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Scope and limitation of the inductive effect: importance of charged substituents

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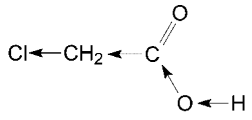
ABSTRACT: The interaction of two relatively distant charged or dipolar groups was evaluated on 1,4-disubstituted bicyclo[2.2.2]octane derivatives as the reaction energy of the isodesmic–homodesmotic reaction, in which this derivative is formed from two mono derivatives. Energies of the individual compounds were calculated at the B3LYP/6–311+G(d,p) level. All combinations of 12 common substituents were investigated, representing 78 reaction energies in a 12×12 data matrix. The behaviour of charged and dipolar substituents is considerably different. Interaction with a charged group is described precisely ($R > 0.997$) by one parameter, essentially identical with the standard inductive constant σ_I. Interaction of two dipolar substituents depends also on σ_I, but requires an additional parameter, important particularly in the case of donor substituents (NH_2, OH, Cl), less important to insignificant with the others. It is significantly correlated with the electronegativity of the first atom. Alternatively, it can be evaluated as a new parameter characterizing the substituent effect, say a new scale of group electronegativity different from the suggested scales. With two parameters, the interaction of polar substituents is expressed with similar high precision ($R > 0.99$) as with charged substituents and one parameter. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: bicyclooctane derivatives; electronegativity; inductive effect; substituent effect

INTRODUCTION

The inductive effect was explained in the classical literature[1] as a concept going through the whole of chemistry: it describes how two atoms or groups within a molecule influence each other when they are sufficiently distant and not conjugated. It is best defined as a change of any measurable quantity, most frequently the ionization constant or rate constant, caused by a variable substituent.[2] Definitions referring to the electron density or to other not observable quantities[3] are less useful. The fundamental feature is that the same groups exert proportional effects on different properties and in different molecules.[2,4] The regular behaviour is expressed in the inductive constants, denoted σ_I or σ_F and characterizing the given substituent in any molecule and at different conditions.[2–4] This general concept has been retained in more recent reviews,[5] although some textbooks give it less attention and mention it just in the case of dissociation constants.[6] A popular picture concerns chloroacetic acid (**1**) and describes the chlorine atom ('substituent') as the initiator of the effect, i.e. of the change in electron density; the carboxyl group functions only as a place where the effect can be measured; sometimes it is denoted as a 'probe'. This point of view was explained most clearly by Taft and Topsom.[4e,7]



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This concept may be somewhat misleading and the dissociation constants in solution are not the best quantity on which the substituent effect can be measured. Even though measurements in the gas phase are now available,[4e,8] the defect remains that the energy changes in the acid molecule and in the anion are merged together. Their separation was attempted[9,10] by means of isodesmic reactions,[11] in which a disubstituted molecule is synthesized from two monosubstituted molecules. It turned out that the substituent effect is greater in the anion of chloroacetic acid than in the acid **1** itself.[9] It was also suggested that presence of a charge is important for regular behaviour in different series and for the existence of empirical relationships.[5a,9a,12] For this reason, attempts to correlate reactivities and properties of uncharged molecules met with little success:[12,13] the carboxylate group does not function as a 'probe', it has greater effect on the electron distribution than a dipolar substituent.

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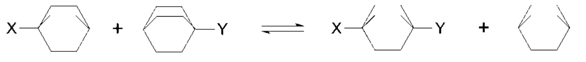
In this work, we used the model in which the inductive effect is defined on an equilibrium reaction, may be as its equilibrium constant, reaction enthalpy or calculated reaction energy. Our example is the isodesmic reaction in Eqn (1).



(1)

2

This definition of the inductive effect[5a,12] has a clear physical meaning and can mean the substituent effect of the group X on Y and also of Y on X, avoiding the problem discussed above. 1,4-Derivatives of bicyclo[2.2.2]octane (**2**) have been used in many experimental[2,4e,14] and theoretical1[9,15,16] studies. They have a defined distance of substituents with exclusion of any resonance; for this reason they were suggested several times as the best model for defining the inductive effect.[2,14] A particular goal of this study was to investigate both charged and uncharged groups by the same method, and to seek for the differences.

