

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/235750517>

Does the Molecular Electrostatic Potential Reflect the Effects of Substituents in Aromatic Systems?

ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · APRIL 2013

Impact Factor: 5.73 · DOI: 10.1002/chem.201204092 · Source: PubMed

CITATIONS

8

READS

34

3 AUTHORS:



Boris Galabov

Sofia University "St. Kliment Ohridski"

117 PUBLICATIONS 1,342 CITATIONS

SEE PROFILE



Valya Nikolova

Sofia University "St. Kliment Ohridski"

5 PUBLICATIONS 59 CITATIONS

SEE PROFILE



Sonia Varbanova Ilieva

Sofia University "St. Kliment Ohridski"

50 PUBLICATIONS 696 CITATIONS

SEE PROFILE

Does the Molecular Electrostatic Potential Reflect the Effects of Substituents in Aromatic Systems?

Boris Galabov,* Valia Nikolova, and Sonia Ilieva^[a]

Abstract: A detailed analysis of the molecular electrostatic potential (MEP) at selected positions in molecular space was performed for a series of substituted benzene derivatives. We show that appropriately selected MEP values can quantitatively reflect the regiospecific effects of substituents on the aromatic ring. Theoretically evaluated electrostatic potentials in close proximity to the ring carbon atoms reflect well both through-space and resonance effects and excellent correlation is established between the MEP values and substituent constants. The best descriptor of the local properties at different ring positions is the electrostatic potential at nuclei (EPN).

Keywords: aromaticity • electrostatic interactions • Hammett constant • substituent effects • through-space interactions

Introduction

The molecular electrostatic potential (MEP) has been employed in characterizing various properties of chemical and biological systems.^[1–14] The electrostatic potential is a well-defined quantum-mechanical quantity.^[1,2,8] It can also be explored experimentally through X-ray diffraction investigations.^[4] Aside from the rigorous definition, an advantage of the application of molecular electrostatic potential is the possibility of characterizing local (or site) properties by evaluating MEP values at particular points in molecular space. It has been shown in various applications^[1–13] that MEP values provide an approach to quantify reactivity at specified positions in a molecule, both for intermolecular interactions (e.g., hydrogen-bonding) and for chemical reactions. Alternative interpretations of the MEP in analyzing the nature of substituent effects in aromatic systems^[15–20] prompted us to investigate the relationship between arene properties and MEP values in detail. Theoretical computations on non-covalent interactions that involve aromatic molecules led Wheeler et al.^[15–18] to the conclusion that through-space effects of the polar groups dominate the MEP of substituted arenes at distances of 2–3 Å above (perpendicular to) the ring. In particular, the variation in MEP value at a distance of 2.4 Å above the ring center was analyzed.^[15] The resonance polarization of the aromatic ring, induced by the substituents, was considered to have a negligible role. Nevertheless, it was found that, for strongly electron-donating and electron-accepting groups, resonance ef-

fects do contribute to the overall influence of substituents. The authors^[15–18] correctly opposed the interpretation that the changes in MEP at specific positions arise from variations in the local electron densities. Indeed, by definition, the MEP values depend, in a complex way, on the positive charges of all nuclei and on the entire electron density [Eq. (1)]. The link between MEP values and local charges can only be qualitative and applicable to cases in which the distance between the substituent group and a given reaction center is considerable (e.g., for *meta* and *para* positions in substituted benzenes or for reaction centers outside the aromatic ring in disubstituted derivatives). In such cases, the 1/*r* dependence of MEP [Eq. (1)] may result in an enhanced role of local charge contributions, in particular, the variation in the electron density caused by the distant substituents. The extent to which this hypothesis holds in particular aromatic systems can be judged from the relationships between the MEP values and alternative theoretical or experimental quantities, which are known to depend on the variation of local charges. By definition, the experimental substituent constants^[21–24] refer to the local properties of the different ring positions. Good correlations between site reactivities and MEP values can be considered as an indication of a dominant contribution of the local charge variations in the shifts of MEP at the respective positions.

Herein, we analyze in detail the variations in numerical MEP values at different points in the molecular space of substituted benzenes. In particular, we examine whether—and to what extent—the resonance interactions in aromatic systems influence the computed MEP values. A series of 17 monosubstituted benzenes is investigated herein. We determined MEP values at 1, 1.5, 2, and 2.5 Å above (perpendicular to) the ring carbon atoms. We also evaluated the MEP values at the positions of the ring carbon nuclei (i.e., the electrostatic potential at nuclei, EPN). Our results provide clear evidence for good correlations between the MEP

[a] Prof. B. Galabov, Dr. V. Nikolova, Prof. S. Ilieva
Department of Chemistry, University of Sofia
Sofia 1164 (Bulgaria)
E-mail: galabov@chem.uni-sofia.bg

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201204092>.

values and the properties of the aromatic systems that have long been established experimentally.^[21–24] In particular, we demonstrated that the MEP values reliably reflect the different effects of substituents, both inductive/field (through-bond and through-space) effects and resonance (conjugative) effects. As already noted, previous studies have demonstrated good correlations between the electrostatic potential values and the site reactivities of aromatic systems,^[12,13,25] thus confirming the usefulness of the molecular electrostatic potential in analyzing molecular properties. Our computational results reveal that numerical MEP values, taken at points inside the region in space that is densely populated by π electrons, describe quite well the resonance interactions in aromatic systems. Correlation analysis with substituent constants reveals that appropriately defined MEP values at particular ring positions can quantitatively characterize the local properties of the respective sites.

