Electrostatic Calculation of the Substituent Effect: An Efficient Test on Isolated Molecules

Otto Exner[b] and Stanislav Böhm*[a]

Abstract: The energy of a disubstituted molecule has often been approximated by simple electrostatic formulas that represent the substituents as poles or dipoles. Herein, we test this approach on a new model system that is more direct and more efficient than testing on acid–base properties. The energies of 27 1,4-derivatives of bicyclo[2.2.2]octane were calculated within the framework of the density functional theory at the B3LYP/6-311+G(d,p) level; interaction of the two substituents was evaluated in terms of isodesmic homodesmotic reactions. This interaction energy, checked previously on some experimental gas-phase acidities, was considered to be accurate and served as reference to test the electrostatic approximation. This approximation works well in the qualitative sense as far as the sign and the order of magnitude are concerned: beginning with the strongest interaction between two poles, a weaker interaction between pole and dipole, and the weakest between two dipoles. However, all the electrostatic calculations yield energies that are too small, particularly for weak interaction, and this fundamental defect is not remedied by some possible improvements. In particular, variation of the effective permittivity would require a physically impossible value less than unity. The explanation must lie in a more complex distribution of electron density than anticipated in the electrostatic model. It also follows that possible conclusions about the transmission of substituent effects "through space" have little validity.

Keywords: density functional calculations · dipole moment · inductive effects · substituent effects

Introduction

In this theoretical approach, called here the electrostatic theory, the energy of a molecule is approximated by the electrostatic interaction ΔE_{el} between its parts, in the simplest case between two charges, Equation (1), or between a charge e and a dipole μ, Equation (2).[1]

$$\Delta E_{el} = e^2 N_A / r(4\pi\varepsilon_o\varepsilon_{ef}) \quad (1)$$

$$\Delta E_{el} = eN_A\mu\cos\theta / r^2(4\pi\varepsilon_o\varepsilon_{ef}) \quad (2)$$

The geometry of the molecule is described by the parameters r (distance between the charges or between the charge and the point dipole) and θ (angle of the vectors r and μ); ε_{ef} is the "effective" relative permittivity. The theory was applied mostly to ionic isodesmic reactions of the type of Equation (3) in which a proton is transferred from a substituted acid X-G-YH to the anion of the unsubstituted acid H-G-Y$^-$.

$$\text{X-G-YH} + \text{H-G-Y}^- \rightarrow \text{X-G-Y}^- + \text{H-G-YH} \quad (3)$$

The Gibbs energy of this reaction was approximated by the electrostatic energy of the ion X-G-Y$^-$, calculated by means of Equations (1) or (2), according to whether the substituent X was charged or dipolar. In this form, the theory has been included into textbooks and has been the subject of reviews.[2, 3] The compounds in Equation (3) were usually aliphatic derivatives, but also aromatic derivatives assuming that the conjugation can be neglected.[4] In these applications, the electrostatic theory has been connected with the term inductive effect[5] and should decide whether this effect is transmitted "through space" or "through bonds".[2, 6] This problem has been discussed at length.[2, 3, 5b, 6] In our opinion[3] no definite conclusions can be formed, since it is ill formulated: it does not operate with well-defined terms and observable quantities. This concerns also the recent definition of the inductive effect.[5a] In this paper, we will confine ourselves to observable quantities. The substituent effect (whether it is called inductive or not) will be defined by reaction energy of a suitable reaction,[3a] see, for example, Equation (3) or later Equations (5)–(7). Our only problem

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[a] Dr. S. Böhm
Department of Organic Chemistry
Prague Institute of Chemical Technology
Technická 3/5, 16628 Praha 6 (Czech Republic)
Fax: (+420)2-24353635
E-mail: bohm@vscht.cz

[b] Prof. Dr. O. Exner
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic
Flemingovo n. 2, 16610 Praha 6 (Czech Republic)

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will be how accurately and with which limitations the electrostatic theory reproduces this effect.

