

Relation between the Substituent Effect and Aromaticity

Tadeusz M. Krygowski,^{*,†} Krzysztof Ejsmont,[‡] Beata T. Stepien,[†] Michał K. Cyrański,[†]
Jordi Poater,[§] and Miquel Solà[§]

Department of Chemistry, University of Warsaw, L. Pasteura 1, 02-093 Warsaw, Poland, Institute of
Chemistry, University of Opole, Oleska 48, 45-052 Opole, Poland, and [§]Institut de Química
Computacional and Departament de Química, Universitat de Girona, E-17071, Girona, Catalonia, Spain

tmkryg@chem.uw.edu.pl

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Molecular geometries of benzene and its 18 monosubstituted derivatives were optimized at B3LYP/6-311+G** level of theory. The changes of π -electron delocalization of the benzene fragment were estimated by use of aromatic stabilization energies (ASE) based on different homodesmotic reaction schemes, geometry-based HOMA model, magnetism-based NICS, NICS(1), NICS(1)_{zz}, and an electronic delocalization index, PDI, derived from the AIM theory. Apart from aromatic stabilization energies the other descriptors of aromaticity vary to a very small extent, indicating high resistance of the π -electron structure to the substituent effect. This is somewhat analogous to a tendency of benzene systems to retain their initial π -electron structure during the reaction course that leads to aromatic substitution.

Introduction

To what extent does a substituent influence the π -electron delocalization in the benzene ring? Benzene is a system that fulfills all the criteria of aromaticity,¹ and hence it is widely considered to be the archetype of the phenomenon. On the other hand, the system plays an important role in the definition of the Hammett substituent constants² and other quantitative descriptors³ of the substituent effects. Despite these facts, the problem of interrelation between the substituent effect and the involved changes of the π -electron delocalization structure commonly described by aromaticity has never been investigated in a systematic and correct way.

The definition of the substituent effect involves a division of the system into three parts:⁴ the substituent that is changed (denoted as X), the functional group on which the studied process takes place (Y), and the transmitting moiety, R (most often benzene). Numerically the substituent effects are frequently described by various substituent constants³ and are clearly related to the electronic properties of the group being the substituent X, the reaction process site Y, and the transmitting moiety.⁴

Another possibility is the definition based on monosubstituted benzene derivatives, taking into account interactions of the substituent with the ring. This idea is best summarized in a review by Katritzky and Topsom,⁵ where the infrared intensity based substituent constants σ°_R were introduced. For most recent results for this see ref 6. The substituent effect is basically considered as composed of two components: the inductive and the resonance effects. The former one is always present and acts both via the bonds and through the space.⁷ In the case of monosubstituted benzene derivatives⁸ it has been associated with electronegativity of the substituent,⁹ e.g., Huheey electronegativity.¹⁰ The substituent resonance effect¹¹ works only in the case of π -electron systems and depends on the system to which the substituent is attached, i.e., on the choice of the probe

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group. Hence a variety of scales of resonance constants is observed.^{3c,4b,12–14}

