticeable from the distance of the benzNH_2 and benzNO_2 points, in Figure 7, from the NH_2 and NO_2 *ortho* line series, respectively. Namely, the benzNO_2 point is much further from the corresponding series than the benzNH_2 point. Moreover, for the NH_2 group, the slopes for the *ortho* and *para* series are almost the same. However, in the first case, the ranges of E_{rel} and $\text{cSAR}(\text{NH}_2)$ variability are ~ 1.4 times greater than in the second. This is mainly due to the much greater stabilization of NH_2 interactions with the ring nitrogen atom in the *ortho* position than in the *para* position.

Small variability in *meta* derivatives is consistent with the well-known fact that the *meta* substituent effects are weaker [3].

Figure 7. Relationships between E_{rel} and $cSAR(X)$ for ortho-, meta-, and para- series of amino and nitro derivatives of monosubstituted heteroarenes. Points representing nitro- (benzNO₂) and aminobenzene (benzNH₂) are shown (including them in the corresponding para series: $y = 0.0188x - 0.1471$, $R^2 = 0.962$, and $y = -0.131x + 0.1041$, $R^2 = 0.974$, respectively).

3.2. Proximity Effects

The heteroatom in position 2 provides an opportunity for various through-space interactions. In such a case, the asymmetric proximity of the substituent causes asymmetry of the two NO (of NO₂) or NH (of NH₂) bonds. Hence, the difference in length (Figure 8) or the electron density at the bond critical point (Figure S1) between these two bonds can indicate the strength of the proximity interaction. The bond depicted with (E) is the bond closer to the heteroatom, whereas (H) is the bond further away from the heteroatom.

Figure 8. Dependence between the two NO (for X = NO₂) (a) or NH (for X = NH₂) (b) bond lengths. The $y = x$ line is included to illustrate the case of symmetric proximity interactions.

As shown in Figure 8a, in the case of the NO₂ substitution, systems deviating from the $y = x$ line are the 2- and 3- NO₂ heteroarenes. The systems above this line (marked with green labels) have a longer NO(E) bond than NO(H) bond, which indicates an attraction between the O and E heteroatom. The systems below the line (marked with red labels) represent an opposite case, thus indicating a repulsion between these atoms. The highest difference occurs in the B-2- NO₂ system. The NO bond pointing towards the B atom is elongated due to a donor–acceptor interaction between the lone pair of O atom and the empty 2p orbital of B. This interaction is detected by the second-order perturbation theory analysis in the NBO theory [70] visible in the results of the NBO calculation as the energy of the intramolecular donor–acceptor interaction O(LP) → B(LP*), $E = 2.76$ kcal/mol, and no steric energy. However, the RDG analysis (at the 0.50 isosurface) does not reveal the B⋯O contact as an interaction (Figure 9). Interestingly, a similar NO bond elongation is observed in As- and P-2- NO₂ systems, but to a much lesser extent, and the RDG analysis shows E⋯O contacts ($E = \text{As or P}$). Moreover, in these cases, according to the NBO results, no donor–acceptor interactions were detected, while the steric energies were 1.61 and 2.55 kcal/mol, respectively. The noticeable difference in the NO(E) bond elongations between these two systems may be related to the difference in the polarizability of As and P atoms (Table 1). In N-2- NO₂, the bond closer to the N_{endo} atom is much shorter, indicating a steric strain caused by the repulsion between the lone pairs of O and N_{endo} atoms. The estimated (NBO) steric energy is 2.09 kcal/mol, while no donor–acceptor interaction was detected, contrary to the RDG results (Figure 9). It can therefore be concluded that the results of the RDG and NBO analyses do not speak the same voice. The 3-NO₂ systems lie slightly below the $y = x$ line; therefore, despite the presence of two CH interactions, there is still some asymmetry. It follows that the interaction with the CH group of the ring closer to the As, P, or N heteroatom causes a slight shortening of the NO(E) bond.

