Most of the field/inductive substituent effect works through the bonds

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Abstract

An application of the quantum chemical modeling allowed to investigate the nature of the field/inductive substituent effect (SE). For this purpose, series of *X-tert-butyl*...*tert-butane* (TTX) complexes (where *X* = NMe₂, NH₂, OH, OMe, Me, H, F, Cl, CF₃, CN, CHO, COMe, CONH₂, COOH, NO₂, NO) were studied. A starting distance between central carbon atoms in substituted and unsubstituted fragments of TTX, *d*_{C1–C4}, was the same as the distance C1–C4 in *X*-substituted bicyclo[2.2.2]octane (BCO), where the SE acts both via bonds and via space. A strength of interaction between substituted and unsubstituted components of TTX was described by deformation and interaction energies. The substituent effect on electronic structure through the bonds and the space was characterized using charge of the substituent active region (cSAR) approach. The comparison of the SE characteristics obtained for alicyclic BCO and for TTX complexes document a significantly stronger field/inductive effect through bonds than through space.

Keywords Field/inductive substituent effects · Electronic structure · Molecular modeling · Deformation energy · Interaction energy charge of the substituent active region

Introduction

Electronic properties of functional groups or substituents are of crucial importance both in organic chemistry and related fields. Numerically, they are most often described by variously defined substituent constants (SC) which are usually

modifications of the fundamental concept introduced by Hammett [1–4]. Already 50 years ago Swain and Lupton [5] mentioned over 20 various SCs. In conclusion, they emphasized that there are only two major factors determining substituent properties: *the resonance and field/inductive effects* (for review, see also [6–10]). In the first case, in *X-R-Y* system, the π -electron delocalization and the charge transfer from one (e.g., a donating *X*) to another part of the molecule (e.g., an attracting *Y*), leading to a quinoid-like π -electron structure $X(+)=C_6H_4=Y(-)$ if the benzene derivative is taken as an example [11–14], are responsible for the effect. A big problem emerges with an interpretation of the field/inductive effect: whether the interaction is transmitted through the space (the direct electrostatic or field effect) or through the bonds (the inductive effect). The problem arose when Roberts and Moreland [15], following the Hammett procedure, quantitatively estimated the substituent effect directly from acid/base equilibrium constants for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. It is a system in which only the abovementioned two types of interactions can work. According to their conclusions, the two abovementioned influences “have to a great extent *resisted disentanglement* and are very often treated together as a composite effect” [15]. Later,

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derivatives of 4-substituted quinuclidine [16, 17] and gas-phase acidities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids [18] have been used for this purpose, leading to the well-correlated data and comparable with the older ones. Several attempts have been undertaken to separate the abovementioned two ways of interactions (components) of the substituent effects in 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. The electrostatic calculations based on Kirkwood and Westheimer formulas [19, 20] occurred to be not effective [21]. Results of the first quantum chemistry calculations [22, 23] supported the field effect as a main factor for these kinds of interactions. A similar conclusion came from the *ab initio* calculations of substituent effect parameters estimated for ketenimines, isocyanides, and nitriles [24]. However, the through bond interactions also have followers (for review of these problems, see articles by Galkin, Charton, and Exner [25–27]). An application of the molecular electrostatic potential topography [28] reveals that the ratio of through bond/through space effects depends strongly on the kind of a link (alkane, alkene, and alkyne chain) between substituents and the benzene ring. For the alkyl chain, the through bond effect is 20.4%, whereas for unsaturated ones is ~55% of all effect. Furthermore, the problem is still open as presented in the detailed review [10].

In the case of π -electron systems, both the resonance and inductive/field effects contribute to the overall observed SE and the problem is in their composition. It is generally accepted that in *para*-substituted benzene derivatives, there are equal contributions of the resonance (R) and inductive/field (I/F) effects, whereas in the *meta* ones, the R-effect is around 1/3 of the overall one [29]. This ratio is not always constant, since in many cases correlations of properties measured or computed for *meta*- and *para*-substituted benzene derivatives sometimes led to other ratio values [6, 8, 30, 31]. In addition, a linear regression of the original 16 Hammett substituent constants used in this study, σ_m vs σ_p , has led to a slope value of 0.488, with the correlation coefficient $cc = 0.935$, indicating even less than 0.33 contribution of the resonance in the *meta* position.

