ATTENUATION OF THE SUBSTITUENT EFFECTS ALONG THE ALIPHATIC CHAIN

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Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday.

Two series of model compounds were devised to follow the attenuation of substituent effects with an interposed methylene group: short-chain aliphatic compounds **1** and derivatives of bicyclo[2.2.2]octane **5**. In all compounds, chlorine atom acts as substituent and charged oxygen atom as the functional group; the interaction of both is measured by the reaction energy of the isodesmic reaction calculated at the B3LYP/AUG-cc-pVTZ//B3LYP/6-311+G(d,p) and/or B3LYP/6-311+G(d,p) levels. Attenuation of the substituent inductive effect with the distance is less steep than observed previously in solution. It depends also markedly on the conformation but cannot be reproduced, not even approximately, by the electrostatic formula. Only for simple regular conformations, it can be described approximately by an exponential function with the transmission factor for one methylene group equal to 0.74. The behavior of isolated molecules differs in this case distinctly from the reactivity in solution. Nevertheless, the significance of the two formulas, electrostatic and exponential, is similar in the isolated molecules and in solution. These formulas represent only two different, rather crude mathematical approximations and cannot be given any physical meaning.

Keywords: Substituent effect; Reaction energy; Isodesmic reaction; Inductive effect; Bicyclooctane derivatives; Methylene groups; Aliphatic compounds; Ab initio calculations; DFT.

The substituent inductive effect, described in the classic literature as a basic principle[1], has retained its general validity[2], although some textbooks inclined to restrict it to the discussion of dissociation constants[3]. In its general notion, it describes interaction of two distant and non-conjugated groups in one molecule. This quantitative description requires an observable quantity – most often the dissociation constant or rate constant – localized at a given place (reaction center); the inductive effect is defined as

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change of this quantity caused by a relatively remote (at least not neighbor) substituent. A salient feature is a decrease of the effect (attenuation) with the distance of the substituent. Mathematically it was expressed in two ways. One is the electrostatic formula[1c,4] as for instance Eq. (*1*), which is valid for a dipolar substituent with the dipole μ at the distance r from the reaction center; ε_{ef} is the effective permittivity, θ is the angle of the vectors μ and r.

$$\Delta E_{\mathrm{elst}} = eN_A \mu \cos\theta / r^2 (4\pi\varepsilon_o \varepsilon_{ef}) \qquad (1)$$

The second approach, called sigma-inductive theory, assumes that the effect is weakened with each bond by a constant factor[5], the transmission factor or fall-off factor π. In Eq. (*2*) the symbol Y may stand for a deliberate quantity (mostly for the Gibbs energy or pK), Y^0 refers to the unsubstituted compound; n is the number of bonds, ρ and σ are empirical proportionality constants, belonging to the functional group and substituent, respectively. Due to the presence of empirical constants, this approach does not allow the inductive effect to be predicted for a given structure but describes only its propagation, i.e. relative intensity in different compounds.

$$Y - Y^0 = \rho\sigma\pi^n \qquad (2)$$

The two theories were reviewed and tested, referring to experimental data on special model compounds[6,7] or to calculated energies[8,9]. Usually the test was associated with the question of whether the substituent effect is "transmitted" through space or through bonds. We brought several arguments[6] that the question is ill-formulated and cannot be answered in a simple way, particularly not on the basis of sophisticated model compounds. Even the term "transmission" is not compatible with the quantum chemical theory. The problem was discussed at length[6–8]. Most recently it has been proven that Eq. (*1*) expresses the reality merely qualitatively with systematic deviations[9b]. Nevertheless, the opinion persists that the electrostatic description should be more correct in principle[7,8,10]. Then it remains to explain why the sigma-inductive theory worked for many experimental quantities rather generally and with reasonable precision. In most organic compounds, the substituent and reaction center are separated by a hydrocarbon chain; in this case π in Eq. (*2*) is the transmission factor (fall-off factor) of the CH_2 group, π_{CH2}. For other groups, this factor need not be equal[11], particularly not for groups containing multiple bonds. The experimental evidence is rather broad, mostly on ionization and rate constants[12], also in the gas phase[13,14]. Even a more sophisticated theory was elaborated describing satisfactorily substituent effects in cyclic and polycyclic compounds[15]. This all is hardly compatible with the electrostatic approach. The problem was analyzed in most detail by Hine[14]. In addition to solvent effects and some unexplained factors, Hine sees the main problem in the constant steep weakening of the effect along the aliphatic chain. In his opinion, the transmission factor must decrease with increasing *n* but an experimental proof is difficult: Either the effect becomes too small to be measured reliably, or the appropriate reaction series have not been studied sufficiently far. Actually some indications of this behavior were recorded but in a reaction with the SN2 mechanism[16] where the unchanged position of the transition state is not warranted.