Computational Methods

DFT computations with the M06-2X functional^[26] and the 6-311+G(2d,2p) basis set^[27] were performed to evaluate the molecular electrostatic potential values at particular positions in the molecular space for benzene and a series of monosubstituted benzenes. Harmonic vibrational frequency computations verified that the optimized structures were true minima on their potential-energy surfaces. The computations were performed by using the Gaussian 09 suite of programs.^[28]

The molecular electrostatic potential, $V(\mathbf{r})$, at a point with positional vector \mathbf{r} is defined by Equation (1),^[2] in which Z_A is the nuclear charge of atom A with position vector \mathbf{R}_A , $\rho(\mathbf{r})$ is the electron density at point \mathbf{r} , and \mathbf{r}' is an integration variable.

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}' \quad (1)$$

As already mentioned, the MEP value has an inverse dependence on distance (Equation (1)). Thus, it can be stipulated that $V(\mathbf{r})$ is quite strongly dependent on the local charges around point \mathbf{r} , the positive charges on the neighboring nuclei, and the electron density in closer vicinity of point \mathbf{r} .

To characterize the local properties of the aromatic systems that we studied, we determined the molecular electrostatic potential values at a distance 1 Å from each ring carbon atom in the direction perpendicular to the ring plane. One of the definitions of the nuclear independent chemical shift aromaticity index, NICS(1), is based on evaluating the NICS at a distance of 1 Å above the ring center.^[29] This definition was considered to better reflect the π -electron delocalization in aromatic systems. Considering the 1/r dependence of MEP in Equation (1) and the uniformity of the carbon nuclei in the ring, the influence of the positive

nuclei charges on the variations of $V(\mathbf{r})$ in the different derivatives is expected to be less important. However, the MEP values for the *ipso*-substituted carbon atom and the atoms at the *ortho* positions in the ring can be much more sensitive to the contributions from the charges on the substituent nuclei. To analyze the sensitivity of MEP values on distance, we also determined the electrostatic potentials at distances of 1.5, 2, and 2.5 Å above the ring carbon atoms (Table 1).

The electrostatic potential at nuclei (EPN) values for all ring carbon atoms were also determined. The EPN parameter was introduced by Wilson in 1962.^[30] Politzer and Truhlar^[2] defined the electrostatic potential at a particular nucleus (Y), at a position \mathbf{R}_Y , by Equation (2).

$$V_Y \equiv V(\mathbf{R}_Y) = \sum_{A \neq Y} \frac{Z_A}{|\mathbf{R}_A - \mathbf{R}_Y|} - \int \frac{\rho(\mathbf{r})}{|\mathbf{r} - \mathbf{R}_Y|} d\mathbf{r} \quad (2)$$

In this relationship, Z_A is the charge on nucleus A at position \mathbf{R}_A and $\rho(\mathbf{r})$ is the electron-density function. The singular term from nucleus Y is excluded. In contrast to atomic charges, the EPN is a rigorously defined quantum-mechanical quantity. EPN values have been shown to provide a good description of the reactivities for processes of hydrogen bonding^[12,25a,b] and for a number of reactions of aromatic systems.^[25c–f]

Atomic charges on the aromatic ring carbon atoms in the studied molecules were also calculated by Hirshfeld population analysis.^[31]

Results and Discussion

As discussed in the preceding section, our investigation of the MEP values of substituted benzenes is based on analyzing the variations in the values of V at points in molecular coordinate space that are linked to particular positions on the aromatic rings. We are especially interested in the shifts in MEP values that are induced by polar ring substituents. As a measure of these effects, we define the shift in V with respect to the value in unsubstituted benzene, according to Equation (3), in which i is an index for a particular position in the ring, $V(\text{benzene})$ refers to MEP values at a particular distance (1, 1.5, 2, and 2.5 Å) above a carbon atom in benzene, and R is the substituent group.

$$\Delta V_i(R) = V_i(R) - V(\text{benzene}) \quad (3)$$

We also calculated the EPN values at the ring carbon nuclei (Equation (2)). The evaluated shifts of the MEP values, $\Delta V_i(R)$, at 1 Å above the carbon atoms for some of the considered derivatives, as shown in Figure 1. The data for all of the compounds that we considered are given in Table 1. As already discussed, we analyze the variations in $\Delta V_i(R)$ that are induced by polar substituents and, in particular, their correspondence with experimentally established

Table 1. Shifts in MEP at 1, 1.5, 2, and 2.5 Å above the ring carbon atoms, EPN values, and atomic charges of the carbon atoms in substituted benzenes.

