

Inductive effect of uncharged groups: dependence on electronegativity

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ABSTRACT: Substituent effects in rigid non-conjugated systems were followed on the series of 3-substituted 1-fluoro-bicyclo[1.1.1]pentanes and 2-substituted 1-fluoroethanes in the fixed *ap* conformation. Their energies were calculated within the framework of the density functional theory at the B3LYP/6-311++G(3df,3pd)//B3LYP/6-311++G(3df,3pd) level and the substituent effects were expressed in terms of isodesmic homodesmotic reactions. The results were confirmed by the energies of 1,4-disubstituted bicyclo[2.2.2]octanes reported in the literature and calculated at a lower level. Interaction of two common substituents of low or medium polarity cannot be described as the classical inductive effect by one term, proportional in all series, but an additional parameter is necessary, which depends only on the first atom of the substituent and may be identified with its electronegativity. The second term decreases with the distance more steeply than the first term and is always much less important. Nevertheless its statistical significance was proved by several sensitive tests at the highest level used in statistics. When one of the substituents is charged (or at least strongly polar as NO₂ or CN), the first term is much increased and the second becomes less significant or insignificant. Therefore, the standard definition of the inductive effect with a uniform, universally valid constant can be retained as far as one treats only the ionization equilibria, both in solution and in the gas phase, or kinetics with a strongly polar transition state.

In contrast to the firm statistical proofs, the physical meaning of the electronegativity term was not established. Any relation to various group electronegativities does not exist, similarity to the ¹³C NMR shifts is merely qualitative. Copyright © 2006 John Wiley & Sons, Ltd.

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KEYWORDS: inductive effect; electronegativity; substituent effect; density functional theory; isodesmic reaction

INTRODUCTION

Representation of substituent effects as a linear combination of several components^{1–3} can be questioned in spite of the undisputed success obtained with correlation of restricted sets of experimental data, both in solution² and in the gas phase.³ The objections raised concerned particularly the decomposition into inductive and resonance components (the DSP treatment), particularly the non-constancy of the resonance component⁴ or too broad application to some physical properties.⁵ However, one principle remained unquestionable in this analysis and was still supported by new data; it is the classical inductive effect.^{6,7} It can be observed separately as interaction of two groups in every molecule when these groups are not sterically adjacent and not conjugated. In our opinion, the exact physical definition,⁸ mathematical

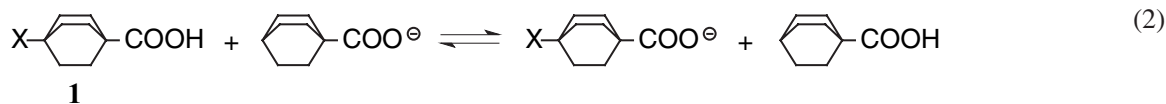
model^{4a,9} or the question^{2,10} of whether the effect is 'pure' are not so important. Essential is the experimental fact that the same effect, almost exactly proportional, is observed in various series, even on very different properties.^{1,11} This is expressed by Eqn (1) where the parameter σ_1 depends only on the variable substituent and ρ_1 only on the given system; E can stand for the reaction energy, Gibbs energy or activation Gibbs energy but similar equation can be formulated even for various physical quantities.^{1,11}

$$\Delta E - \Delta E^\circ = \rho_1 \sigma_1 \quad (1)$$

The constants σ_1 have been determined on various systems with essentially concordant results.^{1b,2} From the theoretical point of view a very suitable system^{1b,2,12} is ionization of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids (1) since it uses molecules of ideally rigid structure. The inductive effect may be defined^{4a} as reaction enthalpy or Gibbs energy of the isodesmic^{11,13} (and homodesmic¹⁴) reaction, Eqn (2). This reaction was investigated broadly both in solution² and in the gas phase.^{3,15}