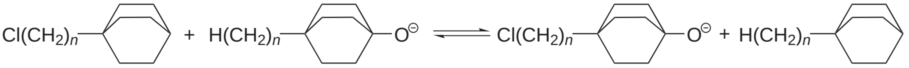
We carried out this study with the idea that what was not possible in experimental way, may be accomplished by calculations at an appropriate level. The substituent effect in chloroalkanoate anion **1** is represented by the reaction energy $\Delta_3 E$ of the isodesmic (and homodesmotic[17]) reaction, Eq. (*3*). It can mean the effect of the substituent Cl on the reaction center O^-, or vice versa. This definition of the substituent effect[6b] is unambiguous and has a clear physical meaning.

$$\mathrm{Cl(CH_2)}_n\mathrm{H} + \mathrm{H(CH_2)}_n\mathrm{O^-} \rightleftharpoons \underset{\mathbf{1}}{\mathrm{Cl(CH_2)}_n\mathrm{O^-}} + \mathrm{H(CH_2)}_n\mathrm{H} \qquad (3)$$

In Eq. (*3*) the substituent effect is related to hydrogen as reference, corresponding to the "unsubstituted" compound. In the case of small molecules, it is advisable[18] to refer rather to the methyl group as in Eq. (*4*), in which the chloroalkanolate anion **1** is synthesized from two molecules **2** and **3**. Comparison of the molecules of the same size minimizes the influence of the substituent polarizability.

$$\underset{\mathbf{2}}{\mathrm{Cl(CH_2)}_n\mathrm{CH_3}} + \underset{\mathbf{3}}{\mathrm{CH_3(CH_2)}_n\mathrm{O^-}} \rightleftharpoons \underset{\mathbf{1}}{\mathrm{Cl(CH_2)}_n\mathrm{O^-}} + \underset{\mathbf{4}}{\mathrm{CH_3(CH_2)}_n\mathrm{CH_3}} \qquad (4)$$

We calculated the reaction energies $\Delta_4 E$ of the reaction of Eq. (*4*) within the framework of the density functional theory[19] (DFT) for different values of *n*. Then we were able to evaluate the transmission factor π_{CH2} and to test its constancy. For higher values of *n*, the calculations become cumbersome due to increasing number of conformations. We carried out the calculations for $n = 2$ and 3 with all conformations and evaluated $\Delta_4 E$ for individual conformers as well as for the real equilibrium mixtures at 298 K. For $n =$ 4 and 5, we restricted the calculations to one conformer with all-*ap* conformations. As further model compounds with a longer chain and more rigid molecule, we used bicyclo[2.2.2]octane derivatives **5**, Eq. (*5*), exploiting the calculations carried out previously on the first compounds of this series[9].



(*5*)

6 **7** **5** **8**

In the case of these larger molecules, the effect of polarizability is negligible and comparison was carried out with reference to hydrogen (compounds **6** and **7**). We calculated the energy of **5**–**8** for *n* = 0–2 and the resulting factor π_{CH2}.

Our aim was thus only to test the two simple theories as far as they contribute to the basic ideas of organic chemistry. We were particularly interested in the questions of whether π_{CH2} diminishes with the chain length and how it depends on the conformation, perhaps whether the electrostatic approach does not yield a better picture. The DFT calculations were used here as firm reference. More sophisticated calculations based on successive polarization of bonds[20] met with fair success and are evidently superior to Eq. (*1*) or (*2*). However, they are less important for the present purpose since they do not result in simple rules.

