

# Relation between the substituent effect and aromaticity. Part II. The case of *meta*- and *para*-homodisubstituted benzene derivatives<sup>†,‡</sup>

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**ABSTRACT:** Thirty-two mono- and homodisubstituted benzene derivatives (*meta* and *para* isomers) were optimized at B3LYP/6-311+G\*\* level of theory. The descriptors of cyclic  $\pi$ -electron delocalization: aromatic stabilization energies (ASE), substituent effects stabilization energies (SESE), NICS and HOMA values were estimated for those systems. Generally, for monosubstituted systems the electron accepting substituents either stabilize the systems or weakly destabilize them. In contrast, the electron donating substituents destabilize the systems in all cases. The  $\pi$ -electron stabilization/destabilization effects for *para*-di-homosubstituted benzene derivatives are much stronger than those for the *meta* analogs. Copyright © 2006 John Wiley & Sons, Ltd.

## INTRODUCTION

Since the introduction of the Hammett equation ( $\sigma\rho$ ),<sup>1</sup> and its numerous modifications<sup>2–4</sup> the substituent effects have been successfully interpreted in a quantitative way. The effect of a changeable substituent X on the reaction (or process) site Y through the transmitting moiety R was a subject of numerous studies.<sup>5</sup> The purpose of most of them was to quantify the substituent effect on some chemical or physicochemical property in a particular series of compounds. This provided information about the mechanism of chemical reaction and/or electronic interpretation for changes of the chemical/physicochemical property in question.

Much less attention has been paid to the substituent effect on the transmitting moiety R (usually aromatic). Few studies, mostly by *infrared* spectroscopy, were devoted to determining the resonance interactions of substituents with the ring.<sup>6</sup> When the substituents have the opposite electronic properties, the resonance substituent effect is usually interpreted in terms of an increase of the quinoid structure among canonical structures applied to describe the

interactions.<sup>7</sup> Recently the changes in  $\pi$ -electron delocalization in the ring as a result of the substituent effect were studied by using of aromaticity indices.<sup>8</sup>

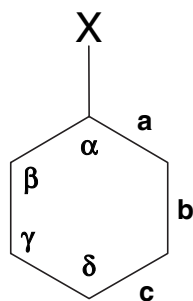
Following the Hellmann–Feynman theorem<sup>9</sup> distribution of electronic density in the molecule determines the forces acting on the nuclei, which in turn define the geometry of the molecule in question. Thus precise geometry may be an important (and useful) source of information to deduce the electronic structure of the substituted systems.<sup>10</sup> Detailed analyses of experimental geometry (bond angles) of monosubstituted benzene derivatives lead to a linear correlation of the ipso angle (labeled  $\alpha$ ) on Huheey's<sup>11</sup> group electronegativity<sup>12</sup> and Taft's inductive substituent constants.<sup>13</sup> Interpretation of these dependences was based on the Bent–Walsh rule,<sup>14</sup> which also predicts a linear dependence of  $\alpha$  on the ipso-ortho CC bond, labeled  $\alpha$  on Scheme 1. This kind of dependence was found based on optimized geometries (at B3LYP/6-311+G\*\* level of theory) of monosubstituted benzene derivatives.<sup>15</sup> Factor analysis<sup>16</sup> applied to bond angles of these systems revealed that the main factor was composed almost exclusively of changes in  $\alpha$  and  $\beta$  angles. This factor correlated nicely with various scales of group electronegativity and hence a new scale of electronegativity has been proposed.<sup>17</sup> Roughly, the values of  $\alpha$  angle in monosubstituted benzene derivatives may be used as a measure of group electronegativity: the greater is  $\alpha$  the more electronegative is the group. It is important to note that the above-mentioned geometry-based analyses refer mostly to the  $\pi$ -electron changes.