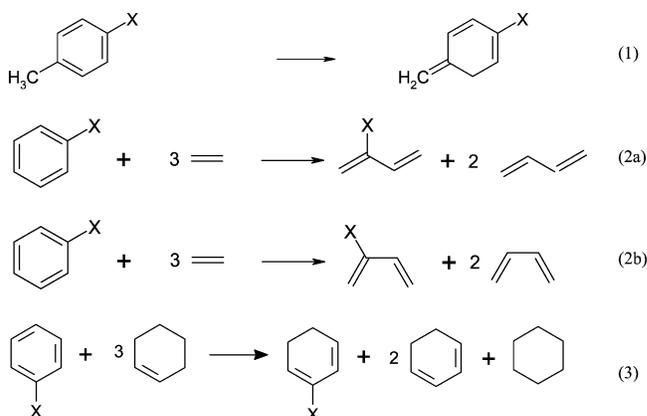
An increased stability of the cyclic π -electron delocalized system was the main feature that distinguished the aromatic compounds from other classes of species. This was first quantified for benzene by Pauling and Sherman¹⁵ and soon later by Kistiakovsky.¹⁶ Using different thermochemical reaction schemes they estimated very similar values of “resonance energy” (RE) for benzene (about 36 kcal/mol). This enhanced stability was defined as a difference in energy between the energy of a compound with cyclic π -electron delocalization and a model reference system with (almost) no π -electron delocalization.¹⁷ The idea has been extended onto other cyclic π -electron systems¹⁸ and presently the term “aromatic stabilization energy” (ASE) is preferred when referring to an increased stability of a system considered to be aromatic.¹⁹ There are many ways of estimating ASE, by applying the isodesmic and preferable homodesmotic^{19,20} reactions, which however may lead to different results for a given system. For instance, in the case of benzene the differences in ASE may vary over 50 kcal/mol.²¹ The differences are due to either (i) the choice and definition of reference molecules and the reaction scheme applied, or (ii) inaccuracies in the energies (both experimental and theoretical) employed. It has been pointed out^{21c} that the ASE values may lead to valuable information about the extent of the π -electron delocalization, provided that the model reaction is thoroughly well constructed and homogeneous in the structure variation for the whole set of systems.

The purpose of this report is to address the problem formulated at the beginning of this introduction, i.e., to analyze the relation between aromaticity (described by indices of aromaticity) and the substituent effect for the benzene ring in a series of its monosubstituted derivatives.

Methods

Four different schemes were used to estimate the aromatic stabilization energies (hereafter abbreviated

SCHEME 1



ASE), as shown in Scheme 1. Equation 1 is the reaction scheme based on the isomerization method recommended recently by Schleyer and Pühlhoffer²² for evaluation of the aromatic stabilization energies. The use of tautomeric equilibria comparisons as the criteria for aromaticity is expected to be of general applicability²³ and to offer a useful quantitative method for investigation of the phenomenon. This method involves the difference between the total energies of two species: a methyl derivative of the aromatic system and its nonaromatic exocyclic methylene isomer. Although the stabilization energies of methyl-substituted benzene derivatives are mostly estimated in this way, and the reaction scheme is rather isodesmic than homodesmotic, we expect to obtain creditable results for further comparisons with homodesmotic reaction schemes (2, 3). Dewar and Schmeising²⁴ proposed that the stability of an aromatic system should refer to an acyclic analogue, e.g., butadiene-1,3. Equation 2(a,b)²⁵ is a very common homodesmotic approach for estimation of aromatic stabilization of benzene. However, a problem arises whether it is more reasonable to use for comparison fragments that most resemble those in the ring, or if the lowest energy conformers should be considered. The advantage of the former is that no extra rotation of the fragment is needed, but it may also show up significant repulsive interactions that are not present in the ring.²² Although the question has been discussed in the literature, no definite answer has yet been given.²⁶ The difference between the *trans* and *cis* conformations of butadiene is ca. 3.5 kcal/mol (at B3LYP/6-311+G** level of theory), which has an impact on the substantial difference in the ASE values of benzene. In this paper we used both *trans* (eq 2a) and *cis* (eq 2b) conformers of butadiene as the reference systems. In both cases they were conformationally unstable, and hence the estimated stabilization energies were perturbed (at least) by unbal-

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anced strain and conjugation. Contrary to eq 2, eq 3 is a relatively well strain-balanced homodesmotic approach, where all reference compounds are six-membered rings computed in their most stable conformation. This is an adapted version of the reaction proposed by Schleyer.^{19b,22} The systems with largely enhanced aromatic stabilization energies (positive values of ASE) are aromatic, whereas those with strongly negative ASE values are considered to be antiaromatic.