In front of the ambiguous interpretations of the nature of the field/inductive effect, we have undertaken quantum chemically based computational model which allows to present a solution of the problem.

Motivation and strategy

Undoubtedly, the substituent effects measured for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids can be composed of two contributions [15]: the direct electrostatic effect (called often as the *field effect*) and the through bond

electric effect named as the *inductive effect*. In order to decide about the nature of the composition of the abovementioned interactions, we have undertaken studies on the substituent effect for an isolated system: the substituted *tert*-butyl interacting through the space with its unsubstituted form, see Scheme 1. Results for this system are compared with the data for mono-substituted bicyclo[2.2.2]octane (BCO) derivatives. For these purposes, *X*-substituted carbon atoms are denoted as C1 whereas the appropriate carbon atoms in unsubstituted part of BCO and part B of TTX are named as C4. Additionally, for simplicity, positions of CH₃ in TTX systems are named as “*ortho*” and “*meta*”, and finally for H at C4, as “*para*”.

The strategy of our research (treatment) is as follows:

- (i) In the first step, the system consists of monosubstituted *tert*-butane TX(A) molecule interacting through the space with its unsubstituted form TX(B) in a TTX complex at the fixed distances between the substituted and unsubstituted carbon atoms in *tert*-butyl- moieties equal to that between C1 and C4 in BCO ($d_{\text{BCO}} \approx 2.60 \text{ \AA}$).
- (ii) Then, this distance is increased by $\Delta d_{\text{C1-C4}}$, in each step by 0.5 Å, up to $\Delta d_{\text{C1-C4}} = 3.0 \text{ \AA}$ (in the first step $\Delta d_{\text{C1-C4}} = 0$).

At each step, for a given distance, there are estimated: interaction energy, E_{int} , deformation energies of both components of interacting system, $E_{\text{def,A}}$ and $E_{\text{def,B}}$, and finally cSAR values for *X* and all CH₃, CH₂ or CH groups. Additionally, the deformation of both isolated molecules from a typical sp^3 geometry for carbon atoms C1 and C4 is determined.

Methods

Series of *tert*-butyl (TTX) substituted systems (Scheme 1) with 16 substituents were used to investigate the nature of the field/inductive substituent effect. The starting distance between C1 and C4 in TTX was the same as the distance in monosubstituted BCO [32, 33]. In order to reduce the overcrowding effect, the substituted *tert*-butyl fragment of the TTX systems was twisted around C1–*X* bonds by 60° in reference to its unsubstituted part. For each studied system, an optimization without any symmetry constraints was performed using the Gaussian09 program [34]. The B3LYP/6-311++G(d,p) method with empirical dispersion D3 correction [35] was used for all calculations. Vibrational frequencies were calculated at the same level of theory to confirm that all calculated systems correspond to the minima on a potential energy surface; energies of the obtained TTX systems are shown in Table S1 (in ESM).

Interaction energy (E_{int}) between two fragments (A and B) in TTX molecules was calculated with the counterpoise

Scheme 1 Schemes and abbreviations of molecular systems discussed in the paper; $X = \text{NMe}_2$, NH_2 , OH , OMe , Me , H , F , Cl , CF_3 , CN , CHO , COMe , CONH_2 , COOH , NO_2 and NO

correction method [36, 37], eliminating basis set superposition errors according to the Eq. (1):

$$E_{\text{int}} = E_{A \cdots B}(\text{basis}_{A \cdots B}; \text{opt}_{A \cdots B}) - [E_A(\text{basis}_{A \cdots B}; \text{opt}_{A \cdots B}) + E_B(\text{basis}_{A \cdots B}; \text{opt}_{A \cdots B})] \quad (1)$$

where $E_A(\text{basis}_{A \cdots B}; \text{opt}_{A \cdots B})$ and $E_B(\text{basis}_{A \cdots B}; \text{opt}_{A \cdots B})$ are the energies of the A and B molecules, respectively, for its geometries obtained during the optimization of the $A \cdots B$ system and calculated using internal coordinates of the A and B molecules, $\text{basis}_{A \cdots B}$; $E_{A \cdots B}(\text{basis}_{A \cdots B}; \text{opt}_{A \cdots B})$ means the energy of the optimal $A \cdots B$ complex.