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Scheme 1

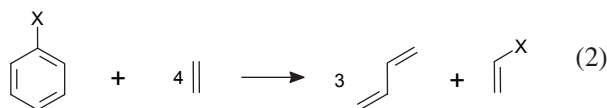
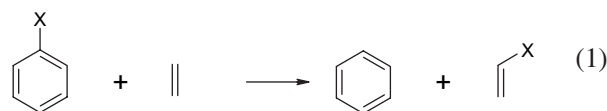
Very recently monosubstituted benzene derivatives were studied to answer the question: to what extent do the substituents affect the cyclic  $\pi$ -electron delocalization in the ring? The analysis of variation of aromaticity indices such as: (1) energy-based criterion—aromatic stabilization energy, (abbreviated hereafter ASE),<sup>18</sup> (2) magnetism-based nucleus independent chemical shift (NICS),<sup>19</sup> geometry-based HOMA<sup>20</sup> and delocalization index PDI<sup>21</sup> led to the conclusion that except ASE-values, varying in the range of  $\sim 8$  kcal/mol (for benzene ASE, based on *trans* butadiene, is equal to 22.4 kcal/mol),<sup>22</sup> all other indices vary insignificantly and only ASE-values and PDI exhibited some correlation with substituent constants.<sup>8</sup> The analysis of geometry-based HOMA of 74 monosubstituted benzenes revealed that for some substituents a decrease of aromaticity of the ring is significantly high.<sup>8b</sup> This is the case of substituents with empty  $2p_z$  orbital (e.g.,  $\text{CH}_2^+$ ) or the  $2p_z$  orbital with an electron pair (as in  $\text{CH}_2^-$ ). In these cases substituents interact strongly with the ring leading to a substantial lowering of the extent of  $\pi$ -electron delocalization. The HOMA illustrates this point very well: it drops down to 0.72 and 0.65, respectively, whereas for benzene it is equal to 0.99.

The purpose of this paper is to analyze the consequences of the substituent effect on  $\pi$ -electron delocalization in *para*- and *meta*-homodisubstituted benzene derivatives. The main problem to solve is: to what extent does the homodisubstitution decrease the stability of the systems in question?

## METHODOLOGY

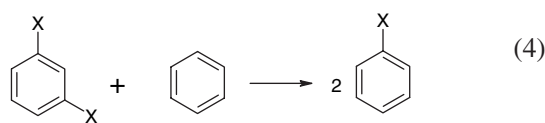
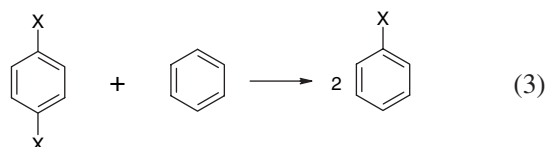
The geometries were computed at B3LYP/6-311+G\*\* DFT level of theory.<sup>23</sup> All species corresponded to minima at the B3LYP/6-311+G\*\* level, with no imaginary frequencies. The GIAO/B3LYP/6-311+G\*\* method was used for the NICS calculations. The HOMA values were also based on molecular geometries optimized at the B3LYP/6-311+G\*\*.

SESE and ASE values for monosubstituted benzene derivatives were computed using Eqn (1) and Eqn (2), respectively.

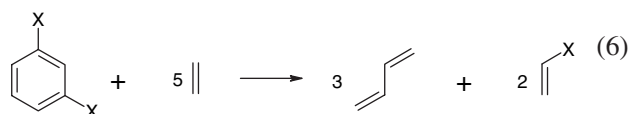
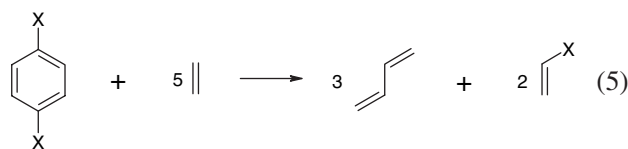


In Eqn (1) the SESE is estimated using ethylene derivatives as the reference,<sup>8c,24</sup> and expresses the difference in substituent effect on  $\pi$ -electron delocalization in the aromatic ring and the olefinic system. ASE in Eqn (2) differs from the classical treatment with 2-substituted *cis*- or *trans*-butadiene-1,3 by introducing ethylene derivatives as the substituted reference. In this way the conformations of substituted butadiene do not interfere the final relative values of ASE. Note that for both Eqn (1) and Eqn (2) the reference molecules are ethylene derivatives and hence the reactions are by definition intercorrelated. However, the values of Table 1 reflect the stabilization energy due to substituent effect while the ASE values may be compared with the aromatic stability of benzene itself (ASE = 23.2 kcal/mol).

To study non-additivity of substituent effects (SESE) for *para*- and *meta*-homodisubstituted benzene derivatives we have applied classical homodesmotic reactions<sup>8c,25</sup> (3) and (4).