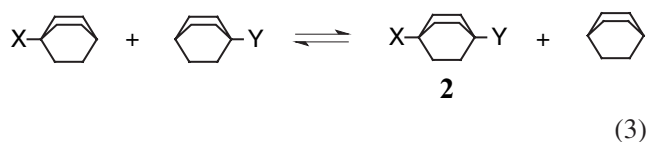
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Further extensive correlations were carried out with Eqn (1) using the reactivity data in solution^{2,7,8} and in the gas phase.^{3,16,17} Recently important confirmation of Eqn (1) was obtained from reaction energies calculated by quantum chemical methods at various levels;^{15,17–20} derivatives of bicyclo[2.2.2]octane played an important role.^{15,19,20} In spite of all this evidence, contemporary textbooks mention the inductive effect as a phenomenon of marginal character.²¹

Although some indications appeared in the literature^{19b,22} that the inductive effect is perhaps not always simple, the first well documented example has been presented²³ on common bis derivatives of bicyclo[2.2.2]octane **2**.



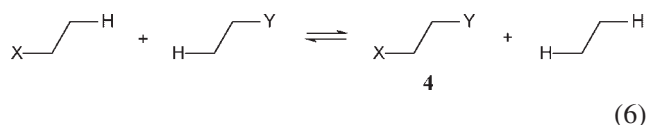
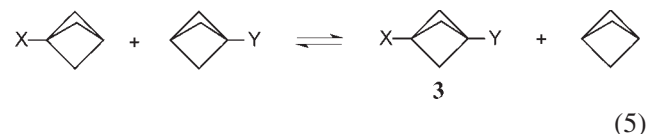
Reaction energy Δ_3E of the isodesmic reaction, Eqn (3), is a measure of interaction of the groups *X* and *Y*. While Δ_3E can be expressed by Eqn (1) when one group *Y* is charged, this equation is insufficient when both groups *X* and *Y* are uncharged. In this case Δ_3E is given²³ by the two-parameter equation, Eqn (4).

$$\Delta E - \Delta E^\ominus = \rho_1\sigma_1 + \zeta\chi^{(1)} \quad (4)$$

The intercept ΔE^\ominus is statistically not different from zero. The additional parameter $\chi^{(1)}$ was identified with the electronegativity²⁴ of the first atom of the substituent (relative to the electronegativity of hydrogen) but the physical meaning of electronegativity and its various definitions^{24–26} are not important in this connection; deciding is that $\chi^{(1)}$ depends only on the first atom. (It is for instance the same for the groups NO₂ and NH₂ in sharp contrast to the pertinent values of σ_1 .) This is difficult to understand since the constants σ_1 depend also on more remote atoms^{2,7} and the inductive effect diminishes regularly with the distance.^{7,27} Nevertheless, the statistical proofs were convincing that the second term in Eqn (4) is significant when the groups *X* and *Y* are uncharged and of medium polarity (for instance NH₂, OH, Cl). When *Y* is charged (COO[−], O[−] NH₃⁺), the first term of Eqn (4) is so great that the second term has not been evidenced; similarly also with *Y* = COOH or CN where still $\chi^{(1)}$ was too small (i.e., the electronegativity little different from hydrogen). Note that the values of Δ_3E are rather small for uncharged groups, at most 10 kJ mol^{−1}, as

compared to more than 40 kJ mol^{−1} when one group is charged.

We wanted to throw some light on the mysterious correlation with electronegativity by means of model molecules with the two substituents situated at a shorter distance. We chose the molecules **3** and **4**.



Some bicyclo[1.1.1]pentane derivatives **3** were previously investigated both experimentally^{28,29} and theoretically^{19a,29} but only for *Y* = COOH and COO[−], that is, the dissociation constants of carboxylic acids. Therefore, only the dependence on the inductive constants was observed. The same applies to the open-chain aliphatic derivatives like **4**: Smaller series of 3-substituted propionic acids and 2-substituted ethylamines were investigated in solution² and several propionic acids in the gas phase;^{16a} population of the conformers remained unknown. Our calculations were carried out for the single conformer **4** (*ap*), uniform for all derivatives. For our purpose it was not important how much this conformer is populated in the equilibrium mixture; it was only necessary that all molecules involved in Eqn (6) had the same conformation. The DFT calculations of molecules **3** and **4** were carried out with a larger basis set (as discussed in the Calculations section) than in previous work²³ since the molecules were smaller.