Figure 9. RDG isosurfaces (isovalue = 0.50) of the studied ortho, nitro, and amino heteroarenes. Isosurfaces are colored according to the value of $\text{sign}[\lambda_2(r)] \cdot \rho(r)$; highly negative values in blue (indicating strong non-covalent interaction), values around zero in green (van der Waals interaction), and highly positive values in red (steric repulsion).

As regards the NH_2 -substituted heteroarenes, the differences between the NH bond lengths are an order of magnitude smaller (up to 0.002 Å, full data available in Table S2) compared with the NO of NO_2 (up to 0.014 Å). This indicates that the proximity interactions of the NH_2 group are relatively weak. The only system in which the NH(E) bond is elongated is N-2- NH_2 (by 0.0017 Å, Figure 8), suggesting an attractive $\text{NH}\cdots\text{N}$ interaction. Additionally, according to the literature, it can be assumed that the electronic interactions in the *ortho* and *para* positions are alike. Thus, this assumption leads to the conclusion that the energy of $\text{NH}\cdots\text{N}$ interaction is ~ 3.7 kcal/mol. However, this is not supported by the geometry (angle $\text{NH}\cdots\text{N}$ equals 71.2°) and the results of the RDG analysis (Figure 9). Such a low value of the angle is well below the minimum threshold for the $\text{AH}\cdots\text{B}$ angle in the H-bond of $\sim 110^\circ$ suggested by Desiraju [71]. On the other hand, the shortening of NH(E) in relation to NH(H) is observed in B-2- NH_2 and As-2- NH_2 (by 0.0020 and 0.0017 Å, respectively) and negligible in P-2- NH_2 and P-, B-, and As-3- NH_2 (by up to 0.0006 Å).

None of the proximity interactions have a bond critical point. However, the results of the RDG analysis (Figure 9) indicate that the proximity interactions of the bulky NO_2 group are stronger than in the case of NH_2 . This explains the lack of correlation observed in the *ortho* NO_2 series in Figure 7. Furthermore, no single proximity interaction of the NH_2 group could be observed in the RDG plots (Figure 9) and in the NBO analysis results.

3.3. Geometric Properties of Substituents and the Substituted Moiety

The changes in structural properties (of both substituents and rings) are shown in Figures 10–12. The values obtained are summarized in Table S2.

Figure 10. The CN bond lengths in nitro (a) and amino (b) substituted heteroarenes.

The greatest variability in d_{CN} of nitro derivatives is observed in the *ortho* series (0.073 Å) due to the proximity effects. Smaller variability is observed in the *para* series (0.02 Å), and the smallest in the *meta* one (0.012 Å). Moreover, for the N, P, and As series, except for N-3- NO_2 , the CN bonds are longer than in nitrobenzene. However, this bond is significantly shorter in the B-2- and B-4- NO_2 derivatives (by 0.045 and 0.013 Å, respectively). This confirms the strongest resonance effect of the NO_2 group, even resulting in its stabilizing intramolecular interaction in the B-4- NO_2 molecules, i.e., negative E_{rel} values (Figure 4). The CN bond in P-2- NO_2 is slightly longer than in As-2- NO_2 (Figure 10), despite the larger size of the As atom (Table 1). This again indicates that the NO_2 proximity interactions with As may be more favorable than with P.

Figure 11. Obtained $\Delta\angle\text{CEC}$ values for heteroarenes substituted in the 2-, 3-, or 4-positions by the nitro (left) or amino (right) groups; data for nitrobenzene and aniline included.

Figure 12. $\angle\text{YNY}$ angles in the nitro ($Y = \text{O}$) (a) and pyramidal angle of the amino group in amino-substituted (b) heteroarenes.