Equation (1) is not only isodesmic but also homodesmotic,[17] hence the values of $\Delta_1 E$ can be calculated fairly reliably. We used the DFT model at the B3LYP/6–311+G(d,p) level. This level was previously found to be adequate for the acidities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids[16] and of other molecules of this size.[10b,c]

Studies of the inductive effect have often been focused on the problem[5,15a,18] of whether the effect is transferred 'through space' or 'through bonds'. In our opinion,[5a] the question is ill formulated and does not have a meaningful answer. It will not be dealt with here.

RESULTS AND DISCUSSION

Conformation and comparison with experiments

The substituent inductive effect in **2** is expressed here by the calculated reaction energies $\Delta_1 E$ collected in Table 1. Let us first add the following remarks concerning their reliability. For comparison with experiments, our previous study[16a] is deciding, restricted to ionization of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, Eqn (2). It reproduced the experimental gas-phase acidities[14b] with the standard deviation $s = 1.1\,\text{kJ mol}^{-1}$, comparable to the experimental uncertainty. This experience was observed several times: the reaction energies ΔE, i.e. electronic + nuclear energies calculated at a level as here, can be directly compared with $\Delta G_g(298)$ of the isodesmic reaction.[12] Calculations of the zero-point energy, $\Delta H(T)$ and ΔS according to the standard programs, resulted mostly in insignificant changes[10b,16a] and did not improve the agreement with experiments; sometimes this was even worsened.[10c]

(2)

With the basicities of 1-aminobicyclo[2.2.2]octanes, an effective comparison is not possible since only three experimental values are available:[14c] the standard deviation $s = 2.0\,\text{kJ mol}^{-1}$ has little significance. In our opinion, the calculated $\Delta_1 E$ are as reliable as any values based on the experimental gas-phase ionization and better than would be any $\Delta_f H^\circ$ based on the enthalpies of combustion.

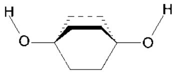
Several compounds of our set can exist in two conformations whose energies are usually very close. Let us quote the most noticeable cases: 1,4-dihydroxybicyclo[2.2.2]octane exhibits two local energy minima in the staggered conformations **2A** and **2B**, which may be denoted as *sp* and *ac*, respectively (the standard nomenclature, *sp*, *ac*, etc., is here slightly extended, treating the axis C1···C4 as it were a bond). The calculated energy difference $\Delta E = 0.43\,\text{kJ mol}^{-1}$ predicts their population as 30 : 70 (chiral **2B** is populated twice); the equilibrium conformer mixture has an effective enthalpy higher than the minimum-energy conformer by $\Delta\Delta H^\circ = 0.13\,\text{kJ mol}^{-1}$. For the analogous

Table 1. Calculated energies $\Delta_1 E$ of the isodesmic reactions of 1,4-disubstituted bicyclo[2.2.2]ctanes, Eqn (1) (kJ mol^{-1})[a]

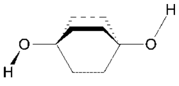
	H	CH_3	CH_2Cl	COOH	CN	NO_2	NH_2	OH	Cl	COO^-	O^-	NH_3^+
H	0	0	0	0	0	0	0	0	0	0	0	0
CH_3	0	0.09	0.12	0.21	0.31	0.33	0.34	0.44	0.47	−1.79	−2.52	−0.94
CH_2Cl	0	0.12	0.17	1.77	3.42	5.06	0.90	1.82	2.56	−14.57	−18.94	13.41
COOH	0	0.21	1.77	1.46	4.33	4.44	0.98	1.75	3.23	−15.55	−19.96	15.94
CN	0	0.31	3.42	4.33	9.15	9.96	1.64	3.36	6.67	−32.75	−42.35	40.98
NO_2	0	0.33	5.06	4.44	9.96	11.62	2.30	4.51	7.91	−35.25	−45.97	45.68
NH_2	0	0.34	0.90	0.98	1.64	2.30	0.86	1.24	1.66	−5.66	−7.33	5.16
OH	0	0.44	1.82	1.75	3.36	4.51	1.24	2.34	3.23	−10.83	−13.98	14.31
Cl	0	0.47	2.56	3.23	6.67	7.91	1.66	3.23	5.69	−23.62	−31.32	27.91
COO^-	0	−1.79	−14.57	−15.55	−32.75	−35.25	−5.66	−10.83	−23.62	210.72	243.31	−265.29
O^-	0	−2.52	−18.94	−19.96	−42.35	−45.97	−7.33	−13.98	−31.32	243.31	284.89	−310.58
NH_3^+	0	−0.94	13.41	15.94	40.98	45.68	5.16	14.31	27.91	−265.29	−310.58	313.62