In investigating the effect of more remote atoms we obtained important support from the recent work of Guo and coauthors³⁰ who calculated the energies of an extended set of derivatives **2** (Eqn (3)), with a different and broad selection of substituents: *X* = CH₃, CN, NO₂, NH₂, OH, SH, F, *Y* = CH₃, CH₂F, CH₂Li, NH₂, NHF, NHLi, OH, OF, OLi, SiH₃, SiH₂F, SiH₂Li, PH₂, PHF, PHLi, SH, SF, SLi. In the original paper³⁰ the energies Δ_3E were correlated only with σ_1 but they gave us the opportunity to test the preference of Eqn (4) against Eqn (1). The merit of this set of substituents is in comparing the pairs like OF and OLi, and similar, differing very markedly on the second atom. Our ultimate intention was to give firm support to the correlation equation, Eqn (4), while it was not possible to offer a physical interpretation at present.

RESULTS AND DISCUSSION

Complex character of the inductive effect of uncharged groups

Detailed analysis of the so-called inductive effect was carried out²³ on the model reaction, Eqn (3), using always a series of derivatives with constant Y and variable X . The reaction energies Δ_3E were correlated with the simple linear relationship, Eqn (1), and with the two-parameter equation, Eqn (4). The predominance of the latter, that is, the statistical significance of the second term, was proven by convincing statistical tests for five such series with $Y = \text{NH}_2$, NO_2 , OH , Cl , or CH_3 . Since Eqn (3) is symmetrical with respect to X and Y , the reaction energy Δ_3E can be also correlated by a general equation valid for all X and Y but it has been established^{19d} that simultaneous dependence on two substituents should be expressed by a more complex equation.

Therefore, we carried out the tests in terms of Eqns (1) and (4) with always one substituent Y fixed. The regression coefficients ρ_1 and ζ were optimized separately in each case irrespective of the assumption that they should be approximately proportional to the constants σ_1 and $\chi^{(1)}$ of the permanent substituent Y . Treatment of this kind is common in the correlation analysis where commonly one group is viewed as substituent, the other as the functional group. We had at disposal the DFT-

calculated reaction energies Δ_3E both from our previous work²³ and from Guo and colleagues³⁰ Since the latter were calculated at a different level, we did not merge the two series and three series were processed twice ($Y = \text{NH}_2$, OH , and CH_3) with a different selection of substituents. With two of these series, the results were practically identical; the series $Y = \text{CH}_3$ is not typical since the interaction energies are too small.

Correlations of our original results were reported,²³ correlation of the Guo's data are described in Table 1. In summary, we had 27 reaction series. The second term of Eqn (4) was statistically significant in 10 series at the confidence level α 0.01 or better ($Y = \text{NH}_2$, OH , Cl , CH_3 , and NH_2 , NHF , OH , OF , SH , F), in three series at α 0.025 ($Y = \text{NHLi}$, OLi , SLi), in 14 series it was not significant ($Y = \text{CN}$, NO_2 , COOH , CH_2Cl , and CH_3 , CH_2F , CH_2Li , PH_2 , PHF , PHLi , SiH_3 , SiH_2F , SiH_2Li , SF). The F -test was in accord with the values of partial correlation coefficients $R_{12,3}$ and $R_{13,2}$ (Table 1), which measure the correlation of Δ_3E with one explanatory variable, as it would be if it were not simultaneously correlated with the second explanatory variable. For σ_1 , $R_{12,3}$ is typically greater than 0.99; for $\chi^{(1)}$, $R_{13,2}$ is very variable and greater than 0.89 only in the 10 named series. The most important series was with $Y = \text{F}$, containing 19 items; the second term was significant at α much smaller than 0.001. (In this series, the substituents X and Y were exchanged and some parameters σ_1 for uncommon substituents had to