In the case of the amino derivatives, the greatest variability in d_{CN} occurs in the *para* series (0.038 Å) and, opposite to the case of the nitro substitution, it is greater than in the *ortho* series (0.019 Å). This fact suggests that stronger proximity interactions of the NO₂ group than of the NH₂, as revealed by RDG analysis (Figure 9), result in more significant changes in the geometry of the NO₂ group. The greatest elongation of the CN bond in the B-4-NH₂ system confirms the strongest disturbance of the observed resonance effect. In turn, the shortening of this bond in N-2- and N-4-NH₂ derivatives, in relation to the CN bond in aniline, shows the enhancement of the resonance effect. The *meta* series has a very small variability of d_{CN} (0.004 Å). In this case, the d_{CN} values are very similar to aniline. This shows that the heteroatom in the *meta* position scarcely changes the strength of the reverse substituent effect. It can also be noticed in Figure 5, where the electron-donating properties of the amino group show little variability in the *meta* series.

In the case of *ortho*-nitro-substituted heteroarenes, changes in the $\angle\text{CEC}$ angle (Figure 11) are much more significant than for the amino substitution. This is another consequence of the strong NO₂ proximity effects. Additionally, *ortho*-nitro and amino substitution causes opposite changes in this angle. Amino substitution of the studied heterocycles in the *para* position leads to the highest changes in the $\angle\text{CEC}$. It is also worth noting that they all are negative, meaning that the $\angle\text{CEC}$ of all heterocycles decreases

upon substitution. Since in the *para* position no steric effects occur, this can be solely associated with the electronic interactions with the substituted system. Interestingly, the greatest change occurs in B-4-NH₂, whereas the lowest change occurs in N-4-NH₂. As mentioned earlier, the B and N heteroatoms have the opposite effect on resonance between the substituent and heterocycle. This can also be noticed by looking at the $\angle\text{ONO}$ angle (Figure 12a). Here, the values are in most cases similar to that of nitrobenzene. However, for B-4-NO₂, N-2-NO₂, and N-4-NO₂ they deviate from the others. The smallest $\angle\text{ONO}$ occurs in B-4-NO₂ and the highest in N-2 and N-4 derivatives. It follows that the enhancement of π -resonance is associated with a decrease in $\angle\text{ONO}$ relative to the nitrobenzene, while an increase indicates a disruption. The greater $\angle\text{ONO}$ in N-2 than in N-4 may also result from proximity interactions.

Since the amino group is non-planar, it is worth analyzing its pyramidalicity instead of the $\angle\text{HNNH}$ angle. In Figure 12b it can be noticed that in 2- and 4- derivatives of B-heterocycles, the NH₂ group has the highest pyramidalicity. This can be associated with an increase in the p character of a hybrid orbital at the N atom, again due to the resonance disruption. For the opposite reason, among the *para* systems, the NH₂ group is the most planar in the pyridine derivative. Moreover, only for this series a very good correlation of pyramidalicity with E_{rel} and cSAR was found ($R^2 > 0.99$, Figure S2).

The substituent also affects the angle α in the ring (at the *ipso* carbon atom, Figure 2). The nitro group increases this angle with respect to the unsubstituted system, while the amino group has the opposite effect. Thus, changes in α (expressed by $\Delta\alpha$) are positive and negative numbers, respectively (see Figure S3). They mainly result from the resonance effect and proximity interactions mentioned above.

Additionally, the correlation coefficients between all pairs of considered parameters for the *para* series (benzene derivatives were also taken into account) are gathered in Table S3. For example, the pyramidalicity of the NH₂ group in this series is well correlated with $\Delta\alpha$, $\Delta\angle\text{CEC}$, d_{CN} , cSAR(X), and E_{rel} .

3.4. Substituent Influence on π -Electron Delocalization

For heteroarenes, the aromaticity of a substituted moiety is an important indicator of the changes induced within it upon substitution. In all cases, the substituted heteroarenes are less aromatic than the unsubstituted systems (Figure S4), as shown by ΔEDDB_p (π) in Figure 13. The smallest decreases in aromaticity occur in systems where the interactions between the substituent and the heteroatom are weak (for the reasons discussed earlier; Figure 6). Such systems are all *meta* and *ortho/para*, in which the heteroatom hinders the resonance effect of the substituent (N-2-NO₂, N-4-NO₂, B-4-NH₂, B-2-NH₂). The strongest decreases in aromaticity occur in the systems where the heteroatom enhances the resonance effect: N-2-NH₂, N-4-NH₂, B-2-NO₂, and B-4-NO₂. Other highly affected systems are the rings in the 2- and 4- P and As systems, but this is more pronounced for NH₂ substitution than for NO₂ substitution. Moreover, in general, the amino group causes greater aromaticity changes than the nitro one. The only exceptions are the above-mentioned B-2- and B-4 derivatives.