CALCULATIONS

Calculations were performed within the framework of the density functional theory[19] using the Gaussian 03 program[21]. With compounds **5**–**8** the B3LYP/6-311+G(d,p) level was used which gave very good results for various derivatives of bicyclo[2.2.2]octane[9a,9c] (fit with the experimental gas-phase acidities 1.1 kJ cm^{-1}). For some smaller molecules, this level appeared to be not entirely satisfactory[22]. Therefore the level B3LYP/AUG-cc-pVTZ//B3LYP/6-311+G(d,p) was used with compounds **1**–**4**. No symmetry conditions were presumed. When *n* = 2 or 3, calculations were carried out for all staggered conformations, with *n* = 4 or 5 only for *ap* conformations on all C–C bonds. All structures were checked by vibrational analysis and were found to be energy minima. The calculated energies *E*(DFT) are listed in Table I.

Population of the conformers was calculated assuming that *E*(DFT) equals $\Delta G^0(298)$. Only the symmetry contribution to entropy was taken into account: unsymmetrical conformations were taken twice in the equilibrium. With the population obtained, the effective energy of the equilibrium mixture of conformers was calculated. The results are given in Table II.

RESULTS AND DISCUSSION

Conformation and Relation to Experimental Values

Model compounds **1** and **5** were devised with the intention to minimize the number of conformers: both interacting functional groups are monoatomic. However, conformation of the hydrocarbon chain in **1**–**4** must be taken into account. As seen from the DFT energies given in Table I, the rela-

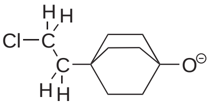
TABLE I
DFT energies of chloroalkanoate anions **1** and **5**, and of reference compounds[a]

n	Conformation[b]	**1**	**2**	**3**	**4**
2	*ap*	**–614.1506460**	**–578.8242104**	**–193.8247152**	**–158.5208871**
	sc	–614.1435321	–578.8241086	–193.8264157	–158.5195102
	equilibrium mixture	–614.1502852	–578.8241436	–193.8257709	–158.5200110
3	*ap,ap*	–653.4706208	**–618.1522876**	–233.1531125	**–197.8489076**
	sc,ap	**–653.4742574**	–618.1507728	**–233.1553457**	–197.8474342
	ap,sc	–653.4652013	–618.1521733	–233.1502544	–197.8474342
	sc+,sc+	–653.4700887	–618.1507728	–233.1540970	–197.8460558
	sc+,sc–	[c]	–618.1483557	–233.1536948	–197.8434299
	equilibrium mixture	–653.4734027	–618.1514205	–233.1542773	–197.8474736
4	*ap,ap,ap*	–692.7973583	–657.4804355	–272.4814583	–237.1769641
5	*ap,ap,ap,ap*	–732.1217505	–696.8085326	–311.8097205	–276.5050975
		5	**6**	**7**	**8**
0		–847.6555311[d]	–773.0023372[d]	–388.0129694[d]	–313.3717029[d]
1		–886.9697633[d]	–812.3212816[d]	–427.3406600[d]	–352.6984378[d]
2	*ap*	**–926.2925103**	**–851.6430689**	–466.6615732	–392.0191784
	sc	–926.2869190	–851.6405507	–466.6615732	–392.0191784
	equilibrium mixture	–926.2917690	–851.6420974	–466.6615732	–392.0191784

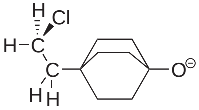
[a] In a.u.; calculated at the level B3LYP/AUG-cc-pVTZ//B3LYP/6-311+G(d,p) for the compounds **1**–**4**, at the level B3LYP/6-311+G(d,p) for the compounds **5**–**8**. [b] The conformations around the single bonds are given successively from right to left with respect to formulas **1**–**4**; the energies of the most stable conformer of a given compound are printed in bold. [c] Stable conformer of this conformation was not observed, calculations starting from dihedral angles 60 and –60° finished at another conformation. [d] Ref.[9]

tive energies differ in the individual compounds. Some conformers could not be obtained as energy minima (footnote *c*), some others are populated by as much as 95% (**1***ap* for $n = 2$). What is most important, related compounds, involved in one reaction, need not prefer the same conformation (**1** and **2** for $n = 3$). This was the main reason why the compounds with a longer chain were investigated only in one fixed conformation.