The nucleus independent chemical shift (NICS) was used as a descriptor of aromaticity from the magnetic point of view. The index is defined as the negative value of the absolute magnetic shielding computed at ring centers²⁷ or another interesting point of the system.²⁸ The NICS denoted as NICS(1) is calculated 1 Å above the center and is expected to better reflect the π -electron structure details.²⁹ Another descriptor is the “out of plane” component of the NICS tensor computed at 1 Å above the ring center [denoted here as NICS(1)_{zz}], which was found to be a good measure for the characterization of the π system of the ring.³⁰ Rings with highly negative values of NICS are quantified as aromatic by definition, whereas those with positive values are anti-aromatic.

Geometry is another very important source of information about aromaticity. Among many easily accessible quantitative definitions of aromaticity based on the geometric criterion, the HOMA (harmonic oscillator model of aromaticity) model was suggested to be the most reliable one.³¹ The HOMA model is defined as³²

$$\text{HOMA} = 1 - \frac{\alpha}{n} \sum (R_{\text{opt}} - R_i)^2 \quad (4)$$

where n is the number of bonds taken into the summation; α is a normalization constant (for CC bonds $\alpha = 257.7$) fixed to give HOMA = 0 for a model nonaromatic system and HOMA = 1 for the system with all bonds equal to the optimal value R_{opt} , assumed to be realized for fully aromatic systems (for CC bonds R_{opt} is equal to 1.388 Å);³³ and R_i stands for running bond lengths.

The degree of π -electron delocalization can be quantified³⁴ on the basis of Bader’s “atoms in molecules” (AIM)^{35,36} theory by using the delocalization index (DI),

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$\delta(A,B)$, that is obtained by double integration of the exchange-correlation density over the basins of atoms A and B:³⁵

$$\delta(A,B) = - \int_A \int_B \Gamma_{XC}(\vec{r}_1, \vec{r}_2) d\vec{r}_1 d\vec{r}_2 - \int_B \int_A \Gamma_{XC}(\vec{r}_1, \vec{r}_2) d\vec{r}_1 d\vec{r}_2 = -2 \int_A \int_B \Gamma_{XC}(\vec{r}_1, \vec{r}_2) d\vec{r}_1 d\vec{r}_2 \quad (5)$$

The basin of an atom in the AIM theory is defined as the region in real space bound by zero-flux gradient surfaces in the one electron density, $\rho(\mathbf{r})$, or by infinity.³⁶ Quantitatively, δ provides an idea of the number of electrons delocalized (or shared) between atoms A and B.^{35b,37} Recently, the mean of all DI of *para*-related carbons in a given six-membered ring, the so-called *para*-delocalization index (PDI),^{34b} has been defined as a new aromaticity criterion based on electron delocalization. It has been shown^{34b} that there are satisfactory correlations between NICS, HOMA, and magnetic susceptibilities with PDI for a series of planar PAHs. The higher PDI indices follow a higher absolute value of NICS and higher HOMA values, thus reflecting greater aromaticity.

Molecular geometries of benzene and its 18 monosubstituted derivatives were optimized by use of Gaussian 98³⁸ at the B3LYP/6-311+G** level of theory. All structures corresponded to minima at the B3LYP/6-311+G** level, with no imaginary frequencies. The energies were corrected by the B3LYP/6-311+G** zero point energies. The GIAO/HF/6-31+G* method was used for the NICS, NICS(1), and NICS(1)_{zz}. The HOMA values were also based on B3LYP/6-311+G** optimized geometries. PDI values were calculated at the B3LYP/6-311G**//B3LYP/6-311+G** level of theory with the AIMPAC package³⁹ using the following expression:

$$\delta(A,B) = 2 \sum_{ij} S_{ij}(A) S_{ij}(B) \quad (6)$$

which has been derived by substituting the exchange-correlation density, $\Gamma_{XC}(\vec{r}_1, \vec{r}_2)$, in eq 5 by its corresponding expression for a monodeterminantal wave function given by:⁴⁰

$$\Gamma_{XC}(\vec{r}_1, \vec{r}_2) = - \sum_i \sum_j \phi_i^*(\vec{r}_1) \phi_i(\vec{r}_2) \phi_j(\vec{r}_1) \phi_j^*(\vec{r}_2) \quad (7)$$

