Computational evaluation of σ_I and σ_R substituent constants

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ABSTRACT

A computational approach for the evaluation of σ_I and σ_R substituent constants is outlined. It is based on correlations between theoretically evaluated electrostatic potential at nuclei (EPN) values for the carbon atoms (V_C) in substituted benzene and bicyclo[2,2,2]octane derivatives containing the same polar group at position 1. Theoretical computations at B3LYP/6-311+G(2d,2p) level were performed. Quite satisfactory correlations linking σ_I and σ_R constants and quantities derived from the respective V_C values in the two series of molecules were obtained. The obtained equations provide a simple and meaningful approach for theoretical evaluation of σ_I and σ_R constants. The method is applicable also to polysubstituted and polynuclear aromatic hydrocarbons.

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sigmal and sigmaR were measured experimentally, but the reference is not accessible from OU.

1. Introduction

The substituent constants first introduced by Hammett [1] still play an important role in quantifying the reactivity of organic compounds as well as in elucidating the mechanisms of organic reactions [2–26]. These property descriptors find also extensive application in QSAR and QSPR studies [27–30]. There is a continuing interest among researchers in the field focusing on designing more advanced experimental or theoretical approaches for the determination of these molecular parameters. A particularly interesting problem is the definition of field/inductive and resonance contributions to substituent constants [3,4,6,7,11,13–16,31–33]. Correlations with the σ_I and σ_R parameters reveal the relative role of these principal mechanisms of substituent influence in different organic systems.

In a recent study we reported the application of the theoretical electrostatic potential at nuclei (EPN) in designing an accurate method for the evaluation of σ^o constants [19]. An excellent correlation between the σ_m^o and σ_p^o constants and EPN values for the respective carbon positions (V_C) in the ring was established as expressed by the equation:

$$\sigma^o = 22.603\, V_C + 334.000 \quad n = 29, r = 0.995, \mathrm{sd} = 0.031 \qquad (1)$$

The main advantage of this equation is that it provides a method for determining substituent constants in arbitrary arenes, including polysubstituted and polynuclear aromatic derivatives. Unlike atomic charges, which depend strongly on their definition and additional

approximations, inherent in their evaluation, the electrostatic potential at nuclei [34,35] values V_Y reflect the variations of electron densities rigorously. The dominant contribution to V_Y comes from the local densities around the respective atomic sites. More negative V_Y values indicate greater electron densities. Politzer [35] has employed Eq. (2) to define the electrostatic potential at a particular nucleus (Y) positioned at $\mathbf{R}_Y$ (in atomic units, bold font denotes vector quantities), in which the singular term $\mathbf{R}_A = \mathbf{R}_Y$ has been excluded:

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

In this equation, Z_A is the charge on nucleus A with radius vector $\mathbf{R}_A$, and $\rho(\mathbf{r})$ is the electron density function. The EPN index was defined and introduced by Wilson [34] in 1962. However, it was first applied as a reactivity index for organic compounds much later in the works of Galabov et al. [36–43]. Further studies in other laboratories [17,44–56] have emphasized the usefulness of this proposed reactivity index.

In the present research we apply the electrostatic potential at nuclei in the evaluation of field/inductive and resonance substituent constants for aromatic derivatives. Correlations between theoretically evaluated EPN values and experimentally determined σ_I and σ_R values [7] are employed.

2. Methodology and computational methods

To derive the σ_I field/inductive constants we assessed the relationships between the experimentally determined reactivity

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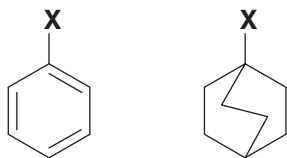
Scheme 1.

parameters as given in the review of Charton [7] with theoretically evaluated EPN values at the carbon atom in position 4 in a series of 23 bicyclo[2,2,2]octane derivatives containing polar group in position 1 (Scheme 1). The variation the electrostatic potential at this carbon atom is expected to reflect the direct through-space field effect of substituents as well as the through bond polarization usually denoted as inductive effect. No resonance interactions are possible in these model systems. The correlation approach provides a way to scale down the variations of V_C into the magnitude of the experimental σ_I constants.

To distinguish between field/inductive and resonance effects of the substituent we carried out further theoretical computations for a series of mono-substituted benzene and bicyclooctane derivatives containing the same polar groups (Scheme 1).

The series of compounds studied is presented in Table 1. The approach in evaluating the pure resonance contribution to substituent effects is analogous to the method employed in the experimental determination of resonance effects [3,7] by employing substituted bicyclooctane carboxylic acids model systems. As already discussed, these derivatives allow the evaluation of the polar effect of substituents at position 4 in the ring in absence of resonance interaction with the X substituent. It should be underlined that the distance between positions 1 and 4 in benzene and bicycle[2,2,2,]octane derivatives is quite similar. The variation of V_C in the bicyclooctane series describes

the field/inductive effect of substituents. Additivity of substituent effects has been employed in the experimental derivation of σ_I and σ_R substituent constants [3]. Following the same approach, the difference between V_C in benzene and bicyclooctane derivatives with identical substituents is assumed to characterize the resonance contribution to the overall effect of substituents:

$$V_C^{res} = V_C^{benzene} - V_C^{bicyclooctane} \tag{3}$$

All computations were carried out by employing the B3LYP hybrid functional [57,58] combined with 6-311+G(2d,2p) basis set [59,60]. Harmonic vibrational frequencies characterized the nature of all optimized structures. All computations were carried out with the Gaussian 03 program package [61].