Plots between ΔEDDB_p (π) and E_{rel} (Figure 14) show that for the *para*-NO₂ series, and for the NH₂ *ortho*- and *para*-NH₂ series, changes in aromaticity due to substitution correlate with E_{rel} . This shows that the changes in the stability of systems in which the heteroatom and substituent can interact by resonance are, to a high extent, related to changes in the aromaticity of the substituted heterocyclic ring. The poor determination coefficient ($R^2 = 0.53$) for the *ortho*-NO₂ series may result from the aforementioned strong proximity interaction of this group, which is another factor affecting the stability of the molecule. For the *para* series, a higher slope can be observed in the case of NO₂ substitution than in the case of NH₂ substitution (0.088 and 0.051, respectively); similarly for the dependence ΔEDDB_p (π) on cSAR(X) (Figure 14c,d). This is consistent with the higher absolute slope value for the NO₂ series of the cSAR(X) vs. E_{rel} relationship (Figure 7). So, we can say that the resonance effect of the nitro group is stronger than that of the amino substituent,

just like in aromatic hydrocarbons. Moreover, the dependence of $\Delta\text{EDDB}_p(\pi)$ on $\text{cSAR}(X)$ shows a good correlation between changes in aromaticity and electronic properties of the substituent for the *ortho*- and *para*- NH_2 series. However, in the case of NO_2 derivatives, in the *para* series a good correlation is observed ($R^2 = 0.979$), while a worse correlation is observed for the *ortho* systems ($R^2 = 0.733$). This fact can be explained by the proximity effects of the nitro group, as shown above.

Figure 13. Obtained $\Delta\text{EDDB}_p(\pi)$ values for heteroarenes substituted in the 2-, 3-, or 4-positions by the nitro (a) or amino (b) group; data for nitrobenzene and aniline included.

Figure 14. Dependences of $\Delta\text{EDDB}_p(\pi)$ on E_{rel} and $\text{cSAR}(X)$ for the NO_2 (a,c) and NH_2 (b,d) substituted heterocycles.

4. Conclusions

This study aimed to investigate to what extent the heteroatom in the six-membered aromatic ring affects the energetic and geometric properties of the strongly electron-attracting or electron-donating substituents, i.e., the nitro and amino groups, respectively. For this purpose, pyridine, phosphorine, arsabenzene, and borabenzene, substituted at the 2-, 3-, or 4-position, were chosen as the substituted moieties. The energetic effect of interactions between the substituent and the substituted system was estimated using the relative energy parameter E_{rel} . This parameter is based on the energetic effect of an appropriate homodesmotic reaction with benzene as a reference system and enables the comparison of the properties of the substituents. To characterize the electron-accepting/donating properties of substituents, as well as their changes, the charge of the substituent active region (cSAR) model was used. Aromaticity of heteroarenes was evaluated using the Electron Density of Delocalized Bonds (EDDB) descriptor.

The NO_2 and NH_2 groups show a significantly different, in most cases opposite, energetic substituent effect. The nitro derivatives in all cases but one have positive E_{rel} values, which indicate lower stability with respect to nitrobenzene. The opposite is the case with the amine derivatives; negative E_{rel} values show greater stability with respect to aniline. In both cases, the exceptions are borabenzene derivatives, namely B-4- NO_2 , B-2- NH_2 , and B-4- NH_2 . This is due to the strengthening or weakening of the resonance effect by the boron atom (the least electronegative in the studied series), respectively.