The energy of deformation (E_{def}) is the amount of energy needed to deform an individual fragment (A and B, Scheme 1) from its optimal (equilibrium) geometry to that obtained in the system $A \cdots B$. For both fragments, deformation energy is defined by Eqs. (2) and (3):

$$E_{\text{def},A} = E_A(\text{basis}_A; \text{opt}_{A \cdots B}) - E_A(\text{basis}_A; \text{opt}_A) \quad (2)$$

$$E_{\text{def},B} = E_B(\text{basis}_B; \text{opt}_{A \cdots B}) - E_B(\text{basis}_B; \text{opt}_B) \quad (3)$$

where $E_A(\text{basis}_A; \text{opt}_{A \cdots B})$ and $E_A(\text{basis}_A; \text{opt}_A)$ are the energies of the A molecule for its geometries calculated during the optimization procedure of the $A \cdots B$ complex ($\text{opt}_{A \cdots B}$) and the monomer (opt_A), respectively. The terms in Eq. (3) should be understood in the same way.

The degree of pyramidalization is described by the difference of 360° and the sum of the valence angles at a given carbon atom (C1 and C4); for planar system, it is equal to 0° .

The use of the cSAR approach [38, 39] allows characterizing the nature of interaction between substituted and unsubstituted forms in TTX. The cSAR(X) parameter is defined as a sum of charges all atoms of the substituent X and the charge of the *ipso* carbon atom. cSAR(CH_3) values were calculated as a mean value for CH_3 fragments in the *ortho* and *meta* positions in TTX. The Hirshfeld method [40] was used to assess atomic charges and then to calculate all cSAR values.

Results and discussion

The obtained results are presented in two subsections devoted to (i) an analysis of interaction and deformation energies of each component of TTX and (ii) a description of their electronic structure in studied systems based on cSAR(X) and cSAR(CH_n) as well as their comparison with X -BCO substituted systems.

Influence of a substituent on strength of interactions in TTX systems

Interaction energies and their statistics for TTX series are shown in Table 1 and Table S2. As expected, at shorter distances, interactions are destabilizing, but for the distance $d_{\text{BCO}} + 2.5 \text{ \AA}$ ($\Delta d_{\text{C1-C4}} = 2.5 \text{ \AA}$), the system is close to equilibrium state, which is confirmed by the data from Table 1 (details in Table S2 in ESM). This is the case for all substituents (substituted TTX series, Table S1). In addition, systems with $\Delta d_{\text{C1-C4}} = 2.5 \pm 0.1 \text{ \AA}$ are characterized by higher energy values (less negative), so below systems with $\Delta d_{\text{C1-C4}} = 2.5 \text{ \AA}$ are called equilibrium state.

When approaching TX(A) towards TX(B), due to the overcrowding, deformations of both components of the interacting systems appear. Mean values of deformation energies and their statistics for TTX series are presented in Table 2 (details in Table S3 in ESM).

Table 1 Mean values of interaction energies, E_{int} , and their statistics for particular C1–C4 distances, $\Delta d_{\text{C1-C4}}$, in studied TTX systems

TTX	$E_{\text{int}}/\text{kcal/mol}$						
$\Delta d_{\text{C1-C4}}/\text{\AA}$	0	0.5	1	1.5	2	2.5	3
Range	7.52	3.98	1.69	0.95	0.50	0.22	0.50
Average	28.39	16.21	8.53	2.99	−0.75	−2.03	−2.00
SD	2.44	1.07	0.50	0.28	0.16	0.05	0.11

Table 2 Mean values of deformation energies, E_{def} , and statistics for particular C1–C4 distances, $\Delta d_{\text{C1-C4}}$, in studied TTX systems

$\Delta d_{\text{C1-C4}}/\text{\AA}$	$E_{\text{def}}/\text{kcal/mol}$											
	0		0.5		1		1.5		2		2.5	
	A	B	A	B	A	B	A	B	A	B	A	B
Range	6.24	5.05	2.42	3.63	1.59	2.49	1.39	0.72	0.10	0.11	0.03	0.02
Average	26.72	28.26	12.80	16.28	5.14	7.65	1.52	2.26	0.18	0.28	0.00	0.01
SD	1.53	1.48	0.64	0.94	0.39	0.59	0.32	0.22	0.02	0.03	0.01	0.00