Conformation of simple derivatives of bicyclo[2.2.2]octane was mostly unambiguous[9]. The compound $\mathbf{5}^{(2)}$ (i.e. compound **5** for $n = 2$) exists in two conformations shown: $\mathbf{5}^{(2)}$*ap* is more populated (87%) than $\mathbf{5}^{(2)}$*sc*. This preference persists even in $\mathbf{6}^{(2)}$ (61%).



$\mathbf{5}^{(2)}$*ap*



$\mathbf{5}^{(2)}$*sc*

For any comparison with the experimental values, only the energies of the conformer mixtures can be used. This comparison can be carried out only in terms of transmission factors π_{CH2} as described in the next section; a direct comparison of energies according to Eq. (*3*) or (*4*) is not possible since the experimental data are not available[23].

The Transmission Factor

Values of the π_{CH2} factor are collected in Table II, the last two columns. They were obtained on the basis of Eq. (*2*) as a ratio of the two reaction energies, Eq. (*6*).

$$\pi_{CH2} = \Delta E_n / \Delta E_{n-1} \qquad (6)$$

From Table II, it is first evident that all π_{CH2} are significantly greater than the values ever found from solution experiments: attenuation in solution is much stronger. Second, the calculation level is of little importance (compare the last and last but one column), although the reaction energies themselves differ, in some cases by as much as 4 kJ mol^{-1} (values not given). We conclude that our level of calculation is sufficient for our purpose, viz. for relative values expressed by the transmission factor.

More detailed examination of Table II reveals that the conformation is of deciding importance. Every value of π_{CH2} is related to two isodesmic reactions, either from the series represented by Eq. (*4*) or (*5*), which differ in fact only by the value of *n*. In these reactions, all compounds involved should possess the same conformation on all single bonds. This condition was fulfilled when calculating Δ_4E and Δ_5E. However, one should still retain analogous conformation in the two reactions for *n* and *n* – 1. This cannot be done unambiguously for two compounds one of which has a carbon atom more. In our opinion, only two definitions of π_{CH2} make sense: either for the equilibrium mixture of all conformers or for the conformers with the *ap* conformation on all single bonds. The equilibrium values were obtained for Eq. (*4*) only for *n* = 3, viz. π_{CH2} = 0.74 or 0.69, depending on the calculation level (Table II). They are approximately twice as big as any experimental value derived from the properties in solution.

TABLE II
DFT energies of the isodesmic reactions (kJ mol^{-1}) and transmission of the inductive effect

n	Conformation[a]	Δ_4E, Eq. (*4*)	ΔE_{elst}, Eq. (*1*)	π_{CH2}[b]	π_{CH2}[c]
2	*ap*	–59.4	–43.5		
	sc	–32.9	–30.8		
	equilibrium mixture	–53.5			
3	*ap*,*ap*	–37.1	–19.3	**0.62**	0.59
	sc,*ap*	–40.9	–31.3	0.69	0.67
	ap,*sc*	–26.8	–14.4	0.81	0.75
	sc+,*sc*+	–29.6	–26.1	0.90	0.90
	equilibrium mixture	–39.8		0.74	0.69
4	*ap*,*ap*,*ap*	–32.6	–12.4	**0.88**	0.87
5	*ap*,*ap*,*ap*,*ap*	–22.6	–7.9	**0.69**	0.64
		Δ_5E, Eq. (*5*)	ΔE_{elst}, Eq. (*1*)		π_{CH2}[c]
0		–31.3	–19.1		
1		–16.4	–7.6		0.52
2	*ap*	–18.5	–8.4		1.13
	sc	–10.4	–4.7		0.63
	equilibrium mixture	–19.1			1.16

[a] See Table I, footnote *b*. [b] The transmission factor relates to the molecule with one CH_2 group less and comparable conformation; the values for all-*ap* conformations are printed in bold; calculations at the level B3LYP/AUG-cc-pVTZ//B3LYP/6-311+G(d,p). [c] Calculated at the level B3LYP/6-311+G(d,p).

