Inductive or Field Substituent Effect? Quantum Chemical Modeling of Interactions in 1-Monosubstituted Bicyclooctane Derivatives

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Supporting Information

ABSTRACT: Inductive substituent constants were obtained for systems lacking the resonance effect. The application of the charge of the substituent active region concept to study the substituent effect in 1-X-substituted bicyclooctane derivatives (B3LYP/6-311++G** calculations, X = NMe₂, NH₂, OH, OMe, CH₃, H, F, Cl, CF₃, CN, CHO, COMe, CONH₂, COOH, NO₂, NO) has revealed inductive interactions, which are through bonds.

INTRODUCTION

1,4-Disubstituted bicyclo[2.2.2]octane (BCO) derivatives are key molecular systems for the estimation of so-called inductive/field substituent constants. The concept of inductive substituent constants (σ_{ind}) was introduced by Roberts and Moreland. For this purpose, ionization constants measured in a 50% (by volume) ethanol−water solution for 4-substituted BCO carboxylic acids (Scheme 1) were applied. Inductive substituent constants obtained for these systems characterize mutual interactions between two relatively distant functional groups acting without the possibility of a resonance effect. Later, for this purpose, 4-substituted quinuclidine and gas-phase acidities of 4-substituted BCO carboxylic acids were used. Many other attempts for the estimation of substituent constants (denoted as: σ_{μδ}, σ_{μπ}, or F) have appeared, and in most cases, they have led to similar numerical results. This is well illustrated in Table 2 in the review by Hansch et al. Along with the development of research methods and accumulation of new results, a question concerning the mechanisms of interactions between the functional groups in 1,4-disubstituted BCO derivatives has arisen. Is the effect transmitted through space or through bonds? The first would be a field substituent effect (SE), whereas the other, an inductive SE.

In the first case, the effect should be described by electrostatic rules. Some attempts were carried out by the use of the isolated molecule approach. Exner and Bohm performed a very detailed study using both these strategies and arrived at the conclusion that transmission of the SE through space, at least of noncharged functional groups, is of “little validity”. The alternative mechanism of interaction, that is, the transmission of the effect through bonds, “cannot estimate the SE explicitly; it describes only attenuation within the molecule”. This means that each bond weakens the effect by a constant ratio. In summary, according to the results of even the most detailed analysis of various theories of SEs, it is impossible to validate these approaches on the basis of experimental facts.

Recently, several quantum chemical models have been developed that are of substantial importance for the discussion of SEs in terms of physically defined concepts. It should also be noted that particular physical characteristics are compared or correlated with substituent constants. One of the frequently applied methodologies made use of various defined electrostatic potentials, as follows: on particular atoms, at atoms of reaction sites, or in other defined sites of molecules. Additionally and importantly, application of the molecular electrostatic potential topography allowed us to appraise the through-bond
and through-space SEs.\(^{17}\) Implementation of the energy decomposition analysis\(^{18}\) allowed us to document that the pi-electron energy of SE can be correlated with the substituent constants.\(^{19}\) Another very important issue is the energetic characteristic termed SE stabilization energy (SESE), obtained by the use of the isodesmic or homodesmotic reaction approach.\(^{20–22}\) In many cases, it was demonstrated that the SESE values correlated well with the substituent constants.\(^{23–25}\)

Quite recently, it has been shown that the sum of charges at the substituent and ipso carbon atom, termed cSAR (acronym derived from the charge of the substituent active region),\(^{23–27}\) is also well correlated with the Hammett substituent constants. Moreover, it should be noted that usually the values of cSAR(X), calculated by means of various atomic charge assessments, are mutually well correlated.\(^{28}\)

The motivation for our report is to provide a new perspective on the inductive/field effect in monosubstituted derivatives of bicyclooctane (1-X-BCO) derivatives. For this purpose, the cSAR approach will be applied and the cSAR(X) values will be confronted with the substituent constants.

## RESULTS AND DISCUSSION

To study the nature of the SE in 1-X-BCO derivatives, the cSAR parameter has been used to characterize all fragments of the studied systems (Scheme 2). Therefore, cSAR(X), cSAR(CH\(_2\)) at the 2 and 3 positions, and cSAR(CH) at the 4 position have been obtained; in the case of cSAR(CH\(_2\)), the mean values of all three CH\(_2\) groups at the C2 and C3 positions have also been taken into account. Figure 1 presents the results and regression lines, wherein cSAR(CH\(_2\)) in positions 2 and 3 and cSAR(CH) in position 4 of 1-X-BCO are plotted against cSAR(X). In all three cases, the regression lines have high determination coefficients, \((R^2 > 0.906)\); hence, the slopes of these lines are reliable data. As observed, their ratio was \(0.19 : 0.12 : 0.06\), which is near the ideal 3:2:1 ratio, as could be expected from the theory of the inductive effect.\(^{1}\) It appears that this result may be accepted as a strong argument for the inductive mechanism of the SE in BCO systems. Additionally, it should be mentioned that the through-space interactions seem to be negligible in our case because the CH\(_2\) and CH groups have a very small dipole moment and hence very low electrostatic energy.