Substituent	Position	$\Delta\text{MEP}^{[a]}$ [kcal mol ⁻¹]				$\Delta\text{EPN}^{[b]}$	$\Delta q(\text{Hirsh})^{[c]}$ [e]	$\sigma^{[d]}$
		1 Å	1.5 Å	2 Å	2.5 Å			
H		0	0	0	0	0	0	0
CH ₃	<i>ortho</i>	-6.17	-1.88	-0.89	-0.41	-3.49	-0.0053	
	<i>meta</i>	-1.04	-1.7	-1.39	-1.05	-1.93	-0.0012	-0.07
	<i>para</i>	-0.14	-2.35	-1.7	-1.24	-3.18	-0.0061	-0.12
OH	<i>ortho1</i>	-3.41	1.4	2.24	2.06	1.89	-0.0269	
	<i>ortho2</i>	-1.77	-1.26	-0.71	-0.7	-2.22	-0.0151	
	<i>meta1</i>	0.86	0.85	0.67	-0.65	3.04	0.0024	0.04
	<i>meta2</i>	1.58	-0.09	-0.41	-0.47	1.79	0.0049	0.04
	<i>para</i>	-4.74	-2.5	-1.23	-0.59	-3.11	-0.0159	-0.13
OCH ₃	<i>ortho1</i>	-4.04	-0.69	0.7	1.01	-0.57	-0.0156	
	<i>ortho2</i>	-4.76	-2.49	-1.73	-1.48	-3.72	-0.0266	
	<i>meta1</i>	-0.57	-0.96	-0.81	-0.53	0.76	0.0028	0.06
	<i>meta2</i>	-0.83	-1.48	-1.54	-1.39	-0.08	0.0005	0.06
	<i>para</i>	-6.08	-3.81	-2.39	-1.59	-4.8	-0.0165	-0.13
NH ₂	<i>ortho</i>	-6.55	-5.42	-4.28	-3.95	-4.7	-0.0252	
	<i>meta</i>	-1.75	-4.12	-3.92	-3.59	-2.45	0.0001	-0.09
	<i>para</i>	-8.39	-7.21	-5.3	-4.19	-8.24	-0.0215	-0.33
F	<i>ortho</i>	5.4	6.02	5.16	3.9	6.64	-0.0106	
	<i>meta</i>	7.23	5.85	4.73	3.81	8.71	0.0082	0.33
	<i>para</i>	3.08	3.81	3.79	3.42	4.36	-0.0061	0.2
Cl	<i>ortho</i>	8.14	7.24	5.53	3.93	9.81	0.0008	
	<i>meta</i>	8.43	7.04	5.68	4.51	9.33	0.0083	0.38
	<i>para</i>	6.46	6.11	5.34	4.47	7.04	0.0011	0.24
Br	<i>ortho</i>	10.22	9.69	7.28	5.11	10.88	0.0133	
	<i>meta</i>	10.24	9.3	7.32	5.63	9.92	0.0091	0.38
	<i>para</i>	8.67	8.56	7.05	5.62	7.92	0.0026	0.24
CCH	<i>ortho</i>	6.44	4.93	3.24	1.89	7.23	0.0133	
	<i>meta</i>	5.36	4.6	3.67	2.78	5.54	0.0044	0.2
	<i>para</i>	5.93	4.93	3.94	3.06	5.9	0.0061	0.22
CHO	<i>ortho1</i>	12.47	9.49	6.95	5.04	10.31	0.0208	
	<i>ortho2</i>	14.66	12.26	9.94	7.89	14.13	0.0126	
	<i>meta1</i>	10.27	9.04	7.51	6.06	10.14	0.0085	0.41
	<i>meta2</i>	10.71	9.96	8.66	7.3	11.09	0.0046	0.41
	<i>para</i>	13.3	10.86	8.76	7.09	12.69	0.0126	0.47
COF	<i>ortho1</i>	18.5	14.84	11.43	8.86	18.34	0.0167	
	<i>ortho2</i>	19.12	15.64	12.34	9.57	17.07	0.0231	
	<i>meta1</i>	14.71	13.22	11.18	9.18	14.89	0.0088	0.55
	<i>meta2</i>	14.82	13.46	11.49	9.54	14.71	0.0101	0.55
	<i>para</i>	18.14	14.93	12.13	9.87	17.22	0.0206	0.7
COCl	<i>ortho1</i>	19.12	15.35	11.83	9	17.58	0.0228	
	<i>ortho2</i>	18.86	15.12	11.6	8.76	18.35	0.0165	
	<i>meta1</i>	14.93	13.53	11.48	9.44	15.02	0.0101	0.55
	<i>meta2</i>	15.12	13.5	11.37	9.31	15.04	0.0092	0.55
	<i>para</i>	18.77	15.33	12.36	9.99	17.63	0.0216	0.69
CN	<i>ortho</i>	19.82	16.41	12.8	9.72	21.19	0.0231	
	<i>meta</i>	16.78	14.87	12.52	10.28	17.07	0.0116	0.65
	<i>para</i>	18.37	15.58	12.91	10.62	18.01	0.0174	0.71
NO ₂	<i>ortho</i>	22.54	18.53	14.4	10.95	21.96	0.0134	
	<i>meta</i>	18.64	16.54	13.91	11.4	19.39	0.0136	0.71
	<i>para</i>	21.01	17.65	14.51	11.87	20.39	0.0206	0.81
NO	<i>ortho1</i>	18.05	13.6	10.35	8.04	15.95	0.0147	
	<i>ortho2</i>	16.91	14.26	10.77	7.71	15.11	0.0125	
	<i>meta1</i>	13.84	12.42	10.38	8.64	14.23	0.0082	
	<i>meta2</i>	14.03	12.49	10.55	8.44	14.54	0.0105	
	<i>para</i>	17.27	14.07	11.31	9.11	16.6	0.0203	
COOH	<i>ortho1</i>	10.92	8.11	5.67	3.86	8.92	0.0187	
	<i>ortho2</i>	11.13	8.97	6.77	5.01	10.57	0.0126	
	<i>meta1</i>	8.07	7.22	5.95	4.69	8.00	0.0063	0.35
	<i>meta2</i>	7.80	7.53	6.42	5.23	8.34	0.0048	0.35
	<i>para</i>	11.16	8.88	6.97	5.49	10.36	0.0147	0.44
CHF ₂	<i>ortho</i>	10.31	10.20	9.50	8.44	9.43	0.0047	
	<i>meta</i>	8.05	7.35	6.90	6.25	8.08	0.0062	0.32
	<i>para</i>	8.4	7.53	6.70	5.96	7.97	0.0071	0.35
Correlation with σ^0		0.988	0.987	0.981	0.975	0.994	0.896	