When Equation (3) is considered in more detail, we can still deal with the interaction in the molecule X-G-YH between the substituent X and the dipolar acidic group YH. The electrostatic energy of two dipoles is expressed by Equation (4), which assumes two co-planar dipoles μ_1 and μ_2 at the angles θ_1 and θ_2 to r.[7]

$$\Delta E_{\text{el}} = -N_{\text{A}}\mu_1\mu_2(2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2)/r^3(4\pi\varepsilon_{\text{o}}\varepsilon_{\text{ef}}) \qquad (4)$$

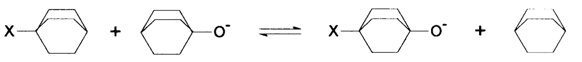
Owing to the dependence on r^{-3}, the interaction of two dipoles is generally small and values of ΔE_{el} calculated according to Equation (4) were used merely as minute corrections for the acidity,[4] although they could be of importance for the conformation of uncharged molecules.[8]

Most of the reactions investigated hitherto proceeded in water or in aqueous solvents; for this reason the effective relative permittivity ε_{ef} has become of deciding importance. An acceptable agreement with certain experiments was only obtained when Kirkwood and Westheimer[9] calculated ε_{ef} from the external permittivity of the solvent (ε_{ext}) and internal permittivity of the molecule (ε_{int}), assuming a simple geometrical form of the solvent cavity occupied by the ion (sphere or prolate ellipsoid). Even so, an ambiguity remained in two respects, that is, for ε_{ef} (shape and dimensions of the cavity) and also for r and θ (conformation, position of the dipole in the given structure). Further development of the theory proceeded along two lines: improving the cavity model[10] and synthesis of special model compounds with more or less fixed geometry, that is, defined r and θ.[11] However, even sophisticated cavity models do not represent well the dependence of pK on the solvent.[12] An essential improvement was reached with acid–base properties measured in the gas phase[3b, 13] or with calculated energies,[14–16] since the acceptable values of ε_{ef} are then between 1 and 2. Nevertheless, ambiguity concerning the geometrical parameters persisted and became even more apparent, since the observed effects are greater. Then it is possible that results on the same compounds were evaluated either as good[15a] or as bad.[16]

In our opinion, significant progress can be reached only by designing new model molecules, which should meet the following requirements:

1) A rigid structure allowing no variable conformations and defining unambiguously the geometrical parameters r and θ.
2) Sufficient distance of the substituent from the reaction center as required by the approximation in Equation (2), whereby the length of the dipole μ is assumed to be small compared to r.
3) Separate determining energies of the ions and of the neutral molecules in terms of isodesmic reactions, not only energies of the ionization.
4) The possibility of comparing effects of polar and dipolar substituents on the same skeleton.

The best models previously devised were 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids.[15, 16] However, even these do not allow exact localization of the pole (COO$^-$) and dipole (COOH) as required above (point 1). Moreover, the effects in the acid and in the anion were sometimes not separated.[15] We have improved the model here by restricting it to 1,4-derivatives of bicyclo[2.2.2]octane with the simplest substituents: O$^-$, NH$_3$$^+$, Cl, CN, and CH$_2$Cl (**1a–1e**, **2a–2d**, **3a–3g**, Table 1). Substituent effects were evaluated in isodesmic reactions, Equations (5)–(7), in which a 1,4-derivative is synthesized from two monosubstituted derivatives.



(5)

1a–1g

(6)

2a–2g

(7)

3a–3l

These compounds meet exactly the requirements of the model. We investigated separately another set of compounds, with the substituents NO$_2$ (**1f**, **2e**, **3h–3j**), COO$^-$ (**1g**, **2f**), and NH$_2$ (**2g**, **3k**,**l**) that violate some of these requirements and will possibly corrupt the results more or less.