Finally, ASE for *para*- and *meta*-disubstituted benzene derivatives were estimated from Eqn (5) and Eqn (6), respectively.



**Table 1.** SESE values in [kcal/mol] for monosubstituted benzene derivatives (derived from the Eqn (1)).

X	SESE	X	SESE	X	SESE	X	SESE
CHO	0.2	CH <sub>2</sub> OH	-1.0	CCH	-0.4	NH <sub>2</sub>	-1.2
COOH	0.4	Br	-0.7	CHCH <sub>2</sub>	-2.8	NO	-0.4
Cl	-0.2	NMe <sub>2</sub>	-5.0	CHCl <sub>2</sub>	-1.4	CN	0.1
F	0.6	NHMe	-1.4	CHF <sub>2</sub>	-0.9	CF <sub>3</sub>	-0.6
OH	-0.7	CCl <sub>3</sub>	-2.8	COCl	0.3	BH <sub>2</sub>	0.8
OCH <sub>3</sub>	-2.0	CH <sub>2</sub> Cl	-0.6	COCH <sub>3</sub>	-0.1	BCl <sub>2</sub>	-0.1
CH <sub>3</sub>	-0.7	CH <sub>2</sub> F	-0.6	CONH <sub>2</sub>	-1.3	BF <sub>2</sub>	0.7
NO <sub>2</sub>	0.8	COF	0.8	COOCH <sub>3</sub>	0.7	B(OH) <sub>2</sub>	2.5

The application of ethylene derivatives to balance the C–X bond in benzene derivatives (instead of butadiene-1,3 derivatives) helps in eliminating the flexibility of butadiene moiety. As a result, a lot of conformers of butadiene derivatives are eliminated.

The NICS is a magnetism-based index of  $\pi$ -electron delocalization. The index is defined as a negative value of the absolute magnetic shielding computed at ring centers.<sup>19a</sup> Now it is also calculated in other points inside or around molecules.<sup>26</sup> The NICS denoted as NICS(1) is calculated 1 Å above the center<sup>19b</sup> whereas NICS(1)<sub>zz</sub> is perpendicular to the plane of the ring component of NICS(1) tensor.<sup>19c</sup> Because the magnetic response properties are tensors it was argued<sup>19d,27</sup> that the latter one is the most appropriate measure to characterize the cyclic delocalization in a  $\pi$ -system. Indeed, in the case of monosubstituted benzene derivatives the NICS(1)<sub>zz</sub>, in line with PDI and HOMA, documented their highly aromatic character.<sup>8a</sup>

The HOMA is defined as follows:

$$\text{HOMA} = 1 - \frac{\alpha}{N} \sum (R_{\text{opt}} - R_i)^2 \quad (7)$$

In Eqn (7),  $N$  is the number of bonds taken into the summation;  $\alpha$  is an empirical constant fixed to give HOMA = 0 for a model non-aromatic system<sup>20b</sup> and HOMA = 1 for a system with all bonds equal to an optimal value  $R_{\text{opt}}$ , assumed to be realized for fully aromatic systems.  $R_i$  stands for a running bond length.

## RESULTS AND DISCUSSION

### Monosubstituted benzene derivatives

Tables 1 and 2 present SESE and ASE, respectively, for monosubstituted benzene derivatives.

Almost in all cases the SESE is negative, which indicates a destabilizing influence of substituents in monosubstituted benzene derivatives at least as compared with the reference systems which are unsaturated species (ethene and its derivatives).

It results from Table 2 that for the monosubstituted benzenes substituted by electron attracting substituents, the ASE is greater than that for the electron donating ones. For many systems ASE is greater than for benzene itself (ASE = 23.2 kcal/mole). To quantify this difference more apparently, we selected four typical substituents with a strong electron accepting power (NO, NO<sub>2</sub>, CN, and CHO) with  $\sigma_p^+ \sim 1$  or more<sup>28</sup> and five typical electron donating substituents (OH, OMe, NH<sub>2</sub>, NHMe, and NMe<sub>2</sub>) with  $\sigma_p^- < -1.0$ .<sup>28</sup> The mean values of ASE for the former case was 23.4 kcal/mole and for the latter one was 21.2 kcal/mole. This is good evidence to support the point that electron accepting substituents lead to small stabilization of benzene, contrary to the electron donating substituents, which work in an opposite way.