3. Results and discussion

3.1. σ_I substituent constants

To evaluate the combined field/inductive effect of polar substituents we carried out DFT computations on derivatives of bicyclo[2,2,2]octane substituted at position 1. The effect of the polar group at position 4 can only be exerted by field/inductive influence, since no resonance effects are expected for these saturated molecules. The electrostatic potential at nuclei (V_C) characterizes in quantitative way the effect of the substituents. The theoretically estimated V_C values are presented in Table 1, together with the experimental σ_I constants as reported by Charton [7]. The σ_I constants are derived from the experimental pK$_a$ values for the respective bicyclo[2,2,2]octane carboxylic acids, measured in water solution [7]. In a previous study on the theoretical evaluation of σ^o constants [19] we showed that the solvent influences the magnitude of substituent effect as reflected in the respective V_C, while the relative values follow the same trend as obtained from gas-phase computations. These results showed that computations referring the gas-phase studies can be employed in determining the relative scales of substituent polar effects. A satisfactory correlation ($r = 0.966$) is obtained as illustrated in Fig. 1. This result is in accord with the conclusions of Bowden and Grubbs that the main polar effect of substituents is electrostatic in nature [62]. In a recent study Suresh and Gadre [32] established a correlation between the minimum of the molecular surface electrostatic potential (V_{min}) and the inductive effect of substituents. Since the position of V_{min} varies from molecule to molecule, the use of EPN

Table 1
Electrostatic potential at nuclei (V_C) in benzene and bicylo[2,2,2]octane derivatives substituted at position 1 and σ_I and σ_R constants.

Substituent	$V_C^{I\,a}$ Benzenes	$V_C^{II\,b}$ Bicyclo[2,2,2]octanes	$\Delta V_C^{res\,c}$	σ_I^d	σ_R^d
H	−14.77568	−14.78089	0.00521	0	0
CH$_3$	−14.78082	−14.78057	−0.00025	−0.01	−0.16
C$_2$H$_5$	−14.78071	−14.78121	0.00050	−0.01	−0.14
NH$_2$	−14.78970	−14.77757	−0.01213	0.17	−0.80
NO$_2$	−14.74255	−14.75825	0.01570	0.67	0.10
OH	−14.78695	−14.77356	−0.01340	0.24	−0.62
Cl	−14.76459	−14.76555	0.00096	0.47	−0.25
CCH	−14.76657	−14.77293	0.00636	0.29	−0.04
CN	−14.74692	−14.75973	0.01281	0.57	0.08
C(CH$_3$)$_3$	−14.78186	−14.78262	0.00076	−0.01	−0.18
CONH$_2$	−14.76291	−14.77296	0.01005	0.28	0.08
COCH$_3$	−14.76039	−14.77237	0.01198	0.30	0.20
N(CH$_3$)$_2$	−14.79496	−14.77940	−0.01556	0.13	−0.88
NHCOCH$_3$	−14.77778	−14.77385	−0.00393	0.28	−0.35
C$_6$H$_5$	−14.77545	−14.77768	0.00223	0.12	−0.11
OCOCH$_3$	−14.77165	−14.77155	−0.00010	0.38	−0.23
Br	−14.76369	−14.76467	0.00098	0.47	−0.25
COOCH$_3$	−14.76272	−14.77433	0.01161	0.32	0.11
SCH$_3$	−14.77815	−14.77356	−0.00459	0.30	−0.38
CF$_3$	−14.75484	−14.76619	0.01136	0.40	0.11
CCl3	−14.75758	−14.76693	0.00935	0.36	0.08
CHCH$_2$	−14.77406	−14.77783	0.00377	0.11	−0.15
COOC$_2$H$_5$	−14.76389	−14.77514	0.01125	0.30	0.11

[a] V_C^I Electrostatic potential at the C4 carbon atom in mono-substituted benzene derivatives.
[b] V_C^{II} Electrostatic potential at the C4 carbon atom in mono-substituted bicyclo[2,2,2]octane derivatives.
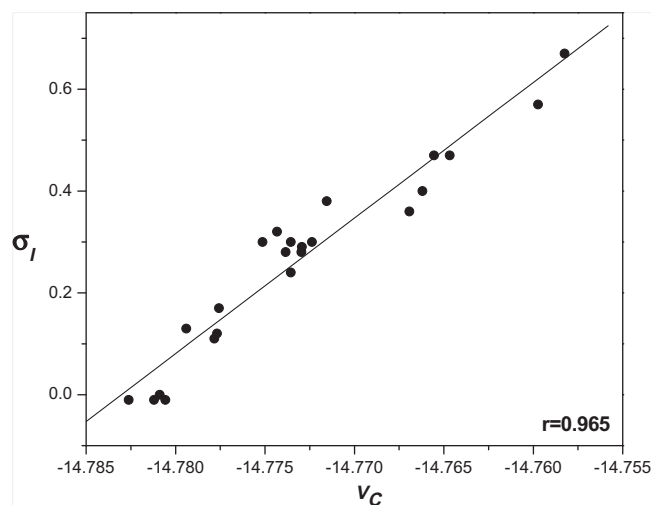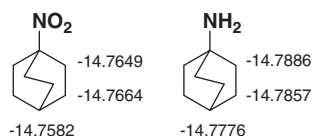[c] $\Delta V_C^{res} = V_C^I - V_C^{II}$.
[d] From Ref. [7].