It is hardly possible to devise experiments of sufficient accuracy as required by our model. We preferred theoretical calculations within the framework of density functional theory at the level B3LYP/6-311 + G(d,p).[17] This theoretical model proved good for [2.2.2]bicyclooctane-1-carboxylic acids[16] as well as for other molecules with a similar distance of substituents.[18]

Results and Discussion

Relation to experimental results: The energies of the isodesmic reactions given in Equations (5)–(7) are based only on DFT calculations (Table 1, column 7). The electrostatic calculations could, in principle, be based on certain experimental quantities, but we preferred calculated values even for the geometric parameters (Table 1, columns 5 and 6) and dipole moments (Table 2, column 3). They are well defined and sometimes more accurate. Nevertheless, we shall consider briefly how accurately all these values match the experiments.

The calculated isodesmic energies cannot be compared with experimental enthalpies of formation. These are not available for our compounds and could not be sufficiently precise.[19] The only possibility is comparison with experimental gas-phase basicities,[20] Equation (8).

(8)

ΔE(DFT) = 26.3, ΔG(exp) = 22.2 kJ mol^{-1}

Table 1. Calculated energies and geometric parameters of 1,4-disubstituted bicyclo[2.2.2]octanes **1a**–**4b**.

	Substituents		E(DFT) [au]	r [Å]	θ [°]	ΔE[a] [kJ mol^{-1}]	ΔE_{el}[b] [kJ mol^{-1}]
1a	O^-	Cl	– 847.6555311	4.938	0	– 31.3	– 19.1 (– 19.9)[c]
1b	O^-	CN	– 480.2957388	6.076	0	– 42.4	– 25.7
1c	O^-	CH_2Cl	– 886.9697633	6.057	53.5	– 18.9	– 7.6 (– 7.5)[c]
1d	O^-	NH_3^+	– 443.8755758	5.502		– 310.6	– 210.4
1e	O^-	O^-	– 462.5457283	5.504		284.9	210.3
1f	O^-	NO_2	– 592.5993789	6.123	0	– 46.0	– 23.5
1g	O^-	COO^-	– 575.9946978[d]	6.233		243.3	185.7
2a	NH_3^+	Cl	– 828.7360169	4.995	0	27.9	18.7
2b	NH_3^+	CN	– 461.3670442	6.147	0	41.0	25.3
2c	NH_3^+	CH_2Cl	– 868.0604860	6.096	56.8	13.4	6.9
2d	NH_3^+	NH_3^+	– 424.7408737	5.612		313.6	206.3
2e	NH_3^+	NO_2	– 573.6675162	6.166		45.7	23.2
2f	NH_3^+	COO^-	– 557.2914584[d]	6.221		– 265.3	– 186.1
2g	NH_3^+	NH_2	– 424.4849769	5.574	81.5	5.2	1.5
3a	Cl	Cl	– 1232.6308041	4.898	0 180	5.7	4.4 (5.4)[c]
3b	Cl	CN	– 865.2664359	5.546	0 180	6.7	4.5
3c	Cl	CH_2Cl	– 1271.9509422	5.517	56.8 171.5	2.6	1.4 (1.5)[c]
3d	CN	CN	– 497.9014925	6.691	0 180	9.1	5.2 (5.4)[c]
3e	CN	CH_2Cl	– 904.5866178	6.617	58.4 172.8	3.4	1.5
3f	CH_2Cl	CH_2Cl *ac*	– 1311.2707956	6.768	[e]	0.2	0.3[e]
3g	CH_2Cl	CH_2Cl *sp*	– 1311.2704521	6.447	65.9 114.7	1.1	0.8
3h	Cl	NO_2	– 977.5682261	5.576	0 180	7.9	4.1
3i	CN	NO_2	– 610.2034490	6.725	0 180	10.0	4.8
3j	CH_2Cl	NO_2	– 1016.8882556	6.389	172.6 58.0	5.1	1.6
3k	Cl	NH_2	– 828.3726358	4.982	0 81.5	1.7	0.3
3l	CN	NH_2	– 461.0086450	6.128	0 81.5	1.6	0.3
4a	CH_2O^-	H	– 427.3300503				
4b	CH_2O^-	Cl	– 886.9707155	5.758	12.3	– 26.3	– 15.0

[a] Calculated at the B3LYP/6-311 + G(d,p) level by means of isodesmic reactions, Equations (5)–(7), using the energies from the third column and the energies of monosubstituted bicyclo[2.2.2]octanes taken from ref. [16]. [b] Calculated by electrostatic equations, Equations (1), (2), and (4). [c] Calculated according to Equation (1) with the dipoles represented as two charges at the end atoms. [d] Ref. [16]. [e] Calculated according to a more complex equation for not coplanar vectors, ref. [7].