### Homo-, para-, and meta-disubstituted benzene derivatives

Table 3 presents the SESE (derived from Eqn (3) and Eqn (4)), ASE (derived from Eqn (5) and Eqn (6)), NICS and HOMA values for *meta*- and *para*-disubstituted benzene derivatives.

In almost all cases the SESE values for *meta*- and *para*-disubstituted benzene derivatives are negative, thus implying a further destabilization of the aromatic system in comparison with the monosubstituted derivatives. At first glance it seems that the stronger is the interacting

**Table 2.** The ASE values [in kcal/mol] for monosubstituted benzene derivatives (derived from the Eqn (2)).

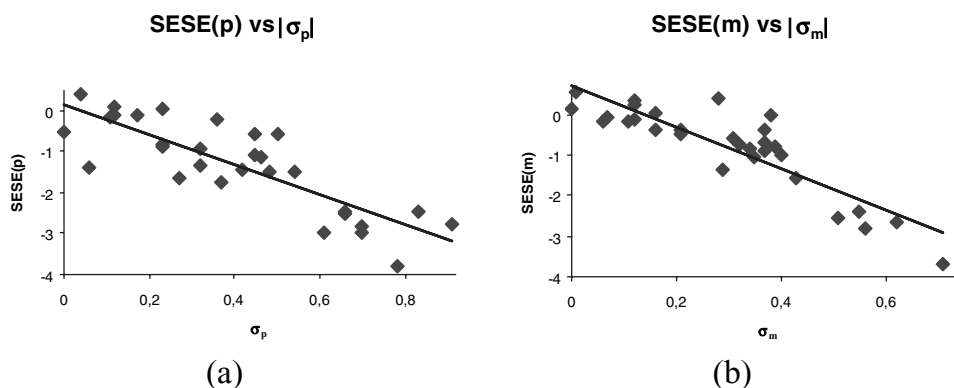
X	ASE	X	ASE	X	ASE	X	ASE
CHO	23.4	CH <sub>2</sub> OH	22.2	CCH	22.8	NH <sub>2</sub>	22.1
COOH	23.6	Br	22.6	CHCH <sub>2</sub>	20.5	NO	22.8
Cl	23.0	NMe <sub>2</sub>	18.2	CHCl <sub>2</sub>	21.9	CN	23.4
F	23.9	NHMe	21.8	CHF <sub>2</sub>	22.3	CF <sub>3</sub>	22.7
OH	22.5	CCl <sub>3</sub>	20.5	COCl	23.5	BH <sub>2</sub>	24.0
OCH <sub>3</sub>	21.3	CH <sub>2</sub> Cl	22.7	COCH <sub>3</sub>	23.1	BCl <sub>2</sub>	23.2
CH <sub>3</sub>	22.5	CH <sub>2</sub> F	22.6	CONH <sub>2</sub>	22.0	BF <sub>2</sub>	24.0
NO <sub>2</sub>	24.0	COF	24.0	COOCH <sub>3</sub>	24.0	B(OH) <sub>2</sub>	25.7

**Table 3.** The descriptors of cyclic  $\pi$ -electron delocalization: SESE in [kcal/mol], ASE in [kcal/mol], NICS in [ppm], and HOMA values for *meta* and *para* homodisubstituted benzene derivatives.