[a] $\Delta\text{MEP}_i^{1\text{\AA}}(\text{R}) = \text{MEP}_i^{1\text{\AA}}(\text{R}) - \text{MEP}_i^{1\text{\AA}}(\text{benzene})$ (R = substituent); [b] $\Delta\text{EPN}_Y = \text{EPN}_Y(\text{R}) - \text{EPN}_Y(\text{benzene})$; [c] $\Delta q(\text{Hirsh}) = q_Y(\text{Hirsh})(\text{R}) - q_C(\text{Hirsh})(\text{benzene})$; [d] data taken from ref. [38].

properties of these aromatic derivatives. The most characteristic reaction of arenes is electrophilic aromatic substitution. The orientation effects of the electron-donating and electron-withdrawing substituents in $\text{S}_{\text{E}}\text{Ar}$ reactions are well-established.^[21–24] Numerous kinetic data for these reactions are also available and can be employed for assessing the predictive potential of various reactivity parameters. The substituent constants, first introduced by Hammett,^[32] represent a well-systematized and generalized set of experimentally derived quantities, describing the regiospecific reactivity of aromatic systems.^[33–35] Herein, we examine the relationships between the evaluated shifts in MEP values, $\Delta V_i(\text{R})$, and the experimentally derived substituent constants. Correlations with reactivity constants can serve as a quantitative probe in analyzing the applicability of MEP values in quantifying chemical reactivity. Figure 1 shows the shifts in MEP (1 Å) values that are induced by the polar substituents for eight selected derivatives. In harmony with expectations, the electron-withdrawing fluoro substituent (Figure 1) leads to overall positive shifts of the MEP (1 Å) at the *ortho* (5.4 kcal mol⁻¹), *meta* (7.2 kcal mol⁻¹), and *para* positions (3.1 kcal mol⁻¹) on the ring, thus reflecting the much lower reactivity of fluorobenzenes in electrophilic aromatic substitution reactions.^[21–24] The predicted regioselectivity for the same reaction is also in good accord with the experimental observations: The *meta* position in fluorobenzene shows the highest positive MEP shift of 7.2 kcal mol⁻¹, in agreement with the experimental orientation effects of the fluoro substituent. Thus, the site selectivity for

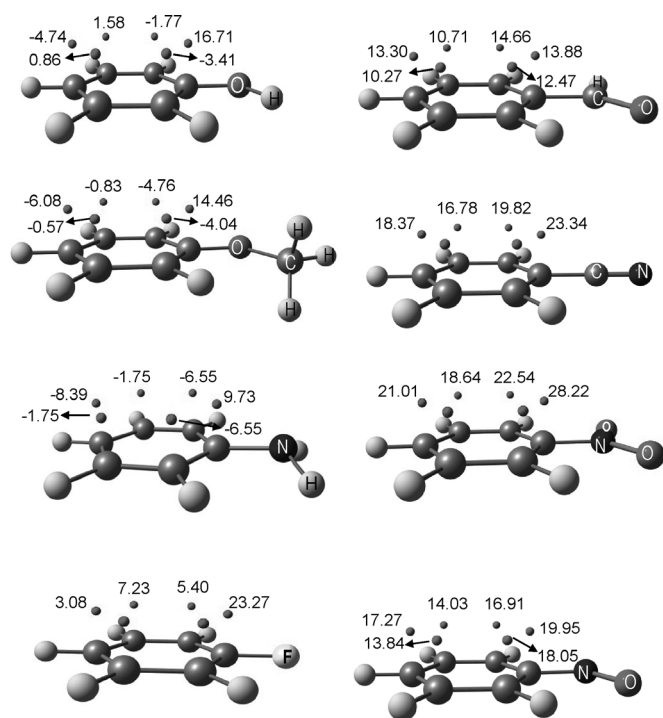


Figure 1. Shifts in the molecular electrostatic potential (MEP) values [kcal mol^{-1}] for selected monosubstituted benzenes with respect to the values for benzene at positions 1 Å above the ring carbon atoms.