[a] Based on the calculation at the B3LYP/6–311+G(d,p) level, Ref. 16 and this work; some values in Ref. 16a were slightly corrected.

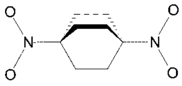
conformations of 1,4-bis(chloromethyl)bicyclo[2.2.2]octane we calculated $\Delta E = 0.90\,\mathrm{kJ\,mol^{-1}}$, population 26 : 74, $\Delta\Delta H^\circ = 0.23\,\mathrm{kJ\,mol^{-1}}$.



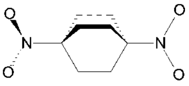
2A *sp*



2B *ac*



2C *sp*



2D *sc*

1,4-Dinitrobicyclo[2.2.2]octane prefers conformations with one N—O bond flanked with one C—C bond, **2C** (*sp*) or **2D** (*sc*); $\Delta E = 0.51\,\mathrm{kJ\,mol^{-1}}$, population 29 : 71, $\Delta\Delta H^\circ$ $0.15\,\mathrm{kJ\,mol^{-1}}$. Similar conformations are possible for the dianion of bicyclo[2.2.2]octane-1,4-dicarboxylic acids. In calculating the substituent effects, i.e. energies of the isodesmic reaction in Eqn (2), we used energies of the most stable conformer given in Table 2, instead of the energies of the equilibrium mixture. In this conception, we are dealing with the idealized substituents not with real compounds at a finite temperature. However, the difference between the two conceptions is minute and cannot spoil any of the following conclusions since the conformers differ little in their energy and are almost equally populated, as seen on the above examples.

Table 2. Calculated energies of some 1,4-disubstituted bicyclo[2.2.2]octanes[a]

Substituents X	Substituents Y	Conformation	*E* (a.u.)
CH_3	CH_3		−392.0251395
CH_3	CH_2Cl		−851.6479692
CH_3	CN		−444.9649570
CH_3	NO_2	O *sp* to one CH_2	−557.2672121
CH_3	NH_2	NH_2 pyramidal	−408.0692362
CH_3	OH		−427.9456874
CH_3	Cl		−812.3288917
CH_3	O^-		−427.3406624
CH_3	NH_3^+		−408.4431068
OH	CH_2Cl	*ac*	−887.5680050
OH	CN		−480.8844785
OH	NO_2	(N)O *sp* to one CH_2, H *sc* to O	−593.1863043
OH	NH_2		−443.9895781
OH	OH	*ac* (**2B**)	−463.8656482
OH	OH	*sp* (**2A**)	−463.8654945
OH	Cl		−848.2485234
OH	O^-		−463.2657117
OH	NH_3^+		−444.3579833
NH_2	CH_2Cl	NH_2 pyramidal, Cl *ac* to(N)H	−867.6918669
NH_2	NO_2	O *sp* to one CH_2, both (N)H *sc* to O	−573.3106554
NH_2	NH_2	both NH_2 pyramidal, mutually *ac*	−424.1132340
NH_2	O^-		−443.3866894
NO_2	NO_2	*sc* (**2D**)	−722.5050788
NO_2	NO_2	*sp* (**2C**)	−722.5048835
COOH	COOH	each=O *sp* to one CH_2, the two OH *ac*	−690.6358383
COOH	COOH	each=O *sp* to one CH_2, the two OH *ap*	−690.6355050
COOH	COO^-	=O *sp* to one CH_2, COO^- *sc*	−690.0843723
COO^-	COO^-	*sc* (similarly as in **2D**)	−689.4402486

[a] Calculation at the B3LYP/6–311+G(d,p) level.