X	SESE	SESE	ASE	ASE	NICS	NICS(1)	NICS(1)zz	NICS	NICS(1)	NICS(1)zz	HOMA	HOMA
	( <i>para</i> )	( <i>meta</i> )	( <i>para</i> )	( <i>meta</i> )	( <i>para</i> )	( <i>para</i> )	( <i>para</i> )	( <i>meta</i> )	( <i>meta</i> )	( <i>meta</i> )	( <i>para</i> )	( <i>meta</i> )
CH <sub>3</sub>	-0.1	-0.1	21.6	21.7	-7.8	-9.5	-26.5	-7.8	-9.7	-26.8	0.98	0.98
NH <sub>2</sub>	-2.5	0.1	18.4	20.9	-8.3	-8.5	-22.3	-7.4	-7.7	-20.0	0.98	0.97
NMe <sub>2</sub>	-2.5	-0.4	10.7	12.8	-8.7	-9.3	-24.3	-7.5	-8.6	-22.6	0.94	0.92
NHMe	-3.0	-0.4	17.4	20.0	-8.3	-9.0	-23.3	-7.3	-7.9	-20.6	0.96	0.95
CH <sub>3</sub> O	-1.6	0.3	17.7	19.7	-10.1	-10.0	-25.7	-9.5	-9.4	-24.2	0.98	0.97
OH	-1.8	0.3	20.1	22.1	-10.2	-9.6	-24.8	-9.7	-9.2	-23.5	0.99	0.99
CH=CH <sub>2</sub>	0.4	-0.2	18.1	17.6	-6.6	-9.1	-23.3	-6.5	-8.9	-23.4	0.95	0.96
CHO	-1.4	-1.0	22.1	22.5	-7.7	-10.1	-26.0	-7.3	-9.9	-25.6	0.97	0.97
COOH	-1.1	-0.7	22.9	23.3	-8.1	-10.2	-26.3	-7.8	-9.9	-26.0	0.98	0.98
Cl	-0.9	-0.9	21.9	21.9	-9.4	-9.8	-25.3	-9.3	-9.7	-25.3	1.0	1.0
F	-1.4	-0.9	23.1	23.6	-11.6	-10.4	-26.9	-11.7	-10.4	-26.8	1.0	1.0
NO	-2.8	-2.7	19.6	19.7	-8.8	-9.5	-23.9	-8.6	-9.6	-23.8	0.98	0.98
NO <sub>2</sub>	-3.8	-3.7	21.0	21.1	-10.2	-10.5	-26.2	-10.1	-10.5	-26.1	1.0	1.0
CN	-2.4	-2.8	21.1	20.7	-8.8	-10.1	-26.4	-8.8	-10.1	-26.4	0.96	0.97
COCH <sub>3</sub>	-0.6	-0.02	22.4	22.9	-7.9	-10.1	-25.6	-7.6	-9.9	-25.4	0.97	0.97
CONH <sub>2</sub>	-0.2	0.4	20.5	21.1	-8.2	-9.9	-26.0	-8.1	-9.9	-26.1	0.98	0.98
COOCH <sub>3</sub>	-0.6	-0.4	24.2	24.4	-8.0	-10.1	-25.8	-7.8	-9.9	-25.7	0.98	0.98
Br	-0.8	-0.8	21.1	21.1	-8.8	-9.4	-24.6	-8.8	-9.5	-24.8	0.99	1.0
CH <sub>2</sub> OH	-0.5	0.1	20.7	21.3	-8.5	-10.3	-28.1	-7.8	-10.0	-27.2	0.98	0.98
CH <sub>2</sub> Cl	-0.1	-0.2	22.0	21.9	-8.3	-9.9	-26.7	-8.4	-10.0	-26.6	0.98	0.98
CH <sub>2</sub> F	-0.1	-0.1	21.9	21.9	-8.4	-10.3	-28.1	-8.5	-10.3	-28.1	0.98	0.98
CHCl <sub>2</sub>	-0.9	-0.6	18.1	19.9	-8.6	-9.9	-25.0	-8.6	-9.9	-25.2	0.99	0.98
CHF <sub>2</sub>	-1.3	-1.4	20.1	20.0	-8.8	-10.4	-28.1	-8.7	-10.4	-28.1	0.99	0.99
COCl	-3.0	-2.5	20.8	21.2	-8.5	-10.3	-25.8	-8.2	-10.2	-25.2	0.97	0.97
COF	-2.8	-2.4	22.0	22.4	-8.3	-10.3	-26.2	-7.9	-10.0	-25.9	0.98	0.98
C≡CH	0.1	-0.5	22.4	21.9	-8.1	-9.6	-24.9	-8.0	-9.4	-25.1	0.94	0.96
BF <sub>2</sub>	-1.5	-0.8	23.2	23.9	-6.9	-10.1	-27.1	-6.6	-10.0	-26.6	0.94	0.95
B(OH) <sub>2</sub>	0.1	0.5	28.3	28.8	-6.9	-10.1	-27.1	-6.8	-10.1	-26.9	0.96	0.96
CCl <sub>3</sub>	-1.2	-1.0	16.6	16.7	-9.0	-9.9	-24.5	-8.9	-9.8	-24.5	0.99	0.97
CF <sub>3</sub>	-1.5	-1.6	20.6	20.6	-9.1	-10.2	-27.7	-9.1	-10.5	-27.8	0.99	0.99
H	—	—	23.2	23.2	-8.1	-10.2	-29.2	-8.1	-10.2	-29.2	0.99	0.99
Mean	-1.3	-0.8	20.8	21.3	-8.5	-9.9	-25.9	-8.3	-9.7	-25.5	0.98	0.98
SD	1.1	1.1	2.98	2.66	1.0	0.5	1.57	1.1	0.68	2.02	0.02	0.02
Variance	1.2	1.1	8.86	7.06	1.0	0.2	2.47	1.2	0.46	4.07	0.00	0.00