Table 1. Statistics of correlation of the stabilization energy of the model compounds **2**, **3**, **4** with Eqn (4): importance of the electronegativity term

Compound	Substituent Y	ρ_1^a (kJ mol ⁻¹)	ζ^a (kJ mol ⁻¹)	R^b	s^b (kJ mol ⁻¹)	N^b	α^c	$R_{ZX,Y}^d$	$R_{ZY,X}^d$
1	2	$Y = \text{CH}_3$	0.54 (31)	+0.566	0.22	8		+0.564	+0.702
2		CH_2F	3.86 (32)	+0.979	0.22	8		+0.988	+0.699
3		CH_2Li	-10.69 (44)	-0.9950	0.30	8		-0.9970	+0.653
4		NH_2	2.31 (12)	0.9961	0.081	8	$\ll 0.001$	+0.9931	+0.981
5		NHF	7.17 (41)	0.9935	0.27	8	0.01	+0.9918	+0.891
6		NHLi	-10.03 (33)	0.9973	0.22	8	0.025	-0.9972	+0.836
7		OH	4.77 (44)	0.987	0.29	8	0.005	+0.979	+0.916
8		OF	10.70 (27)	0.9988	0.17	8	< 0.001	+0.9985	+0.961
9		OLi	-12.36 (51)	0.9959	0.34	8	0.025	-0.9958	+0.832
10		SiH_3	2.98 (47)	+0.934	0.32	8		+0.964	-0.673
11		SiH_2F	4.76 (38)	+0.981	0.26	8		+0.989	-0.666
12		SiH_2Li	-8.99 (42)	-0.9934	0.29	8		-0.9947	-0.518
13		PH_2	4.43 (20)	+0.9941	0.13	8		+0.9951	+0.481
14		PHF	6.60 (24)	+0.9961	0.16	8		+0.9961	+0.259
15		PHLi	-6.73 (61)	-0.977	0.41	8		-0.982	+0.498
16		SH	6.72 (19)	0.9983	0.13	8	0.01	+0.9980	+0.894
17		SF	9.72 (34)	+0.9964	0.23	8		+0.9978	+0.672
18		SLi	-4.83 (25)	0.9932	0.17	8	0.025	-0.9932	+0.848
19		F	8.84 (14)	0.9982	0.17	19	$\ll 0.001$	+0.9982	+0.969
20	3	$Y = \text{F}$	11.9 (32)	0.976	2.1	9	$\ll 0.001$	+0.827	+0.970
21	4	$Y = \text{F}$	20.9 (41)	0.930	2.5	9	0.05	+0.902	+0.747

^aRegression coefficients of Eqns (1) or (4); Eqn (4) used only when the second term was significant at least at $\alpha = 0.05$; standard deviations are given in parentheses.

^bCorrelation coefficient R (R_{ZX} in the simple regression or $R_{ZX,Y}$ in the multiple regression as the case may be), standard deviation from the regression s and number of data N , respectively.

^cSignificance level of the second term (F -test).

^dPartial correlation coefficients for σ_1 and $\chi^{(1)}$, respectively.

be estimated; the estimated values are given in Table 2 and will be discussed later.)