Difference between charged and dipolar substituents

The reaction energies $\Delta_1 E$ of the isodesmic reaction in Eqn (1) obtained in this and previous[16] work are collected in Table 1. This source matrix is symmetrical, has the dimensions 12 × 12 and contains 78 independent items. As expected, $\Delta_1 E$ is greater when one substituent is charged (COO^-, O^-, NH_3^+), and much greater when both substituents are charged. When both substituents are dipolar, $\Delta_1 E$ exceeds only exceptionally $10\,\mathrm{kJ\,mol^{-1}}$ and is always positive (destabilizing). In the case of charged substituents, the sign of $\Delta_1 E$ depends on the charge and is in accord with the laws of electrostatics.

The most remarkable finding is probably the relatively great absolute value of $\Delta_1 E$ for dipolar substituents. This finding is in contradiction with the common procedure of estimating the enthalpies of formation $\Delta_f H^\circ$, which are calculated by an additive scheme from group contributions.[19] If $\Delta_1 E$ of Eqn (1) were represented as a sum of four $\Delta_f H^\circ$ values and these were calculated as a sum of group contributions, the results would be $\Delta_1 E = 0$ for any substitution. Even the recent, very detailed system of group contributions including some specific corrections[19] would give this result. The explanation is on the one hand in the lower precision of the additive relationships ($\pm 4\,\mathrm{kJ\,mol^{-1}}$ for 50% of compounds[19]) on the other in the selection of compounds: the majority of the experimental enthalpies of formation concern hydrocarbons and their mono derivatives; interaction of polar groups has rarely been investigated. For instance, the destabilizing interaction of two electron-attracting groups in four 1,4-disubstituted benzenes[20] is of the same order of magnitude as our $\Delta_1 E$ for the same substituents.

The different behaviour of charged and dipolar substituents was confirmed by principal component analysis (PCA). When applied to the whole of Table 1, PCA requires two components: the first explains 94.2% of the total variance and the second 5.6%. Although this result could be considered satisfactory, the PCA loadings and the correlation matrix reveal that the set is not homogeneous and should be divided into two subsets: one containing compounds with at least one charged substituent and the other only those with dipolar substituents. These sets are shown in Table 1 by the two boxes and will be treated separately in the following two sections.

Table 3. Correlations of substituent effects in 1,4-disubstituted bicyclo[2.2.2]octanes

No.	Response function[a]	Explanatory variables	b[b]	R[c]	s[c]	N[c]
1	σ_I (this work)	σ_I (Ref. 4e)	1.00 (6)	0.9856	0.014	9
2	$\Delta E[COO^-]$	σ_I (this work)	−52.8 (8)	0.9992	0.55	9
3	$\Delta E[O^-]$	σ_I (this work)	−68.7 (11)	0.9991	0.74	9
4	$\Delta E[NH_3{}^+]$	σ_I (this work)	69.7 (21)	0.9969	1.43	9
5	ΔG Quin[d]	σ_I (this work)	82 (4)	0.9870	2.97	12
6	ΔE BCP[e]	σ_I (this work)	−78 (3)	0.9945	2.15	9
7	$\Delta E[CN]$	σ_I (this work)	14.9 (3)	0.9987	0.19	9
8	$\Delta E[NO_2]$	σ_I (this work), $\chi^{(1)}$	16.2 (5), 1.0 (3)[f]	0.9972	0.35	9
9	$\Delta E[COOH]$	σ_I (this work)	6.7 (4)	0.9900	0.25	9
10	$\Delta E[CH_3]$	σ_I (this work), $\chi^{(1)}$	0.21 (9), 0.33 (6)	0.9448	0.062	9
11	$\Delta E[CH_2Cl]$	σ_I (this work)	6.6 (10)	0.9276	0.68	9
12	$\Delta E[Cl]$	σ_I (this work), $\chi^{(1)}$	10.7 (3), 1.00 (17)	0.9984	0.18	9
13	$\Delta E[OH]$	σ_I (this work),$\chi^{(1)}$	5.28 (20), 1.03 (12)	0.9968	0.13	9
14	$\Delta E[NH_2]$	σ_I (this work), $\chi^{(1)}$	2.44 (13), 0.62 (8)	0.9945	0.085	9
15	χ^*(this work)	$\chi^{(1)}$ (Ref. 21b)	1.10 (14)	0.9506	0.15	9
16	ΔE[dipolar]	Eqn (5)	24.6 (4), 1.01 (12)	0.9954	0.29	45
17	ΔE[dipolar]	Eqn (6)	25.3 (6)	0.9876	0.46	45
18	ΔE[all]	Eqn (5)	14.90 (17), 2.8 (5)	0.9955	1.41	72
19	ΔE[all]	Eqn (6)	15.02 (21)	0.9934	1.69	72