In eq 6, the summations run over all the occupied molecular spin-orbitals; $S_{ij}(A)$ is the overlap integral between molecular orbitals ϕ_i and ϕ_j within the basin of atom A. The numerical accuracy of the AIM calculations

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TABLE 1. Aromaticity Indices: ASE(1), ASE(2), ASE(3), NICS, NICS(1), NICS(1)_{zz}, HOMA, and PDI

X	ASE(1)	ASE(2a)	ASE(2b)	ASE(3)	NICS	NICS(1)	NICS(1) _{zz}	HOMA	PDI
NN ⁺	35.8	31.0	36.2	28.8	-10.6	-11.2	-28.6	0.96	0.080
NO	31.3	26.9	30.3	33.1	-9.8	-11.2	-29.9	0.98	0.091
NO ₂	33.4	28.5	31.7	31.3	-10.9	-11.7	-30.5	0.99	0.096
CN	33.5	24.9	31.9	31.6	-10.3	-11.6	-30.9	0.98	0.096
COCl	34.2	28.0	32.2	30.9	-9.9	-11.5	-30.1	0.98	0.095
COCH ₃	34.1	27.9	31.5	31.3	-9.7	-11.4	-30.4	0.98	0.097
COOCH ₃	33.5	28.0	32.2	32.0	-9.8	-11.4	-30.4	0.98	0.097
COOH	33.7	27.9	33.1	31.7	-9.7	-11.4	-30.5	0.98	0.097
CHO	32.3	26.4	28.9	33.0	-9.6	-11.4	-30.6	0.97	0.095
CONH ₂	33.4	26.4	31.1	31.6	-9.9	-11.7	-31.3	0.98	0.098
CCH	33.4	24.8	31.6	32.1	-10.1	-11.4	-30.4	0.97	0.096
Cl	34.6	23.7	30.1	31.9	-10.7	-11.5	-30.5	0.99	0.099
F	33.1	22.6	29.3	32.2	-11.7	-11.8	-31.1	0.99	0.098
H	33.2	24.7	30.7	32.7	-9.7	-11.5	-31.9	0.99	0.103
Ph	33.5	25.8	32.2	32.7	-9.3	-10.9	-30.0	0.98	0.098
CH ₃	32.6	23.7	30.4	32.1	-9.7	-11.3	-31.0	0.98	0.100
OCH ₃	35.0	21.8	28.2	31.1	-10.8	-11.3	-30.2	0.98	0.094
NH ₂	33.2	24.6	29.6	33.3	-9.8	-10.5	-28.3	0.98	0.093
OH	34.1	22.5	29.2	32.1	-10.8	-11.3	-29.9	0.99	0.095
mean	33.6	25.8	31.1	31.8	-10.1	-11.3	-30.3	0.98	0.096
esd	1.0	2.4	1.8	1.1	0.62	0.30	0.82	0.01	0.005
variance	1.0	5.6	3.2	1.1	0.38	0.09	0.67	8.5 × 10 ⁻⁵	2 × 10 ⁻⁵