Table 2. Calculated and experimental dipole moments of the derivatives of methane [in D].

Compound	μ B3LYP/6-311 + G(d,p)	μ MP4SDQ/AUG-cc-pVDZ //B3LYP/6-311 + G(d,p)	μ experimental[a]
CH_3CN	4.052	3.942	3.92
CH_3NH_2	1.412	1.300[b]	1.27[c]
CH_3NO_2	3.803	3.659	3.52
CH_3Cl	2.106	1.933	1.90

[a] Ref. [22]. [b] At an angle of 81.5° to the C–N bond. [c] Ref. [23].

The fit is reasonable, although worse than for similar 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids with the same theoretical model as here, for which a standard deviation of 1.1 kJ mol^{-1} was achieved.[16] Such a fit is typical for isodesmic reactions;[16, 18] for absolute values of energies much lower accuracy was anticipated.[17]

Good prediction of the geometric parameters, r and θ, is of less importance, since Equations (5)–(7) are not very sensitive to their exact values. An agreement to 0.01 Å is more than sufficient for our purpose.[21] For μ in Equations (5)–(7) we introduced calculated dipole moments of the methyl derivative X–CH_3, which in our opinion best represent the original meaning, namely, the difference of bond moments of the bonds C–X or C–H. Since the moments calculated at the level B3LYP/6-311 + G(d,p) (Table 2) were lower by several percent than the experimental values,[22] we recalculated them using the model MP4SDQ/AUG-cc-pVDZ//B3LYP/6-311 + G(d,p), which is more suitable for dipole moments.[24] Agreement with the experimental values is then of the same order as the experimental uncertainty.

An important quantity is the effective relative permittivity ε_{ef} [Eqs. (1), (2), and (4)], which cannot be obtained experimentally. For the isolated molecule or in the gas phase, it cannot exceed the range between the value for vacuum ($\varepsilon_{ef} = 1$) and for a hydrocarbon (ε_{ef} approximately 2). Comparison of various cavity theories[9, 10] revealed[12] that they all predict a linear dependence of ε_{ef}^{-1} on ε_{ext}^{-1}. Extrapolation to $\varepsilon_{ext} = 1$

yielded ε_{ef} near to 1.2 for various cavity models and various molecules. We used this value as the first approximation, but retain ε_{ef} as a disposable parameter to be discussed later.

We conclude that the following considerations based on DFT calculations should be valid also for experimental values without a significant decrease of their precision. For any event, some small values of ΔE (say less than 3 kJ mol^{-1}) calculated according Equation (4) should be given less confidence.

Electrostatic calculations

Regular substituents: In the following test, we will consider the energies ΔE (Table 1, the last but one column) of isodesmic reactions Equations (5)–(7) as true values, whose reliability will not be doubted. Their better or worse fit with the electrostatic energies ΔE_{el} (Table 1, last column) will be attributed solely to the restricted accuracy of the electrostatic approximation. First we shall deal with simple substituents as they were defined for an ideal model: one charged atom or one polar bond. Some more complex cases will be mentioned in the next section.

Two general features emerge immediately from Table 1: All ΔE_{el} are too small in absolute values, but in relative values the agreement is rather good. In particular, the ΔE_{el} values have the right sign and reproduce correctly the big differences between the three categories of interaction: between two charges [Eq. (1)], between a charge and a dipole [Eq. (2)], and between two dipoles [Eq. (4)].[25] This is shown in Figure 1 by using the logarithmic scale of absolute values: the electrostatic theory reproduces the interaction energies in a qualitative sense and distinguishes well the three categories. However, all ΔE_{el} values are too small: the agreement is best for the large values for the charged substituents [Eq. (1), compounds **1d**, **1e**, **2d**] and becomes worse for small interaction between dipoles [Eq. (4)]. This is seen more clearly in the plot of original energies in Figure 2 (not covering the whole range of values). We considered three physically meaningful possibilities how the agreement could be improved.