this reaction is *ortho/para*, as established experimentally.^[21–24] The electron-donating NH_2 , OH , and OCH_3 groups lead to negative shifts of the MEP value, in accordance with the expected increase in the negative charge in the space around all of the ring carbon atoms (Figure 1, Table 1). For electrophilic attack, the most plausible positions are predicted to be the *ortho* and *para* positions, in harmony with the experimental data. For instance, in the derivative that contains the strongly electron-donating NH_2 group, the MEP shifts are $-6.5 \text{ kcal mol}^{-1}$ for the *ortho* position, $-1.7 \text{ kcal mol}^{-1}$ for the *meta* position, and $-8.4 \text{ kcal mol}^{-1}$ for the *para* position. Again, in accordance with the experimental data,^[21–24] the most susceptible positions to electrophilic attack are predicted to be the *ortho* and *para* positions on the ring. We should underline that the correlation between the partial electric charges on the ring positions and the reactivity is only qualitative. As reported recently,^[36] the theoretically estimated complexation energy of the respective arenium ions (σ complexes), denoted as the electrophile affinity ($E\alpha$), provides a quantitative measurement of the reactivity for electrophilic aromatic substitution processes, as conducted in polar solvents and following the classical $\text{S}_{\text{E}}\text{Ar}$ mechanism. Nevertheless, the transition states that lead to these complexes are expected to be stabilized by increased negative charges on the respective ring positions.

Conversely, strong electron-withdrawing groups, such as CN , CHO , COF , COCl , NO , and NO_2 groups, cause considerable positive shifts of the MEP values for the ring carbon atoms, in accordance with the lower electron density above

the aromatic ring (e.g., 18.4 and $21.0 \text{ kcal mol}^{-1}$ at the *para* positions in cyanobenzene and nitrobenzene, respectively), thus leading to deactivation of the respective derivatives towards $\text{S}_{\text{E}}\text{Ar}$ processes (Figure 1, Table 1). Again, the site reactivity is well-predicted. The *meta* positions in these derivatives bear less positive charge compared to the *ortho* and *para* positions and they are more susceptible to electrophilic attack. The calculated atomic charges (Table 1) on the respective ring sites are in qualitative accord with the conclusions from the MEP shifts.

At this point, we emphasize that the theoretically evaluated orientation effects of the substituents clearly indicate the simultaneous influence of the classic substituent effects, as widely discussed in organic chemistry textbooks, that is, inductive/field effects and resonance effects. If only through-space effects were in force, no *o,p*-orientation of electron-donating groups or *m*-orientation of electron-accepting groups would have been predicted. We remind the reader here that negative MEP values do not necessarily indicate negative local electric charges at the respective positions. Nevertheless, the very good correspondence between the variations in MEP values and the expected changes in electron densities at the different ring sites that are induced by the substituents suggests that the $1/r$ dependence of the MEP value [Eq. (1)] indeed plays a strong role in determining the respective electrostatic potential values. As Wheeler and Houk have justifiably mentioned,^[15] a charge of only $0.1e$ at a distance of 3 Å results in an MEP value of about 11 kcal mol^{-1} . However, the same charge ($0.1e$) at a typical distance of 0.35 Å near the 1 Å MEP point leads to a MEP value of 94 kcal mol^{-1} . The relative contributions of long- and short-distance effects on particular MEP values are not immediately deducible from the estimated shifts of the MEP values in the substituted benzenes. However, the good correspondence between the MEP shifts and the expected variations of electron densities under the influence of substituents suggest that local charges dominate the variation in the electrostatic potential at positions that are sufficiently distant from the substituents.

One of the approaches that is used in determining the effects of resonance interactions^[15,37] in aromatic structures on the MEP values involves a special type of model computations. The MEP values for a normal configuration of the arene are compared with the respective values in model structures, in which the polar groups are twisted by 90° with respect the ring plane, thus eliminating the conjugative interaction. The shortcoming of such computations is that it is unclear to what extent the through-space effects of substituents in the planar and twisted configurations would be identical. Nevertheless, we repeated this approach herein for two typical electron-donating and electron-withdrawing substituents, that is, NH_2 and NO groups. The MEP values at 1 Å for the twisted and normal configurations of aminobenzene and nitrosobenzene are compared in Figure 2. Our results demonstrate considerable changes in the MEP values at the ring carbon atoms upon rotation of the polar groups. The shifts in the MEP value at a distance of 1 Å above the

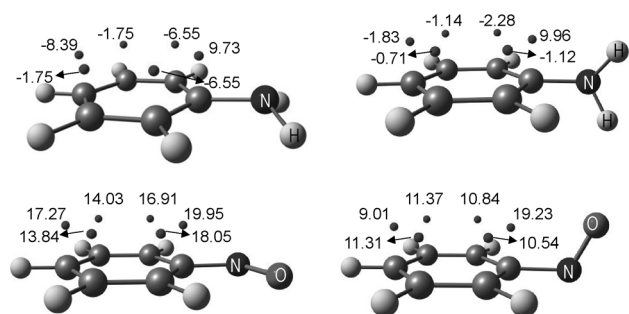


Figure 2. MEP values at positions 1 Å above the ring carbon atoms for NH₂- and NO₂-substituted benzenes in normal configurations and twisted by 90° along the C_{ipso}-X bond.

para-ring carbon atom are $-8.4 \text{ kcal mol}^{-1}$ in the normal configuration of aniline and just $-2.3 \text{ kcal mol}^{-1}$ for the twisted structure. For the nitroso derivative, the MEP value is $17.27 \text{ kcal mol}^{-1}$ in the normal configuration and $9.01 \text{ kcal mol}^{-1}$ for the twisted structure. Similarly, the value for the *ortho* position in nitrosobenzene shifts from 16.9 to $10.8 \text{ kcal mol}^{-1}$ in the twisted analogue (Figure 2). These distinct differences between the MEP values of the normal and twisted configurations suggest that the MEP values reflect, in qualitative terms, the resonance mechanism of transfer of the substituent effect. Recent electrostatic potential studies of Pingale^[19] and Sayyed et al.^[20] underline the importance of the resonance mechanism in the transfer of electronic effects in conjugated systems.