TABLE 2. Substituent Constants:^{3c} σ^+ , σ^- , σ_m , σ_p , σ_R° , R^+ and R^-

X	σ^+/σ^-	σ_m	σ_p	σ_R° ^a	R^+/R^-
NN ⁺	3.43	1.76	1.91		1.85
NO	1.63	0.62	0.91	0.25	1.14
NO ₂	1.27	0.71	0.78	0.17	0.62
CN	1	0.56	0.66	0.09	0.49
COCl	1.24	0.51	0.61	0.21	0.78
COCH ₃	0.84	0.38	0.5	0.22	0.51
COOCH ₃	0.75	0.37	0.45	0.16	0.14
COOH	0.77	0.37	0.45	0.29	0.43
CHO	1.03	0.35	0.42	0.24	0.70
CONH ₂	0.61	0.28	0.36	0.13	0.35
CCH	0.53	0.21	0.23	-0.09	0.31
Cl	0.19	0.37	0.23	-0.22	-0.31
F	-0.03	0.34	0.06	-0.34	-0.52
H	0	0	0	0	0
Ph	-0.18	0.06	-0.01	-0.1	-0.30
CH ₃	-0.31	-0.07	-0.17	-0.1	-0.32
OCH ₃	-0.78	0.12	-0.27	-0.43	-1.07
NH ₂	-1.3	-0.16	-0.66	-0.47	-1.38
OH	-0.92	0.12	-0.37	-0.4	-1.25

^aData for σ_R° were taken from ref 5.

were assessed using two criteria: (i) the integration of the Laplacian of electron density ($\nabla^2\rho(r)$) within an atomic basin must be close to zero; (ii) the number of electrons in a molecule must be equal to the sum of all of the electron populations of a molecule and also to the sum of all of the localization indices and half of the DIs in the molecule.^{37b} For all atomic calculations, the integrated absolute values of $\nabla^2\rho(r)$ were always less than 0.001. For all molecules, the errors in the calculated number of electrons were always less than 0.01.

Results and Discussion

Table 1 presents the indices of aromaticity: ASE values (eqs 1, 2a,b, and 3), NICS, NICS(1), NICS(1)_{zz}, HOMA,³² and PDI,^{34b} whereas Table 2 presents substituent constants used in the analyses.^{3c}

Despite substantial variation of the nature of the substituent (the σ_p varying from -0.66 for strongly electron-donating NH₂ substituent to $\sigma_p = 1.91$ for strongly electron-accepting NN⁺ one), no dramatic changes in the π -electron structure of the benzene ring is observed. This may be better quantified by high, and not much differentiated, values of the descriptors of aromaticity: HOMA, NICS, and PDI for substituted systems. The mean value of HOMA is 0.98, which is very close to the value of benzene (HOMA = 0.99), while the variation of the descriptor described by the standard deviation is only 0.01. The NICS indicators are also in line with this finding. The smallest variation is observed for NICS(1), the mean value of which differs only by 0.2 ppm from the value for the unsubstituted system. Note that only NICS (1)_{zz} indicate the highest aromaticity among all substituted species, the two other (NICS and NICS(1)) fail in this matter. The small differentiation of the π -electron structure is consistent with the resistance of the benzene system against the changes in π -electron structure as observed from the point of view of reactivity. In typical reactions the benzene system tends to retain its initial π -electron structure and the substitution reaction is preferred against addition.⁴¹ This so-called aromatic substitution¹ is an important criterion of aromaticity, always considered by synthetic organic chemists. Interestingly, the aromatic stabilization energies, considered as the most basic operational criterion influencing the reactions and much of physicochemical behavior, estimated here by using three independent approaches, deviate much more. The largest differences, in the range of about 9–10 kcal/mol, are found in the case of the schemes based on substituted butadiene-1,3 as the reference systems (eq 2a,b). Although both reactions suggest that the highest stabilization energy is for Ph-NN⁺ (ASE(2a) = 31.0 kcal/mol and ASE(2b) = 36.2 kcal/mol) and the smallest is for anisole (ASE(2a) = 21.8 kcal/mol and ASE(2b) = 28.2 kcal/mol) in the whole set, no further good agreement exists. For instance, following the reac-

(41) Yamdagni, R.; McMahon, T. B.; Kebarle, P. *J. Am. Chem. Soc.* **1974**, *96*, 4035–4035.