Fig. 1. Relationship between theoretical electrostatic potential for the carbon atom at position 4 in mono-substituted bicyclo[2,2,2]octane derivatives and σ_I constants.

Scheme 2.

appears more practical in view of easiness of computations and standardized approach. In a later paper Sayyed and Suresh [63] used in fact EPN values in characterizing the resonance effects of substituents in aromatic systems.

The correlation between σ_I and V_C obtained in the present study is expressed by the following equation:

$$\sigma_I = 26.617\,V_C + 393.482 \quad r = 0.965, n = 23, sd = 0.050 \qquad (4)$$

Eq. (4) provides a simple and efficient approach in evaluating σ_I constants for arbitrary substituent. The use of the model independent EPN values is preferable compared to atomic charges, because of the approximations implicit in their evaluation.

3.2. σ_R substituent constants

The methodology followed in assessing the pure resonance effect of substituents was discussed in the preceding section. As mentioned, Sayyed and Suresh [63] also applied the electrostatic potential at nuclei in evaluating the resonance effects of substituents. The approach used by these authors was, however, different. They assumed that the inductive effect of substituents would be equal for all positions in the aromatic ring, following an early hypothesis of Roberts and Moreland [64]. From the differences in V_C values for meta and para positions in the aromatic ring they estimated the resonance effect of the polar group. In Scheme 2 we show the V_C values for positions 2, 3 and 4 in 1-nitrobicyclo[2,2,2]octane and 1-aminobicyclo[2,2,2]octane. These model systems provide a qualitative description of the field/inductive effect at different distances from the substituents. It is seen that V_C varies quite substantially for positions 2, 3 and 4 in these molecules. As already mentioned, in the bicyclo[2,2,2]octanes the distances from substituent in position 1 to the carbon atoms (or substituents) in position 2, 3 and 4 positions are quite close to the respective distances for positions 2, 3 and 4 in the benzene

derivatives. Thus, the hypothesis of Roberts and Moreland does not appear correct.

In Table 1 we show the obtained results for the quantitative evaluation of the purely resonance influence of substituents on the carbon atom at position 4 in the aromatic ring, as measured by ΔV_C^{res}, using the methodology of the present research. The σ_R parameters were taken from the review of Charton [7]. A satisfactory correlation between ΔV_C^{res} and σ_R is obtained ($r = 0.968$). The plot between the two quantities is illustrated in Fig. 2.

The equation linking σ_R and ΔV_C^{res} is:

$$\sigma_R = 32.711\Delta V_C^{res} - 0.252 \quad r = 0.968, n = 23, sd = 0.075 \qquad (5)$$

Eq. (5) provides a simple approach for the evaluation of σ_R constants.

4. Conclusions

In accord with previous studies on hydrogen bonding and chemical reactivity [36–43] the present research shows that the electrostatic potential at nuclei provides a powerful tool in evaluating various molecular quantities. A simple and meaningful approach for the theoretical determination of σ_I and σ_R constants is outlined. The method is based on correlations between quantities derived from the electrostatic potential at nuclei values and literature data for experimentally evaluated substituent constants.

Acknowledgement

Fig. 2. Relationship between ΔV_C^{res} and σ_R constants.

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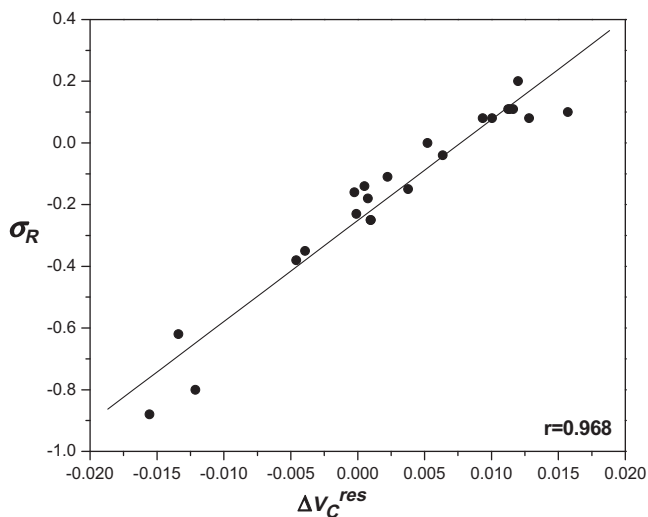[33] C.G. Swain, E.C. Lupton Jr., J. Am. Chem. Soc. 90 (1968) 4328.

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