substituent, irrespectively of whether it is electron attracting or electron donating in nature, the greater is the nonadditivity in energy, estimated by SESE values. Figure 1a,b presents the scatter plot of SESE values for

*meta*- and *para*-substituted species against absolute values of  $\sigma_m$  and  $\sigma_p$ .<sup>28</sup> These dependences clearly support the above-mentioned trend: correlation coefficients are 0.880 and 0.835, respectively indicating that from the



**Figure 1.** The dependence between (a) SESE(p) versus  $|\sigma_p|$  [correlation coefficient (cc)=0.835] (b) SESE(m) versus  $|\sigma_m|$  [correlation coefficient (cc)=0.880]

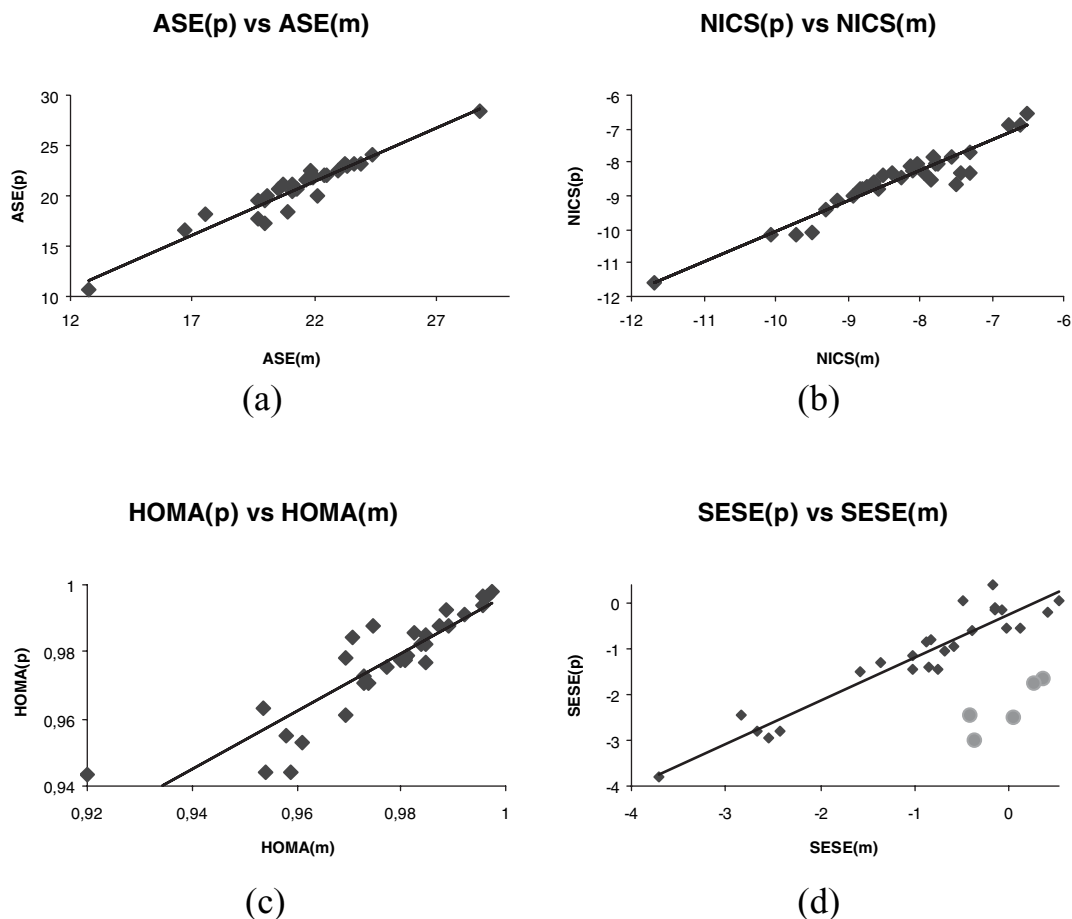
statistical point of view linear regression are significant at the level 0.05.<sup>29</sup>