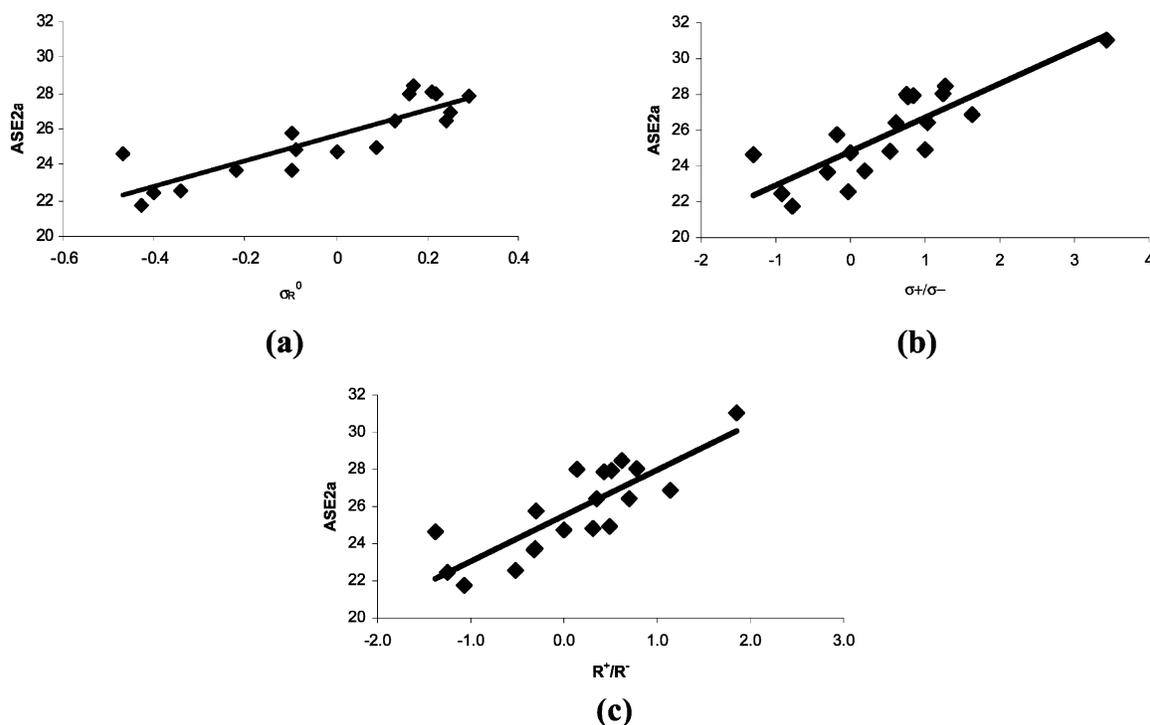


FIGURE 1. Dependence of ASE(2a) vs σ_R^0 (a) σ^+/σ^- (b), and R^+/R^- (c). The correlation coefficients are 0.870, 0.830, and 0.829, respectively.

tion scheme 2b the formyl group (strong electron-accepting substituent) destabilizes the benzene ring to a similar extent as methoxy-, hydroxy-, and amino groups (the electron-donating substituents). The point is that the lowest energy reference systems are conformationally unstable and hence the energies are biased by additional effects such as unbalanced *syn-syn* interactions, unbalanced strain, hyperconjugation, etc, which have no roots in cyclic π -electron delocalization. Also, the other reaction schemes are biased by factors that vary from case to case. The value of ASE(3) is similar for formyl-benzene, nitroso-benzene, and amino-benzene, ranging for these cases between 33 and 33.3 kcal/mol. The high value for the amino substituent may be the result of a difference in pyramidalization of this group in the aromatic and the reference system, thus influencing the final stabilization energy value. For ASE(1) additional interactions between the electron-donating methyl group and the substituents have to be taken into account. It is important to note that a rough tendency however exists: the electron-accepting substituents stabilize the benzene ring and electron-donating ones destabilize it. Does this mean that the electron-accepting groups make the delocalization in the ring more effective? In other words: do these substituents cause some systems to be more stable than benzene itself? HOMA, NICS(1)_{zz}, and PDI values do not support these findings, suggesting that higher values of energy are artifacts of not fully balanced homodesmotic (and isodesmic) reactions. However, a point has to be made that the differences in stabilization energy values of benzene are at the same level as other weak interactions present in the structure of benzene (and reference systems). The correlation analyses between the aromatic stabilization energies and substituent constants reveal that only ASE(2a) correlates reasonably well with σ_R^0 ,