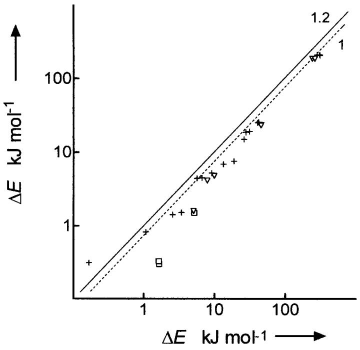


Figure 1. Plot of the substituent effects (energies of the isodesmic reactions) in 1,4-disubstituted bicyclo[2.2.2]octanes in the logarithmic scale; x axis calculated by the DFT theory, y axis calculated by the electrostatic approximatio. +: simple monoatomic or linear substituents; ▽: NO_2 and COO^-; □: NH_2; full and dotted lines represent prediction of the theory with the given value of $\varepsilon_{ef} = 1.2$ or 1, respectively.

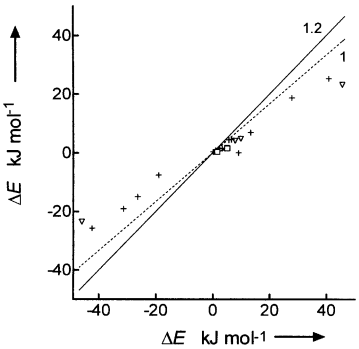


Figure 2. The same plot as in Figure 1 in the original scaling, not representing all data.

1) The point-dipole approximation can be improved by correction for the finite dipole length.[7] Instead of this, we proceeded directly to the opposite approximation of point charges, representing the dipole as two charges at the end atoms. Several examples in Table 1, footnote [c] reveal minute differences: sufficient distance between the two substituents warrants that any of the two approximations is equally good and correction for the dipole length will not help.
2) In addition to the pole/pole and pole/dipole interactions also pole/induced dipole interactions[4, 13, 26] can be taken into account. In Equation (9),[26] the polarizability α (for one molecule) can be derived from the molar refraction of individual atoms or groups.[27]

$$\Delta E_{ind} = -N_A \alpha q^2/2(4\pi\varepsilon_o\varepsilon_{ef})^2 r^4 \qquad (9)$$

Due to the dependence on r^{-4}, the values of ΔE_{ind} are small and sensitive to the exact value of r. What is more important, they are always negative, that is, stabilizing the disubstituted derivative. For **1a** ΔE_{ind} is relatively large. We calculated -0.96 kJ mol^{-1} and the fit was very slightly improved. However, for **2a** we obtained practically the same value (-0.92 kJ mol^{-1}) and the fit got worse in the same extent. Generally, correction by ΔE_{ind} will improve the fit for any anion and deteriorate it for any cation. The most systematic application to date deals predominantly with anions.[4]

3) The effective permittivity (ε_{ef}) is a rather arbitrary quantity and its proper assessment could improve the results significantly. Our value of 1.2 was obtained from an analysis of the cavity models[12] and is not necessarily the best choice. However, Figures 1 and 2 reveal that any reasonable estimation is not possible: the best fit would require a physically impossible value smaller than unity: for charged substituents say 0.9, for dipoles still less. In the literature, the value $\varepsilon_{ef} = 1$ was used very often.[4, 8, 13–16, 29] Of course, even this value is unacceptable, since the molecule cannot be described as vacuum.

In practice, the above corrections were used rather arbitrarily, mostly in such cases when they could improve the fit as mentioned with ε_{ef} and ΔE_{ind}. In addition, many manipulations can be found in the literature that result in the same consequence.[30] For instance, the dipole of the substituent CN was placed in the C atom[4] instead in the middle of the C≡N bond; of course, the fit was improved. Also the distance r can be defined differently, instead up to the charge in the anion up to the hydrogen atom in the acid molecule.[31] As an extreme case, the factor $\cos\phi$ in Equation (2) was completely omitted,[32] or intentionally neglected[6b] when $\phi < 45°$.