The interpretation of our results is unambiguous: when the fixed substituent Y has a small value of $\chi^{(1)}$ and relatively great σ_1 , ρ_1 in Eqn (4) is much greater than ζ and significance of the electronegativity term cannot be proven. A simple graphical representation may be

perhaps more impressive than statistical proofs. In Fig. 1 the values of Δ_3E predicted either according to Eqn (1) or Eqn (4) were plotted against Δ_3E calculated by DFT. This means that the quantum chemical calculations were used as reference standard, similarly as it would be experimental data. All available data were included. It is evident that Eqn (1) describes the relationship well for

Table 2. Inductive substituent constants derived from isolated molecules

Substituent	Δ_2E Eqn (2) kJ mol^{-1}	Reference	σ_1	σ_1 in solution ^a
H	0		0.000	0
CH ₃	-2.00 ^b	20	0.032	-0.01
C(CH ₃) ₃	-2.02 ^b	20	0.033	-0.01
CH ₂ Cl	-16.34 ^b	20	0.270	0.17
CF ₃	-26.62 ^b	20	0.440	0.40
CCl ₃	-27.82 ^c	This work	0.460	0.36
CHO	-25.1 ^d	19a Supplementary information	0.458	(0.35) ^f
COOH	17.01	23	0.281	0.30
COOCH ₃	-13.12 ^b	20	0.217	0.32
CONH ₂	-15.95 ^c	This work	0.264	0.28
CSNH ₂	-21.82 ^c	This work	0.361	(0.24) ^f
CN	-37.08 ^b	20	0.613	0.57
SiH ₃	-10.0 ^d	19a Supplementary information	0.191	(0.16) ^f
NH ₂	-6.64	20	0.109	0.17
N(CH ₃) ₂	-5.23 ^c	This work	0.087	0.17
N = NCH ₃ -(E)	-10.68 ^b	20	0.173	
NO ₂	-39.69 ^b	20	0.657	0.67
PH ₂	-13.99 ^c	This work	0.231	0.18
OH	-12.58 ^b	20	0.208	0.24
OCH ₃	-10.01 ^b	20	0.166	0.30
SH	-12.6 ^d	19a Supplementary information	0.235	0.27
SO ₂ CH ₃	-37.50 ^c	This work	0.620	0.59
SO ₂ CF ₃	-51.02 ^c	This work	0.844	0.71
F	-21.97 ^b	20	0.364	0.54
Cl	-26.85 ^b	20	0.444	0.47
Br	-29.15 ^c	This work	0.482	0.47
CH ₂ F		Estimated ^e	0.16	(0.20) ^f
CH ₂ Li		Estimated ^e	-0.46	
NHF		Estimated ^e	0.31	
NHLi		Estimated ^e	-0.43	
OF		Estimated ^e	0.45	
OLi		Estimated ^e	-0.53	
SiH ₂ F		Estimated ^e	0.19	
SiH ₂ Li		Estimated ^e	-0.39	
PHF		Estimated ^e	0.27	
PHLi		Estimated ^e	-0.30	
SF		Estimated ^e	0.41	
SLi		Estimated ^e	-0.21	
COO ⁻	226.27	23	-3.74	-0.19
O ⁻	263.28 ^b	20	-4.36	
NH ₃ ⁺	-281.22 ^b	20	4.65	

^a Ref. 2, based either on pK of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in 50% ethanol or of 2-substituted acetic acids in water; these two models gave compatible results.

^b The values of ΔE in Ref. 16 are by 4% too low due to a mistake in the program; the values of σ_1 are correct.

^c Obtained from the following energies calculated at the level B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p): 4-CCl₃-C₈H₁₂-1-COOH, -1920.1784146; 4-CCl₃-C₈H₁₂-1-COO⁻, -1919.6310671; 4-NH₂CO-C₈H₁₂-1-COOH, -670.7588476; 4-NH₂CO-C₈H₁₂-1-COO⁻, -670.2069784; 4-NH₂CS-C₈H₁₂-1-COOH, -993.7102525; 4-NH₂CS-C₈H₁₂-1-COO⁻, -993.1606202; 4-N(CH₃)₂-C₈H₁₂-1-COOH, -635.9950604; 4-N(CH₃)₂-C₈H₁₂-1-COO⁻, -635.4391085; 4-PH₂-C₈H₁₂-1-COOH, -843.9719749; 4-PH₂-C₈H₁₂-1-COO⁻, -843.4193587; 4-CH₃SO₂-C₈H₁₂-1-COOH, -1089.9764341; 4-CH₃SO₂-C₈H₁₂-1-COO⁻, -1089.4327743; 4-CF₃SO₂-C₈H₁₂-1-COOH, -1387.7730726; 4-CF₃SO₂-C₈H₁₂-1-COO⁻, -1387.2345592; 4-Br-C₈H₁₂-1-COOH, -3075.5530138; 4-Br-C₈H₁₂-1-COO⁻, -3075.0061717 (a.u.).