the absolute values of σ^+ (for electron-donating substituents) and σ^- (for electron-accepting ones), and R^+/R^- . The absolute scale of substituents is necessary, since they perturb the π -electron delocalization, decreasing the aromaticity independently of their electron donating or accepting character. Figure 1 presents these dependences.

Very small variation of cyclic π -electron delocalization, at the level of other subtle interactions, has an impact on weak dependencies of correlations between HOMA, NICS, NICS(1), and NICS(1)_{zz} on substituent constants. The best regression was found only for HOMA plotted against the absolute values of σ^+ (for electron-donating substituents) and σ^- (for electron-accepting ones), with the correlation coefficient (cc) of 0.67. All other regressions were much worse, despite using many various scales of substituent constants:^{3c} σ^+ and σ^- , σ_R^0 .⁵ Apart from possible influences of other subtle effects, the disagreement may also be due to the nature and the origin of most substituent constants. Except the σ_R^0 value,⁵ all other values refer to the transfer of the substituent effect from the substituent to the reaction site. Thus the benzene ring is characterized mostly as the transmitting moiety where the changes, at least in energy, are substantially bigger. For example, the difference in enthalpy of dissociation of substituted *p*-nitroso- and *p*-amino benzoic acid in the gas phase is about 12 kcal/mol.⁴¹ Oppositely to this, the aromaticity indices presented in this paper refer to the π -electron delocalization of the ring.

Contrary to the former relationships, all scatter plots employing the indices based on the PDI model correlate much better.

Figure 2a presents the dependence of the aromaticity index PDI on the absolute values of σ^+ and σ^- . Again,

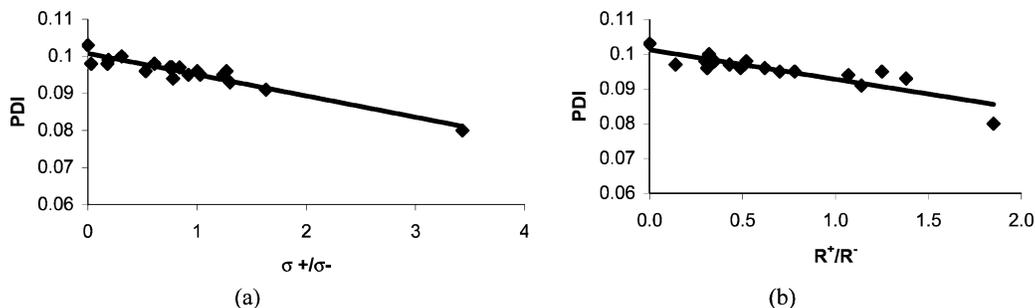


FIGURE 2. Dependence of PDI plotted against (a) the absolute values of σ^+ and σ^- , and (b) the absolute values of R^+ and R^- . The correlation coefficients are -0.95 and -0.87 , respectively.

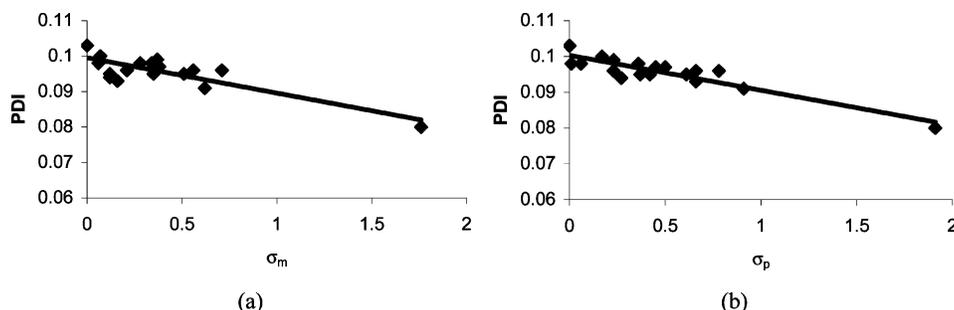


FIGURE 3. Dependencies of PDI vs σ_m (a) and σ_p (b). The correlation coefficients are -0.83 and -0.91 , respectively.