The values for the all-*ap* conformations (Table II, printed in bold) are evidently more telling. The three values are not constant and do not show an evident decrease as predicted[14]. Obviously the ratio of two consecutive values is a too sensitive quantity and a better insight can be reached from the whole dependence. In Fig. 1 the decrease of the substituent effect, $\Delta_4 E$, with increasing n is shown by the black points. This dependence is interpolated by means of Eq. (*2*) with $\pi_{CH2} = 0.74$ (full line). One can conclude that the trend is represented reasonably, although the values of π_{CH2} calculated from the two neighboring points would differ rather much. The value of 0.74 can be accepted as the transmission factor for isolated molecules. It is much greater than any value determined in solution, similarly as the substituent effects themselves are much greater in the gas phase than in solution.

The second model, bicyclooctane derivatives **5**, Eq. (*5*), yielded rather divergent results (Table II, the lower part). Particularly striking is the value of π_{CH2} for the *ap* conformer and $n = 2$. This is obviously caused by the position of the substituent dipole. The angle θ as defined in Eq. (*1*) is 15.3°, while it is 53.5° for reference compound **5** with $n = 1$. Equation (*1*) and dependence on the angle θ will be tested in the next section. This dependence appears to be less spectacular when comparing together all the model compounds. In Fig. 1 compounds **5** (open squares) deviate only moderately from the extrapolated solid line derived from compounds **1**. We conclude

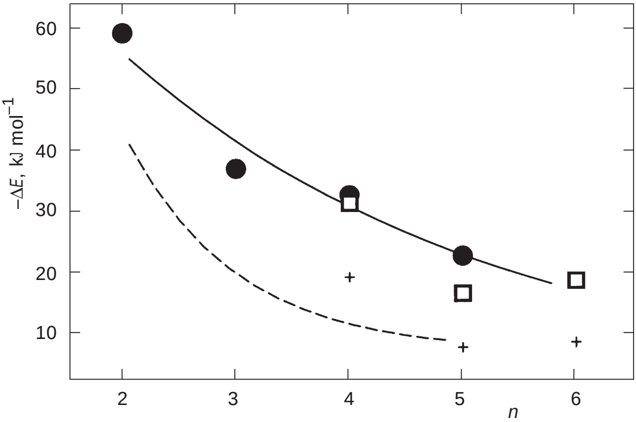


FIG. 1

Attenuation of the inductive effect with the number n of interposed methylene groups; model compounds **1** and **5** were restricted to all-*ap* conformers: ● DFT energies of the isodesmic reactions, Eq. (*4*), full line is the interpolation with Eq. (*2*), broken line shows the values calculated according to the electrostatic theory, Eq. (*1*); □ DFT energies for the bicyclooctane derivatives, Eq. (*5*), + the corresponding electrostatic calculations that attenuation in bicyclooctane derivatives **5** is similar to that in **1**, although for individual conformers rather variable values of the transmission factor may be obtained. Summarizing the results obtained on various conformers and their mixtures, we can agree with the opinion of Hine[14] that a constant attenuation can be possibly expected for the equilibrium mixture but hardly for the separate conformers.

The Electrostatic Approximation

The deviation from the full line in Fig. 1 as well as the rather divergent values of π_{CH2} for various *sc* conformations can be evidently attributed to the influence of the orientation of the substituent dipole. This effect is inherent in the electrostatic theory. The angle θ is involved in Eq. (*1*) while no corresponding quantity appears in Eq. (*2*). The problem of which theory is better (or even which is "right") was discussed broadly in the recent literature[6–10]. On the basis of most rigorous model compounds, 1,4-disubstituted bicyclo[2.2.2]octanes, the main defect of the electrostatic approach was revealed, viz. that all calculated effects are too small[9b]. In this work, the discussion will not be extended, only an additional test will be added using compounds **1** and **5**.