As discussed, we evaluated MEP values at a distance of 1 Å above the ring carbon atoms because, at this distance, the π -electron densities are expected to be high. It was certainly of interest to follow how the MEP values change at longer distances from the ring carbon atoms. Table 1 shows the variations in the MEP shifts at distances of 1, 1.5, 2, and 2.5 Å above the ring carbon atoms for the series of benzene derivatives considered. Overall, the correlations between the MEP shifts and the σ^0 constants still hold for distances of more than 1 Å from the ring. However, a survey reveals worsening relationships between the ΔMEP values and the arene properties at distances of 2 and 2.5 Å above the ring carbon atoms. Incorrect overall and orientation effects of some substituents are predicted, even for the set of MEP values at a distance of 1.5 Å above the ring. For instance, a positive shift in the MEP value is suggested for one of the *ortho* carbon atoms in phenol, in disaccord with the expected orientation effect of the OH group. The MEP values for the electron-withdrawing CHO, COF, COCl, CN, NO₂, and NO groups at 2.5 Å above the ring show an *ortho* orientation effect, whereas, as is well-known, all of these group possess a *meta*-orientation influence on S_EAr reactions. These data clearly suggest that the MEP values may only characterize the local properties of aromatic systems if taken at points in space at which the local electron densities, associated with the respective ring positions, are high. Figure 3 shows the electron-isodensity curves for benzene and nitrobenzene. The electron density quickly falls with increasing

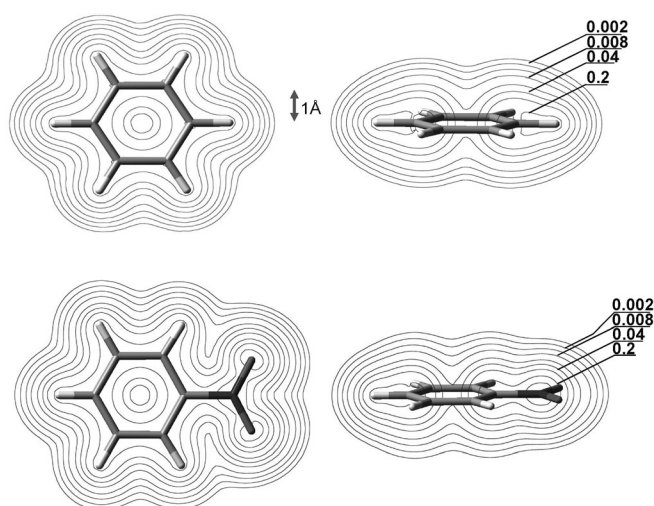


Figure 3. Electron-isodensity curves (in electrons) for benzene and nitrobenzene.

distance from the ring. For instance, the $0.04e$ curve corresponds to a distance of about 1 Å above the ring carbon atoms, whereas, at a distance of about 2 Å, the electron density is almost 20-times lower (isodensity curve of $0.002e$). It is not surprising that the MEP values at a distance of 2.4 Å above the ring center as reported by Wheeler and Houk^[15] do not reflect well the effects of polar groups on the π -electron system of arene derivatives. Certainly, we should underline here that these authors studied non-covalent interactions in aromatic derivatives, which are strongly dependent on purely electrostatic influences. For the purposes of their study, the evaluated MEP values (at a distance of 2.4 Å over the ring center) are quite appropriate. As we have seen, the MEP values, taken at appropriate positions in space, in which the concentration of π -electron densities is expected to be high, reflect well both the through-space and resonance effects of substituents.

To quantify the effects of aromatic substituents on the computed MEP values, we examined the correlation between the shifts in MEP values and the experimental substituent constants. The standard Hammett constants, as well as alternative definitions (i.e., σ^+ , σ^- , and σ^0), reflect the overall effects (including both through-space and resonance influences) of substituents in a particular reaction series. In fact, the notions of inductive, field, and resonance effects have been defined in connection with the Hammett relationships.^[21–24] The most appropriate set for the purpose of this investigation are σ^0 constants,^[38] which have been defined to describe the effects of polar groups in monosubstituted benzenes. Further to the computed MEP values at particular positions above the ring, we also evaluated their respective EPN values (Table 1). These latter quantities were shown to quantitatively describe the reactivity of molecules in hydrogen-bonding processes, as well as in a number of reactions of aromatic systems.^[13,25] The EPN values are expected to better reflect the local properties of the different ring positions, because these values depend equally on the electron

densities on both sides of the ring, thus enhancing the role of the local charges compared to the MEP values (at 1–2.5 Å above a single side of the ring) discussed above. The evaluated atomic charges on the ring carbon atoms, as obtained from Hirshfeld population analysis,^[31] are also shown in Table 1. The correlation coefficients for the relationships between the computed electrostatic potential and the σ^0 constants are shown in the last row of Table 1. Figure 4