For $\Delta d_{\text{C1-C4}} = 3 \text{ \AA}$, the data presented for A and B fragments are 0.00

As can be seen from the data in Table 2, averaged deformation energies of A and B parts for TTX equilibrium systems are very small (at the level of 0.01 kcal/mol). Interestingly, these values are larger (by ca 20%) for part B than for A. All these observations are in line with the observed deviation from sp^3 geometry of carbon atoms (C1 and C4), described by degree of pyramidalization, shown in Tables 3 and S4 (ESM). A greater deformation from sp^3 of the carbon atom for an unsubstituted fragment than that for the substituted one may be understood as a stabilizing effect due to the direct substituent impact on the *tert*-butyl group. For comparison, the degree of pyramidalization of methane as an ideal trigonal pyramid is 31.7° , while for unsubstituted *tert*-butyl is 27.0° (Table S4).

The influence of a substituent on electronic structure

The key point of the solution to the main problem of this paper is the analysis of linear relationships between $\text{cSAR}(\text{CH}_n)$ ($n = 3, 2$ and 1) on $\text{cSAR}(X)$ values (collected in Table S5 in ESM) in TTX and BCO, respectively, an example of the equation: $\text{cSAR}(\text{CH}) = a \text{cSAR}(X) + b$. Table 4 presents slopes and determination coefficients (R^2) for these dependences.

The interactions between X and CH_n in all BCO positions and in the *ortho*-position of TTX complex work more via the bonds than through the space [32], whereas they are only through the space for the *meta*-position of TTX. The comparison of the obtained slope values for the *ortho* and *meta*

equations reveals the difference in the substituent effect between both types of interactions. Taking into account slopes of $\text{cSAR}(\text{CH}_3)$ on $\text{cSAR}(X)$ relations for TTX systems with $\Delta d_{\text{C1-C4}} = 0 \text{ \AA}$, the slope ratio for *meta* and *ortho* CH_3 group is equal $0.068/0.259 \approx 0.26$. The corresponding slope ratio for BCO [$\text{cSAR}(\text{CH}_2)$ on $\text{cSAR}(X)$ relation] is $0.125/0.189 \approx 0.66$. In the first case, there is no bond between the *ortho* and *meta* TTX fragments (they belong to substituted and unsubstituted parts of the complex; see Scheme 1). Therefore, assuming that the deformation of the CH_3 group of the TTX complex with $\Delta d_{\text{C1-C4}} = 0 \text{ \AA}$ does not affect too much its electronic structure, these data reflect relation between the substituent effect acting via the space (TTX) and that working rather through bonds (BCO). This leads to the conclusion that the substituent effect in the TTX system (on the *meta* position) is almost 3 times weaker than in BCO. As expected, the substituent effect decreases with increasing $\Delta d_{\text{C1-C4}}$ distance (documented by the ratios of slopes *meta/ortho*, Table 4).

Furthermore, for TTX systems, an increase (absolute value) of the slopes (a) for the *ortho* relation is proportional to its decrease for the *meta* one, as shown in Fig. 1. For the *meta* position, the absolute a values are decreasing (with elongation of $\Delta d_{\text{C1-C4}}$) since less charge can be transmitted to the B-fragment due to the lack of the through-bond interactions. Thus, more charges are accumulated in the fragment A, what is confirmed by increasing a values for the *ortho* position. Interestingly, the a -values for the *para* position for all

Table 3 Mean values of the degree of pyramidalization and their statistics (in degree) at C1 and C4 carbon atoms in studied TTX systems

	TX	TTX													
		$\Delta d_{\text{C1-C4}}/\text{\AA}$													
		0		0.5		1		1.5		2		2.5		3	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	
Range	11.5	3.9	0.6	7.26	1.97	9.3	2.4	10.6	1.5	11.1	0.8	11.5	0.5	11.6	0.3
Average	28.4	2.0	0.3	7.45	3.27	14.1	9.2	20.6	16.8	25.6	23.5	28.2	26.7	28.7	27.4
SD	3.0	1.3	0.2	2.18	0.45	2.6	0.6	2.8	0.4	2.9	0.2	3.0	0.1	3.0	0.1