Actually, both kinds of interactions, via bonds and through space, are described by the substituent constants, \(F.\(^{26}\) Figure 2 shows the relationship between cSAR(X) and \(F\) values for two groups of substituents: (i) with electron-donating properties (\(\sigma_p < 0\)), \(X = \text{Me, OMe, OH, NH}_2, \text{NMe}_2\)) and (ii) with electron-accepting properties (positive \(\sigma_p\) values, \(X = \text{NO, NO}_2, \text{CN, CF}_3, \text{COMe, COOH, CHO, CONH}_2, \text{Cl, F}\)). In both cases, cSAR(X) values decrease with an increase in \(F\) constants. However, the electron-attracting ability of the substituents of the first group is significantly weaker than that of the substituents of the second group.

The next, new result is associated with the application of cSAR(X) as a measure of the electron-donating/attracting properties of \(X\). It has already been shown that the values of cSAR(X) depend on the kind of system to which \(X\) is attached,\(^{23,24}\) and this kind of SE is termed reverse SE.\(^{28}\) The obtained cSAR(X) values for 1-X-BCO and monosubstituted benzene (X-Ph) derivatives are listed in Table 1, together with the differences (\(\Delta\)) between the values estimated for the X-Ph and 1-X-BCO systems, whereas Figure 3 illustrates these differences by means of linear regression. Its slope indicates that the SE in phenyl derivatives is \(\sim 1.7\) times stronger than that in the BCO derivatives. This is due to the difference in the nature of interactions. In the BCO series, only the inductive effect works, whereas in the phenyl series, both inductive and resonance effects are in use.

Additionally, according to the Taft approach,\(^{29}\) the separation of the resonance and inductive effects of a substituent, \(\Delta\), may be considered as a measure of the resonance effect. Indeed, when \(\Delta\) is plotted against the resonance substituent constants, \(R\), the image is as shown in Figure 4. The high determination coefficient supports this assumption.

## CONCLUSIONS

The estimated values of cSAR(CH\(_2\)) and cSAR(CH) for groups in the 2, 3, and 4 positions of 1-X-BCO, influenced by substituent \(X\), are attenuated in a regular ratio, which is 3:2:1.
Hence, it seems justified to accept that \( F \) constants mostly represent the inductive effect. Electron-donating substituents, by means of Hammett \( \sigma_p \), are sometimes electron attracting, when determined in monosubstituted BCO derivatives.

The SE in monosubstituted benzene derivatives is \(~1.7\) times stronger than that in the 1-X-substituted BCO systems, that is, the aliphatic ones. Furthermore, the differences in cSAR(X) values for substituents in phenyl and BCO derivatives may be used as measures of the resonance effect of substituent X.

### COMPUTATIONAL METHODS

An optimization, without any symmetry constraints, of all studied systems was performed using the B3LYP hybrid functional\(^{30,31}\) with the 6-311++G(d,p) basis set.\(^32\) The vibrational frequencies were calculated at the same level of theory to confirm that all calculated structures correspond to the minima on the potential energy surface.

The cSAR parameter\(^{26,33}\) was calculated by summing the atomic charges of all atoms of group X and the charge at the ipso carbon atom to which X is attached

\[
cSAR(X) = q(X) + q(C_{ipso})
\]

For assessments of the atomic charges, the Hirshfeld\(^{34}\) method was applied. All calculations were performed using the Gaussian09 program.\(^35\)

### ASSOCIATED CONTENT

- Supporting Information
  - Cartesian coordinates of equilibrium geometries of 1-X-BCO and monosubstituted benzene derivatives (PDF)

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**Notes**

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### DEDICATION

Dedicated to our friend, professor Guenter Haefelinger, on the occasion of his 80th birthday.

### REFERENCES

1. Exner, O.; Bohm, S. Theory of substituent effects: Recent advances. *Curr. Org. Chem.* 2006, 10, 763–778.
2. Roberts, J. D.; Moreland, W. T. Electrical effects of substituent groups in saturated systems. Reactivities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. *J. Am. Chem. Soc.* 1953, 75, 2167–2173.
3. Grob, C. A.; Schlager, M. G. Polar Substituent Effects on Rates and Equilibria of 4-Substituted Quinolines. Preliminary communication. *Helv. Chim. Acta* 1974, 57, 509–511.
experimental studies on the aminolysis of phenyl acetates. III Predicting reactivities of organic molecules. Theoretical and computational studies of substituents on the dissociation constants of organic acids. II. Substituent effects in 1-substituted 4-anilines.