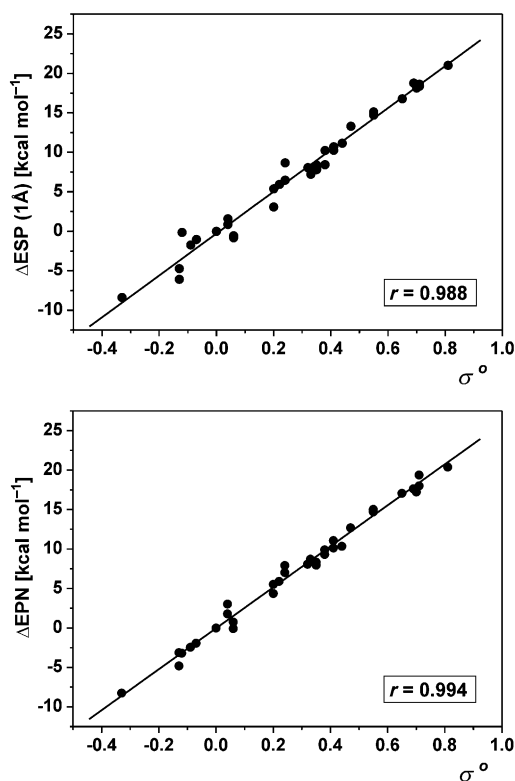


Figure 4. Plots of MEP (1 Å) and EPN values versus the σ^0 constants for the substituents.

shows the plots of MEP (1 Å) and EPN values versus the σ^0 constants. A quite good correlation is established between the MEP values (1 Å) and the σ^0 constants ($r=0.988$, $n=37$). An excellent correlation is found for the plot of EPN values versus σ^0 values ($r=0.994$, $n=37$). These results reveal quantitative correlations between the substituent constants and the electrostatic potential values. As expected, the best fit is obtained with the EPN values. The shifts in the Hirshfeld charges at the ring carbon atoms (Table 1) qualitatively reflect well the expected changes of electron densities that are invoked by the substituents. Electron-donating groups cause negative shifts at the *ortho* and *para* carbon atoms. Electron-accepting groups lead to positive charge shifts.

The emerging conclusion from these results is that appropriately taken MEP values depend quantitatively on the local properties of the aromatic systems and reflect both through-space and resonance contributions.

We would like to emphasize here that these results do not contradict the conclusions of Wheeler and Houk^[15–18] regarding the effect of substituents on non-covalent interactions. Indeed, the results of their research clearly showed the dominance of through-space effects of substituents on the non-covalent interactions of aromatic systems. As is known, the complexes that result from such processes involve interactions at some considerable distances from the ring. The present results deal with the effect of the substituents on chemical reactivity, which is determined by the barriers that are associated with bond-breaking and bond-formation. Naturally, such processes involve the participation of the ring atoms or atoms at reaction centers outside the aromatic ring. Thus, MEP values in the close vicinity of the atoms (or at the respective nuclei) that are involved in chemical reactions are most appropriate for analyzing chemical reactivity of arenes.

Concluding Remarks

These computational results provide clear evidence that numerical molecular electrostatic potential (MEP) values, taken at points in molecular space with a high concentration of π -electron density (e.g., 1 Å above each carbon atom, perpendicular to the ring plane), can quite satisfactorily describe the regiospecific influence of polar substituents (at the *meta* and *para* positions) and reflect both through-space and resonance effects. In this respect, the best choice is provided by the electrostatic potentials at nuclei (EPN) parameter.

Acknowledgements

This research was supported by the Bulgarian National Science Fund (Grant DCVP 02/2-2009) and by EU Grant FP7-REGPOT-2011-1 (BeyondEverest).

- [1] E. Scrocco, J. Tomasi, *Top. Curr. Chem.* **1973**, 42, 95–170.
- [2] *Chemical Applications of Atomic and Molecular Electrostatic Potentials* (Eds.: P. Politzer, D. G. Truhlar), Plenum Press, New York, **1981**.
- [3] J. S. Murray, *Molecular Electrostatic Potentials: Concepts and Applications*, (Ed.: K. Sen), Elsevier, Amsterdam, **1996**.
- [4] R. F. Stewart, *Chem. Phys. Lett.* **1979**, 65, 335–342.
- [5] P. Politzer, J. S. Murray in *Reviews in Computational Chemistry*, Vol. 2 (Eds.: K. B. Lipkowitz, D. B. Boyd), VCH Publishers, New York, **1991**.
- [6] J. S. Murray, P. Politzer, *Chem. Phys. Lett.* **1988**, 152, 364–370.
- [7] J. S. Murray, T. Brinck, M. E. Grice, P. Politzer, *J. Mol. Struct.* **1992**, 256, 29–35.
- [8] J. S. Murray, P. Politzer, *WIREs Comput. Mol. Sci.* **2011**, 1, 153–163.
- [9] G. Naray-Szabo, G. Ferenczy, *Chem. Rev.* **1995**, 95, 829–847.
- [10] C. H. Suresh, S. R. Gadre, *J. Am. Chem. Soc.* **1998**, 120, 7049–7055.
- [11] C. H. Suresh, S. R. Gadre, *J. Phys. Chem. A* **2007**, 111, 710–714.
- [12] B. Galabov, P. Bobadova-Parvanova, *J. Phys. Chem. A* **1999**, 103, 6793–6799.
- [13] B. Galabov, S. Ilieva, H. F. Schaefer, *J. Org. Chem.* **2006**, 71, 6382–6387.