We calculated ΔE_{elst} according to Eq. (*1*) with $\varepsilon_{ef} = 1.2$, separately for all conformations of **1** and **5**. The dipole moment $\mu = 1.933$ D (lit.[9b]) was located in the middle of the C–Cl bond, the negative charge at the oxygen atom. The results are given in Table II, column 4. Their plot vs the DFT-calculated energies is shown in Fig. 2. The salient feature is again that the electrostatic energies are too small in absolute values as observed previously[6b,9a,9b]. A remedy was sought in giving, more or less arbitrarily, smaller values[24] to *r* or to ε_{ef} . Our value[9b] of 1.2 need not be the best choice but the often used value[8,24,25] $\varepsilon_{ef} = 1$ is physically impossible and is to be viewed as an ad hoc correction. Moreover, even this improvement would not be sufficient: Fig. 2 reveals that for most compounds ε_{ef} should be still smaller than unity. One can guess that the main reason of this disagreement is delocalization of the negative charge, or even of the dipole, over the molecule while according to Eq. (*1*) both should be located at definite points. This is, however, the essential assumption of the simple theory and cannot be improved within its framework. On the other hand, it is true that Eq. (*1*) reproduces qualitatively the dependence on conformation, i.e. on the angle θ. In the previous test[9b] it was found that it reproduces also great differences between the interaction of two dipoles, pole/dipole, and two poles. In this work, we are dealing only with the interaction pole/dipole, hence the apparent result of the test is worse.

The two approaches, Eqs (*1*) and (*2*), can be compared even directly using a restricted set of compounds with the regular conformation all-*ap*. In Fig. 1 the energies calculated according to Eq. (*1*) have been plotted as dashed line for compounds **1** and as small crosses for compounds **5**. When comparing with the full line, pertinent to Eq. (*2*), one could conclude that Eq. (*2*) is clearly superior. Note, however, that Eq. (*2*) contains an adjustable parameter (π_{CH2}) while Eq. (*1*) does not. We are of the opinion that both theories are of comparable value for these regular models and cannot be tested on them more efficiently.

CONCLUSIONS

Our results were obtained on two very similar model systems but they allow some more general conclusions. Attenuation of substituent effect with the distance in isolated molecules, particularly in individual conformers, cannot be mathematically expressed by a single transmission factor, valid, for instance, generally for one interposed methylene group. The relative success of this approach for solution reactivities is to be attributed to offset within the equilibrium mixture of conformers, possibly also to solvent effects and cancellation of effects in anions and in acids. Last but not least, it

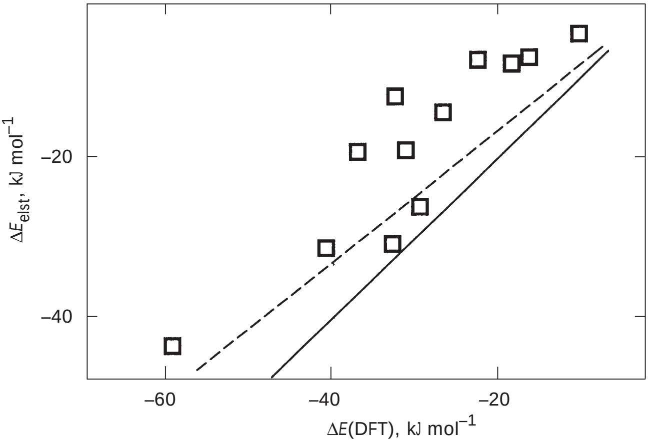


FIG. 2

Comparison of the substituent effect in the model compounds **1** and **5** (all conformations) with the approximate calculation according to the electrostatic theory, Eq. (*1*); full line is the straight line $y = x$ for $\varepsilon_{ef} = 1.2$, broken line is valid for $\varepsilon_{ef} = 1$

is partly due to the fact that the attenuation could not be followed up to sufficiently long distances. The popular rule that the substituent effect drops to less than one half with each CH_2 group can serve as a first estimate for some common systems, not for separate conformers and not for long-chain compounds.

Substituent effects in separate conformers differ strongly depending on the conformation. The dependence on the orientation of the substituent dipole can be expressed by the electrostatic formula but only qualitatively. The two formulas, electrostatic and attenuation, give both only a very rough fit with the actual energies. They are to be viewed only as mathematical approximations and cannot be used to draw any theoretical conclusions[26].

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