Analyses of ASE values for *meta*- and *para*- systems allow one to observe that homodisubstitution leads to a decrease of stability due to cyclic  $\pi$ -electron delocalization. Similarly as in the case of monosubstituted species, generally the electron accepting substituents lower aromaticity less effectively than electron donating ones. To make this difference more apparent we repeated the procedure applied for monosubstituted systems. Again four typical substituents with strong electron accepting power (NO, NO<sub>2</sub>, CN, and CHO) with  $\sigma_p^+ \sim 1$  or more<sup>28</sup> and five typical electron donating substituents (OH, OMe, NH<sub>2</sub>, NHMe, and NMe<sub>2</sub>) with  $\sigma_p^- < -1.0$  were selected. In the case of *para*-disubstituted species the differences between the systems substituted by electron accepting and electron donating substituents are similar to those observed for monosubstituted systems. The mean ASE value for the systems with electron accepting substituents is 20.9 kcal/mole whereas for electron donating ones 16.1 kcal/mole. When the same procedure is applied to *meta*-substituted systems, no qualitative difference is observed: 21.0 kcal/mole for electron accepting and 20.7 kcal/mole for electron donating systems, respect-

ively. It is clear that the electron donating substituents in *meta*-disubstituted systems lead to a smaller decrease of aromaticity as compared with *para*-analogs. It may be concluded that

- (i) electron accepting substituents in *para*-disubstituted systems destabilize aromatic systems to a lesser extent than electron donating ones, and
- (ii) *meta*-substitution equalizes the effects of destabilization due to electron accepting and electron donating substitution.

The other parameters used frequently to describe  $\pi$ -electron delocalization, that is, HOMA and NICS do not exhibit any dependence on substituent constants. HOMA values are practically independent of substituent effect, the variance for HOMA for *meta*- and *para*-derivatives is very small. The NICS values deviate more strongly, in the range of about 7–9 ppm for NICS(1)zz for both types of substituted species. The lack of correlation between the substituent constants and  $\pi$ -electron delocalization descriptors of the ring may be due to the different blend of the resonance/field contributions to the substituent



**Figure 2.** The dependence between ASE(p) versus ASE(m) [correlation coefficient (cc) = 0.960] (a); NICS(p) versus NICS(m) [correlation coefficient (cc) = 0.952]; (b) HOMA(p) versus HOMA(m) [correlation coefficient (cc) = 0.891] (c); SESE(p) versus SESE(m) [correlation coefficient (cc) = 0.949, for all points, except five downshifted (see text)] (d)



effect in the reference reactions determining the substituent constants and in the studied systems.<sup>30</sup>

On the other hand, the regression analyses of dependences of ASE, HOMA and NICS for *para* disubstituted species on the values for *meta* ones show a good linear correlation with the best dependences found for ASE and NICS and a little worse correlation for HOMA (see Fig. 2(a)–(c)). Also NICS(1)zz for *para* and *meta* systems correlate very well, with the correlation coefficient  $cc = 0.944$ . This means that qualitatively the influence of substituent on  $\pi$ -electron delocalization in the ring of *meta*- and *para*-substituted disubstituted benzene derivatives is fairly similar. The most interesting correlation has been found for SESE(p) versus SESE(m) (see Fig. 2(d)). For all the substituents, there is roughly linear regression, with correlation coefficient  $cc = 0.69$ . Five points for NH<sub>2</sub>, NHMe, NMe<sub>2</sub>, OMe, and OH deviate down by ca 2 kcal/mole, which supports the finding that the electron donating substituents destabilize benzene system much more effectively when they are situated in *para* position as compared with the *meta* one. This is accompanied by a more efficient decrease of the resonance energy of the ring, being in line with the resonance saturation effect,<sup>31</sup> observed for *p*-substituted aniline derivatives, when counter substituents were electron donating ones. If these five points are omitted then a very good relation is preserved with the correlation coefficient  $cc = 0.949$ .

## SUPPLEMENTARY MATERIAL

Total energies, zero-point energies and the Cartesian coordinates at B3LYP/6-311+G\*\* for all analyzed systems are available in Wiley Interscience.

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