Table 4 The obtained slopes of linear equations, a , and determination coefficients, R^2 , for dependences of cSAR(CH₃), cSAR(CH₂), and cSAR(CH) values on cSAR(X) in TTX and BCO

	cSAR(CH _n) on cSAR(<i>X</i>)						Ratio of <i>a meta/ortho</i>
TTX	<i>ortho</i>		<i>meta</i>		<i>para</i>		
	<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²	
Δ <i>d</i> _{C1-C4} /Å							
0.0	−0.259	0.970	−0.068	0.722	−0.019	0.666	0.26
0.5	−0.278	0.979	−0.052	0.654	−0.009	0.256	0.19
1.0	−0.292	0.990	−0.040	0.703	−0.017	0.534	0.14
1.5	−0.293	0.997	−0.034	0.838	−0.021	0.872	0.12
2.0	−0.301	0.998	−0.025	0.841	−0.022	0.914	0.08
2.5	−0.312	0.999	−0.017	0.793	−0.020	0.912	0.05
3.0	−0.317	0.999	−0.006	0.348	−0.025	0.442	0.02
BCO	−0.189	0.951	−0.125	0.912	−0.059	0.939	0.66

distances are nearly constant (~ -0.02 , except in the case of $\Delta d_{C1-C4} = 0.5$ Å), what indicates a very weak influence of the substituent on the *para* position via the space. Examples of charge-change relationships in the unsubstituted TTX (TB) fragment, for $X = \text{NO}_2$ and NH_2 , as a function of increasing Δd_{C1-C4} are shown in Fig. S1 (ESM). It is noteworthy that a greater charge changeability of the unsubstituted TTX fragment (TB part) for the NO_2 group than for the NH_2 group reflects a stronger attracting power from the TB part by the first substituent than the NH_2 donating ability towards electron rich methyl groups.

Additionally, for the TTX complexes with $\Delta d_{C1-C4} = 0$ Å, the changes in the slopes of linear equations cSAR(CH_n) vs cSAR(X) are realized at a ratio of approximately 12:3:1 for the *ortho*, *meta*, and *para* positions, whereas for BCO systems the analogous ratio [32] is 3:2:1 (see Fig. S2 in ESM). Thus, it is again confirmed that the transmission step between TX(A)

and TX(B) (from *ortho* to *meta* CH₃ groups) dramatically reduces the substituent effect due to the lack of bonds.

Conclusions

The use of the cSAR concept allows to investigate the nature of the field/inductive substituent effect in monosubstituted BCO and *tert*-butyl (TTX) systems. For this purpose, the charge flow from substituent X to the rest of the molecule (*ortho*, *meta*, and *para* CH_n groups) was compared in the BCO and TTX systems (X -*tert*-butyl...*tert*-butane, with a different distance between C1 and C4). In the latter complexes, the starting distance between central carbon atoms in substituted and unsubstituted fragments of TTX was the same as the distance C1–C4, d_{C1-C4} , in BCO ($\Delta d_{C1-C4} = 0$ Å). In this case, as expected, interactions are destabilizing, while the

Fig. 1 Relationships between the obtained slope values, a , (Table 4) and Δd_{C1-C4} (in Å) for TTX systems

TTX system with $\Delta d_{C1-C4} = 2.5 \text{ \AA}$ is close to equilibrium state (average values of interaction and deformation energies: -2.03 and 0.01 kcal/mol , respectively).

A good illustration of the substituent effect in both types of systems is the comparison of charge transfer to *ortho* and *meta* CH_n groups based on slopes of $\text{cSAR}(\text{CH}_n)$ on $\text{cSAR}(X)$ dependences. The slope ratios obtained for *ortho* and *meta* CH_n group indicate that for TTX systems, the field effect is from almost 3 times (for $\Delta d_{C1-C4} = 0 \text{ \AA}$) to even more than ~ 10 times weaker (for equilibrium state, $\Delta d_{C1-C4} = 2.5 \text{ \AA}$) than in the case of monosubstituted BCO.

The estimated values of $\text{cSAR}(\text{CH}_n)$ for methyl groups in the *ortho*, *meta*, and *para* positions of TTX systems with $\Delta d_{C1-C4} = 0 \text{ \AA}$ (d_{C1-C4} the same as in BCO systems), influenced by substituent X , are attenuated by a ratio of 12:3:1, while for BCO- X system it is 3:2:1. In conclusion, the obtained results confirm again that the field/inductive effect is realized clearly stronger through the bonds than the space.

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