[a] The invariable substituent within the given series is given in square brackets.
[b] Regression coefficients with their standard deviation in parentheses.
[c] Correlation coefficient R, standard deviation from the regression s and number of data N.
[d] Basicity of 4-substituted quinuclidines.[3]
[e] Acidity of 3-substituted [1.1.1]bicyclopentane-1-carboxylic acids.[15a]
[f] The second term is significant only at the level $\alpha = 0.05$.

Table 4. Substituent parameters

Substituent	σ_I (this work)	σ_I (Ref. 4)	χ^* (this work)	$\chi^{(1)}$ (Ref. 21b)	χ(Ref. 22)
H	0	0	2.20	2.20	2.176
CH_3	0.019	0.00	2.59	2.55	2.472
CH_2Cl	0.248	0.22[a]	2.39	2.55	2.538
COOH	0.271	0.24	2.53	2.55	2.824
CN	0.608	0.60	2.18	2.55	3.204
NO_2	0.664	0.65	2.86	3.04	3.421
NH_2	0.096	0.14	3.14	3.04	2.992
OH	0.205	0.30	3.47	3.44	3.494
Cl	0.435	0.45	3.16	3.16	
COO^-	−3.774				2.779
O^-	−4.398				3.194
NH_3^+	4.674				3.711

[a] Refers to the substituent CH_2F.

Charged substituents—the classical inductive effect

When one substituent is charged, the data matrix contains only 3 × 12 items (see Table 1), but the results obtained are significant since the correlation is very close: one component explains 99.98% of the variance. This component is essentially identical with the classical term of the inductive effect and correlates closely with its other scales,[2] denoted σ_I or σ_F. An example is given in Table 3, line 1. Similar results were obtained previously[4] and a set of inductive constants was advanced, derived only from the acidity of 4-substituted bicyclo[2.2.2] octane-1-carboxylic acids.[16a] In order to obtain the possibly most precise set, we used the above component derived from the three series and transferred it by a linear transformation into the standard scale[2] of σ_I. Our values are listed in Table 4, column 2. We do not claim that they are generally better than the standard scales, but they are certainly free of solvent effects and more appropriate for energies of isolated molecules. We applied them first, according to Eqn (3), to the three reaction series from which they were derived as mean values:

$$\Delta_1 E - \Delta_1 E^\circ = \rho_I \sigma_I \qquad (3)$$

In this application of the Taft equation, Y is constant in each series, $\Delta_1 E^\circ$ refers to the compound with X = H and should equal zero with the statistical uncertainty; the proportionality constant ρ_I is different for each series. As expected, very tight correlations were obtained (Table 3, lines 2–4), not usual in correlations of solution reactivities. In the literature, two reaction series with calculated data were found: $\Delta G^\circ(298)$ of the basicities of 4-substituted quinuclidines[4d] (model CBS-4M) and ΔH of the acidities of 3-substituted [1.1.1]bicyclopentane-1-carboxylic acids[15a] (model MP2/6–311++G**//B3LYP/6–311+G*) yielded a close fit (Table 3, lines 5 and 6). The somewhat worse result in the former case may be partly due to a different theoretical model; nevertheless, it is still excellent compared with common correlations in solution.

The general validity of the inductive effect was thus confirmed, provided that it is restricted by the presence of one charged group. One can also confirm Charton's statement[2a] that the inductive effect is a 'pure' effect in the sense that it is observed unchanged in various reaction series.