In general, in the substituted *ortho* and *para* nitro and amine series, the order of changes in the energetic and electronic properties of the substituent is related to the changes in electronegativity of the heteroatoms. These properties of NO_2 and NH_2 in a given heterocycle are almost entirely due to the enhancement or weakening of the resonance effect by the heteroatom. The greatest strengthening occurs for the *ortho* and *para* B- NO_2 and N- NH_2 systems, while the greatest weakening occurs for the B- NH_2 and N- NO_2 derivatives.

In *ortho* systems, in addition to the resonance effect, there are also different proximity effects. They can cause significant changes in the energetic, electronic, and structural properties of the substituent. The easiest way to observe asymmetric proximity interactions is to compare the lengths of both NO (or NH) bonds in the nitro (amino) group. The largest difference occurs in the B-2- NO_2 system. The NO bond towards the B atom is elongated due to a donor–acceptor interaction between the lone O pair and the empty 2p orbital B. In contrast, in N-2- NO_2 , the bond closer to the N_{endo} atom is much shorter, indicating a steric strain caused by the repulsion between the lone pairs of O and N_{endo} atoms. The differences between the NH bond lengths of the NH_2 group are significantly smaller (up to 0.002 Å) compared with the NO bond lengths of the NO_2 group (up to 0.014 Å). Thus, the proximity effects are much greater for the bulky NO_2 group than for the small NH_2 group, which is also confirmed by the RDG analysis results. It is also reflected in the fact that the correlations between cSAR, E_{rel} , and ΔEDDBP (π) for *ortho* NO_2 systems are worse than for NH_2 derivatives.

The above-mentioned effects are accompanied by changes in the structural properties of both the substituents and the rings. The substitution of the group at different positions of the heteroarene affects the CN bond lengths, the CEC and α (at the *ipso* carbon) angles in the ring, and the pyramidity of the NH_2 group. The greatest changes in structural parameters in relation to benzene derivatives are generally observed for 2- and/or 4-derivatives.

Substituted heteroarenes are less aromatic than unsubstituted systems, while the latter are less aromatic than benzene. In general, the amino group causes greater aromaticity changes than the nitro one. The only exceptions are the B-2- and B-4 derivatives (B hinders the resonance effect of the NH_2 substituent, hence the smaller changes). The greatest decreases in aromaticity occur in the systems in which the heteroatom enhances the resonance effect: N-2- NH_2 , N-4- NH_2 , B-2- NO_2 , and B-4- NO_2 . Moreover, for *para* series, higher slopes (or their absolute values) of the linear dependences ΔEDDBP (π) on E_{rel} , ΔEDDBP (π) on cSAR(X), and cSAR(X) on E_{rel} are observed in the case of NO_2 substitution than for the

NH₂ one. It can therefore be said that the resonance effect of the nitro group is stronger than that of the amine group, as is the case with aromatic hydrocarbons.

In summary, the ring heteroatom and the substitution position can significantly change the electron-attracting and electron-donating abilities of the substituent. Moreover, the substituent can significantly affect the electronic and structural properties of the ring.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/sym14010145/s1>, Figure S1: Dependence between the electron densities at critical points of two NO (for X = NO₂) or NH (for X = NH₂) bonds; Figure S2: Dependences of the pyramidalicity of the amino group on its cSAR and energetic descriptor, E_{rel} , for the studied systems; Figure S3: Obtained $\Delta\alpha$ values for heteroarenes substituted in the 2-, 3-, or 4-positions by the nitro or amino groups; Figure S4: Obtained EDDBP (π) values for heteroarenes unsubstituted and substituted in the 2-, 3-, or 4-positions by the nitro or amino groups; Figure S5: Relationships between electron densities at the critical point of CN bonds and their length for the studied nitro and amine derivatives; Table S1: Comparison of experimental and calculated geometries of pyridine, arsabenzene, and phosphorine; Table S2: Values of all calculated parameters for all studied systems; Table S3: Correlation coefficients for all *para* derivatives, including benzene derivatives (nitrobenzene and aniline, respectively).

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