the σ^+ are used for electron-donating substituents and σ^- for electron accepting ones because, despite the electronic character of the substituent, it causes a decrease of the PDI value when attached to the ring. The correlation coefficient of this dependence is equal to -0.95 . The σ^+ and σ^- values are complex substituent constants that contain both inductive (field) and resonance effects. If the substituent constants σ^+ and σ^- are replaced by R^+ and R^- , Figure 2b, then the correlation with PDI is clearly worse: the correlation coefficient is -0.87 , because the descriptors of the substituent contain no inductive contribution. It is clear that both the inductive and the resonance effects operate effectively in the interactions between the substituent and the π -electron structure of the ring. Similar findings may be found on the basis of the dependencies of PDI vs σ_m and σ_p , as shown in Figure 3. The correlation coefficients of these dependencies are -0.83 and -0.91 , respectively, pointing out the importance of the resonance. It is generally accepted that the ratio of the inductive and the resonance effects in σ_m is around 1:0.33⁴² and between 1:1⁴³ and 1:1.14⁴⁴ for σ_p constants.

We have also noted good dependencies between the absolute values of σ^+/σ^- and (i) the average of all DI of *ortho*-related carbons in a given six-membered ring, the DI(1,2), and (ii) the average of all DI of *meta*-related carbons in a given six-membered ring, the DI(1,3). The correlation coefficients for these regressions are 0.84 and 0.74, respectively, indicating that not only PDI but also other delocalization indices account for substituent effects having an impact on the π -electron delocalization in the ring of monosubstituted benzene derivatives.

The small variation in indices of aromaticity describing in fact small changes in π -electron delocalization indicates a strong resistance of the system against the perturbation caused by a substituent. It recalls in a qualitative way a tendency of the π -electron system in the benzene ring to maintain its electron structure unchanged during aromatic substitution. However the aromatic substitution commonly occurs via mechanisms in which the σ complex is formed first,⁴⁵ and this is considered to be nonaromatic. Nevertheless the HOMA for sp^2 fragment of the cation (four CC bonds) is still very high, 0.93 (based on geometry optimized at MP2/4-31G*⁴⁶). The value of NICS calculated in the center of the ring is equal to -1.54 , whereas $NICS(1) = -6.59$ and $NICS(1)_{zz} = -15.3$. For benzene these values are -9.7 , -11.5 , and -31.9 , respectively. It means that the σ complex still exhibits some aromatic character.

Conclusions

The substituents attached to benzene influence only very weakly the π -electron delocalization in the ring, as shown by the small variation of the geometry-based index of aromaticity HOMA, the magnetism-based indices NICS, $NICS(1)$, and $NICS(1)_{zz}$, and the electronic delocalization indices PDI. This finding reflects well the tendency of aromatic systems to retain their initial π -electron structure during the reaction course, leading to aromatic substitution. The stabilization energies derived from homodesmotic reaction schemes vary to a greater extent due to the imbalanced additional effects, such as strain, conjugation, repulsive interactions, etc, which contaminate the estimated ASE values. In this

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context, the aromatic stabilization energies do not seem to be good descriptors of the changes of π -electron delocalization in substituted benzenes. Contrary, the delocalization indices PDI^{34b} derived from the AIM theory³⁶ seem to be very successful for this purpose. The aromaticity index PDI correlates nicely with substituent constants.

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Supporting Information Available: Sum of electronic and zero-point energies, total energies, and the Cartesian coordinates at B3LYP/6-311+G** for all analyzed systems. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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