Interaction of dipolar substituents

The data matrix for dipolar substituents has dimensions 8×9 with 36 independent items. PCA would require three components explaining 90.7, 7.3 and 1.3% of the total variance, respectively. The first component is again tightly correlated with σ_I ($R = 0.971$). The results are somewhat impaired by several high values in the correlation matrix (for instance, of the two series with the constant substituent COOH on the one hand and NO_2 on the other). In order to eliminate the inductive effect and to detect clearly the additional effects, we combined PCA with linear regression. Each series was correlated with σ_I and the inductive effect was subtracted. The residual matrix obtained was subjected to PCA. The first component obtained was then systematically examined whether it is related to known parameters: polarizability[4c,e] σ_α, resonance constants[2a] σ_R, electronegativity[21] χ, electronegativity parameter[3c] σ_χ, group electronegativity[22] χ or ι, steric parameters, molar refraction and several parameters derived from NMR data.[21c,23] Most remarkably, a correlation was found only with the electronegativity of the first atom of the substituent, denoted here $\chi^{(1)}$. From various values of χ those of Allred[21b] gave the best fit but differences are very small. Hence we correlated our $\Delta_1 E$ for dipolar substituents according to Eqn (4) for the individual series:

$$\Delta_1 E - \Delta_1 E^\circ = \rho_I \sigma_I + \zeta \chi^{(1)} \tag{4}$$

Correlations were excellent (Table 3, lines 7–14); for only two series, $Y = CH_2Cl$ and $Y = CH_3$, were they somewhat worse. The second term in Eqn (4) was very highly significant in the series $Y = NH_2$, OH, Cl and CH_3 (significance level $\alpha < 0.001$, *F*-test), less for $Y = NO_2$ ($\alpha = 0.05$) and insignificant for Y = CN, COOH or CH_2Cl.

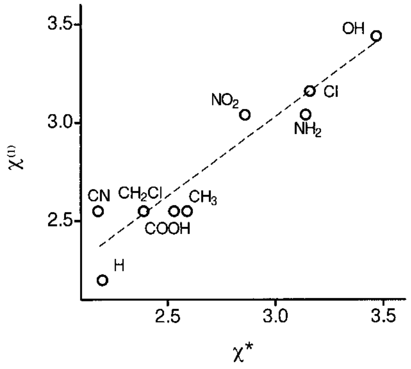


Figure 1. Comparison of the group electronegativities χ^* determined from Eqn (1) with the standard electronegativities of the first atom of the substituent $\chi^{(1)}$ [21b]

In our opinion, the results prove conclusively that interaction of two polar groups is not only weaker but also more complex than interaction involving charged groups. The inductive effect expressed by the constant σ_I remains important and describes satisfactorily the substituent effect when one of the substituents is strongly polar. With less polar groups, an additional effect can be observed, the nature of which is not easy to understand. When it is controlled essentially by the first atom of the substituent (say by its electronegativity), this is in contradiction with the distance of the substituents in our model compounds **2**. However, the statistical proofs are firm. We have still recalculated our first component only from the four series where this term was significant and rescaled it to be comparable to the common scales of χ. The resulting values are denoted χ^* and are given in Table 4, column 4. In Fig. 1 they are plotted against $\chi^{(1)}$. The correlation is evident (Table 3, line 15); nevertheless, χ^* seems to be slightly influenced also by the second atom of the substituent. We cannot suggest χ^* values as a preferable scale of group electronegativity but they are certainly comparable to other scales[22,23] and possibly better physically based. In no case do we suggest χ^* as a new scale of substituent parameters since they were calculated in a complex way and their uncertainty is difficult to estimate. We only feel ourselves obliged to report the values in order that they could be tested on other model systems.