- [14] E. G. Hohenstein, C. D. Sherrill, *J. Phys. Chem. A* **2009**, *113*, 878–886.
- [15] S. E. Wheeler, K. N. Houk, *J. Chem. Theory Comput.* **2009**, *5*, 2301–2312.
- [16] S. E. Wheeler, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10854–10855.
- [17] S. E. Wheeler, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 3126–3127.
- [18] R. K. Raju, J. W. G. Bloom, Y. An, S. E. Wheeler, *ChemPhysChem* **2011**, *12*, 3116–3130.
- [19] S. S. Pingale, *Phys. Chem. Chem. Phys.* **2011**, *13*, 15158–15165.
- [20] F. B. Sayyed, C. H. Suresh, S. R. Gadre, *J. Phys. Chem. A* **2010**, *114*, 12330–12333.
- [21] M. B. Smith, J. March, *March's Advanced Organic Chemistry Reactions: Mechanisms and Structure*, 6th ed., Wiley-VCH, New York, **2006**.
- [22] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, Springer, New York, **2007**.
- [23] G. A. Olah, R. Malhotra, S. C. Narang, *Nitration: Structure and Mechanisms*, VCH Publishers, New York, **1989**.
- [24] K. P. C. Vollhardt, N. E. Schore, *Organic Chemistry: Structure and Mechanism*, Freeman, New York, **2007**.
- [25] a) P. Bobadova-Parvanova, B. Galabov, *J. Phys. Chem. A* **1998**, *102*, 1815–1819; b) V. Dimitrova, S. Ilieva, B. Galabov, *J. Phys. Chem. A* **2002**, *106*, 11801–11805; c) B. Galabov, D. Cheshmedzhieva, S. Ilieva, B. Hadjieva, *J. Phys. Chem. A* **2004**, *108*, 11457–11462; d) B. Galabov, S. Ilieva, B. Hadjieva, Y. Atanasov, H. F. Schaefer, *J. Phys. Chem. A* **2008**, *112*, 6700–6707; e) B. Galabov, V. Nikolova, J. J. Wilke, H. F. Schaefer, W. D. Allen, *J. Am. Chem. Soc.* **2008**, *130*, 9887–9896; f) B. Galabov, S. Ilieva, G. Koleva, W. D. Allen, H. F. Schaefer, P. v. R. Schleyer, *WIREs Comp. Mol. Sci.* **2013**, *3*, 37–55.
- [26] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- [27] a) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639–5649; b) A. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650–655; c) T. Clark, J. Chandrasekhar, G. W. Spitznagel, P. v. R. Schleyer, *J. Comput. Chem.* **1983**, *4*, 294–301.
- [28] Gaussian 09, Revision A.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A.: Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cio-slawski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian Inc., Wallingford CT, **2009**.
- [29] a) P. v. R. Schleyer, H. Jiao, N. J. R. v. E. Hommes, V. G. Malkin, O. Malkina, *J. Am. Chem. Soc.* **1997**, *119*, 12669–12670; b) Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. v. R. Schleyer, *Chem. Rev.* **2005**, *105*, 3842–3888.
- [30] E. B. Wilson, *J. Chem. Phys.* **1962**, *36*, 2232–2233.
- [31] a) F. L. Hirshfeld, *Theor. Chem. Acc.* **1977**, *44*, 129–138; b) J. P. Ritchie, *J. Am. Chem. Soc.* **1985**, *107*, 1829–1835; c) J. P. Ritchie, S. M. Bachrach, *J. Comput. Chem.* **1987**, *8*, 499–509.
- [32] L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96–103.
- [33] J. Shorter, *Correlation Analysis in Organic Chemistry: An Introduction to Linear Free-Energy Relationships*, Clarendon Press, Oxford, **1973**.
- [34] *Correlation Analysis in Chemistry* (Eds.: N. B. Chapman, J. Shorter), Plenum, London, **1978**.
- [35] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
- [36] a) G. Koleva, B. Galabov, J. Wu, H. F. Schaefer, P. v. R. Schleyer, *J. Am. Chem. Soc.* **2009**, *131*, 14722–14727; b) B. Galabov, G. Koleva, H. F. Schaefer, P. v. R. Schleyer, *J. Org. Chem.* **2010**, *75*, 2813–2819.
- [37] P. Politzer, P. Lane, K. Jayasuriya, L. N. Domelsmith, *J. Am. Chem. Soc.* **1987**, *109*, 1899–1901.
- [38] O. Exner in *Advances in Linear Free Energy Relationships* (Eds.: N. B. Chapman, J. Shorter), Plenum, London, **1972**.

Received: November 15, 2012
Published online: February 27, 2013