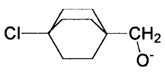
Irregular substituents and more complex cases: Here we shall mention several substituents that do not meet our requirements in an exact model and allow more or less uncertainty in choosing the parameters of Equations (1), (2), and (4). The substituent NO_2 is not linear, but is axially symmetric and its dipole must be placed in the symmetry axis. A most convenient place seems to be in the middle between the atoms N and O. Table 1 and Figures 1 and 2 reveal that the fit is not worse than say for the substituent CN. When the point dipole was placed on the N atom,[4] the fit was of course better.

The carboxylate group COO^-, very important in previous work, is usually represented as a pole placed between the two oxygen atoms.[4, 15, 16] Figure 1 (compounds **1g** and **2f**) reveals the same fit as for other charged groups. When the charge was situated nearer to the carbon atom, the fit was better.

As an example of more complex substituent, we shall mention the amino group. The calculations (Table 2) yield both the absolute value and direction of the dipole; its position must be arbitrary. We placed it at the N atom; any other reasonable choice is hardly possible. Table 1 and Figure 1 reveal a bad fit. Of course, the values are small and in Figure 2 they are practically invisible. Evidently the theory works badly for angular substituents; however, the values are sometimes minute and can escape attention in a series of compounds.

Transmission "through space" and "through bonds": As said in the Introduction, this much-discussed problem is not in the center of our interest. Let us add only the following comment. The better or worse agreement of ΔE_{el} [Eqs. (1) and (2)] with experiment was used as argument that the substituent effect is transmitted through space.[2, 6b] The alternative theory, transmission through bonds, cannot predict the substituent effect; it describes only its propagation: by each bond it is weakened through the constant transmission factor.[2, 3, 6a] In our opinion,[3] the two theories should be viewed merely as two rough numerical approximations: no kind of transmission is compatible with quantum chemistry. Among our data, we can compare the compound **1c** with **1a**, **2c** with **2a**, or **3c** with **3a**. In terms of through-bond transmission, introducing a CH_2 group should reduce the substituent effects by the same transmission factor. This is fulfilled very roughly: the factors obtained from the data of Table 1 were 0.60, 0.48, and 0.46, respectively. However, predictions of the electrostatic theory, 0.40, 0.37, and 0.32, respectively, are not better.

We designed still the compound **4b** for a more efficient test. In terms of through-bond transmission, the substituent effect should be equal to that of **1c**; according to the electrostatic theory, it should be greater by 1.97 (Table 1) in consequence of the more favorable angle ϕ. Actually, it is greater by 1.39: evidently we have to deal with two opposite approximations.



4b

One can understand that two analogous compounds, 4-chlorophenylacetic acid and 4-(chloromethyl)benzoic acid, disclosed equal substituent effects in solution[11c] apparently supporting the through-bond transmission. We have already stated that special model compounds cannot bring a solution of this problem.[3]

Conclusion

The electrostatic theory was tested here only on one set of compounds, but it was from several points of view the best possible model system. The results were reasonable in the relative sense, although they were too small in the absolute values. One can show on further examples that the prediction gets worse when the model compounds are less strictly defined. Particularly important is a sufficient distance of the interacting groups; this was shown on derivatives with sterically close substituents, either in the *ortho*-position on the benzene ring[33] or directly bonded.[34] The theory thus remains applicable only to specified model compounds and is of no practical value for estimating some energy values, also for the reason that much more powerful methods are available. What is particularly important is that it failed (when combined with any cavity model) even for predicting the dependence on solvent.[3, 12]

Computational Methods

The DFT calculations at a B3LYP/6-311+G(d,p) level were performed according to the original proposal[17] by using the standard program.[35] No symmetry conditions were presumed. All energy-optimized structures were checked by the vibrational analysis.

Acknowledgement

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