Note that fundamental differences between charged and dipolar substituents were already anticipated on the basis of solution reactivities but under these conditions the behaviour of charged groups was more complex.[24]

General relationship

Both Eqn (1) and the data matrix (Table 1) are symmetrical with respect to the substituents X and Y. It follows that the substituent effect can be described generally by one symmetrical relationship, Eqn (5). The general symbol χ can mean either the electronegativity of the first atom, $\chi^{(1)}$, or the group electronegativity derived here, χ^*.

$$\Delta_1 E_{(\mathrm{XY})} - \Delta_1 E^\circ = \mathrm{A}\sigma_{\mathrm{I(X)}}\sigma_{\mathrm{I(Y)}} + \mathrm{B}[\chi_{(\mathrm{X})} - \chi_{(\mathrm{H})}][\chi_{(\mathrm{Y})} - \chi_{(\mathrm{H})}] \quad (5)$$

Equation (5) was applied first for dipolar substituents only. When using the constants $\chi^{(1)}$ an excellent fit was achieved (Table 3, line 16) and was not improved with χ^*: any advantage of our specialized constants is not evident in the broad context. Particularly important is the comparison with the simpler Eqn (6) (Table 3, line 17): the second term in Eqn (5) is significant at $\alpha = 10^{-6}$ (*F*-test).

$$\Delta_1 E_{(\mathrm{XY})} - \Delta_1 E^\circ = \mathrm{A}\sigma_{\mathrm{I(X)}}\sigma_{\mathrm{I(Y)}} \quad (6)$$

When Eqns (5) and (6) are applied to the whole set, including charged and dipolar substituents, the values of $\chi^{(1)}$ for the charged substituents may be taken as for the first atom or simply as equal to zero. We chose the second possibility but there is practically no difference. The results of correlation are somewhat less definite but remain highly significant (Table 3, lines 18 and 19). At first sight, one could be satisfied with Eqn (6) since the fit is controlled by the charged substituents. However, the second term in Eqn (5) is still significant at $\alpha = 10^{-6}$. The importance of the electronegativity term is also seen very clearly from the contribution to the explained variance. When Eqn (5) is applied only to dipolar substituents, the single term with σ_I explains 97.5% of the total variance and the added term with $\chi^{(1)}$ a further 1.6%; 0.9% remains unexplained. This might be seen as an apparent contradiction to the *F*-test and one could conclude that the simple Eqn (6) is sufficient within the common accuracy of the empirical relationships. The figures may appear to be still more convincing when extended also to charged substituents: 98.7% explained by σ_I, 0.9% by $\chi^{(1)}$ and 0.9 unexplained. However, the results change dramatically when we focus attention on a single reaction series, for instance with $\mathrm{Y} = \mathrm{NH_2}$ (Table 3, line 14). Then σ_I explains 87.5% of the variance, $\chi^{(1)}$ 10.4% and 1.1% is unexplained; hence $\chi^{(1)}$ is inevitable in describing the reactivity. We conclude that the interaction of dipolar groups is insufficiently described by the inductive effect and in the case of slightly polar groups still another mechanism is operative. It is connected with electronegativity, whatever the exact meaning of this word may be.

CONCLUSIONS

Our results were obtained on only one set of model compounds but their structure was the possibly most advantageous with respect to the common definition of the inductive effect—remote substituents, fixed geometry, no multiple bonds, thermodynamically defined property. It has been proved that the interaction of two polar groups is not negligible even at a relatively large distance (five bonds). The classical inductive effect is observed when one of the interacting groups is charged or at least strongly polar (CN, $\mathrm{NO_2}$): then the substituent effect can be described by one parameter, very generally and with high precision. Interaction of less polar groups (OH, $\mathrm{NH_2}$, Cl) depends also on the inductive effect but in addition on another parameter, which has some relation to the not well-defined concept of electronegativity. We evaluated this parameter as a possible scale of group electronegativity (χ^*) but do not give much significance to it. Instead, we used the standard value of χ of the first atom of the substituent as sufficient [$\chi^{(1)}$]. All these results concerns charged or dipolar substituents and are evidently connected with the charge distribution within the molecule. Effects of non-polar groups (alkyls) are small and correlated less precisely by the above equations. In the overall picture of substituent effects they would appear merely as noise and will require a separate investigation.

CALCULATIONS

The DFT calculations at the B3LYP/6–311+G(d,p) level were performed according to the original proposal[25] using the standard program.[26] No symmetry conditions were presumed. All energy-optimized structures were checked by vibrational analysis. The minimum-energy conformations and calculated energies are given in Table 2 and reaction energies of the isodesmic reaction in Eq (1) in Table 1.

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