^d Calculated at the level MP2/6-311++G**//B3LYP/6-311+G*; Δ_2E are smaller in absolute values than our values but σ_1 have been scaled and are comparable with the other constants.

^e Estimated from the regression of Δ_4E (Ref. 29) on σ_1 when the values for the substituents COOH and COO⁻ were not available.

^f Ref. 1b, mostly derived from 19 F NMR shifts.

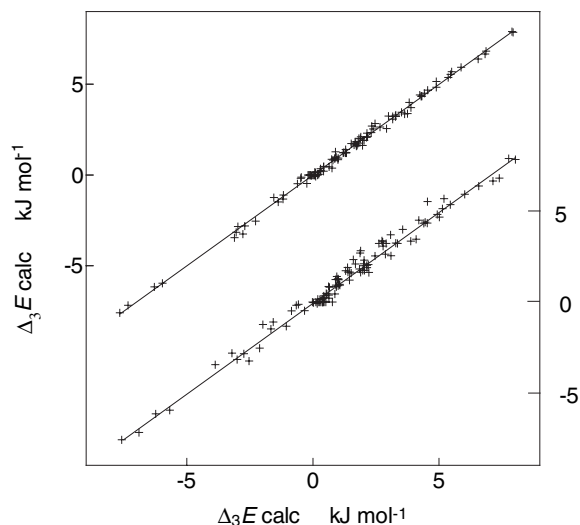


Figure 1. Comparison of the fit of the empirical equations with one parameter or two parameters: reaction energies Δ_3E of the reaction of Eqn (3); x-axis DFT-calculated energies, y-axis energies calculated with Eqn (1) (at the bottom) or with Eqn (4) (at the top)

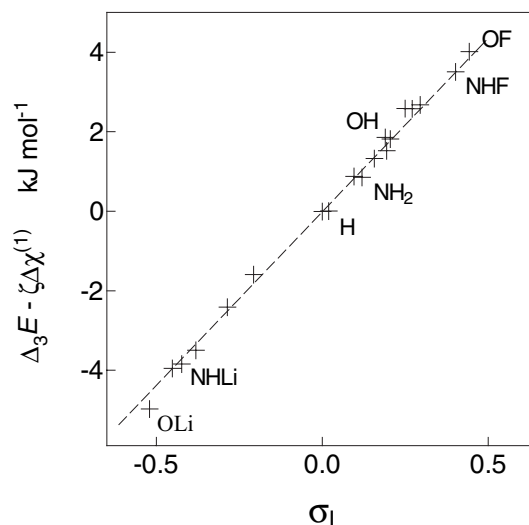


Figure 3. Significance of the two terms of Eqn (4): Reaction energies Δ_3E (with $Y = F$) without the subtracted second term of Eqn (4) have been plotted against σ_1 ; some typical substituents X are noted at the points

many substituents but for some of them the improvement with Eqn (4) is obvious; the σ_1 term is decisive, the $\chi^{(1)}$ term is valid only in the named cases but it is necessary.

A particularly sensitive graphical test may show the significance of the electronegativity term in a given series. The first term of Eqn (4) was subtracted from Δ_3E ; the differences may be viewed also as residuals after processing with Eqn (1). In Fig. 2 these residuals were

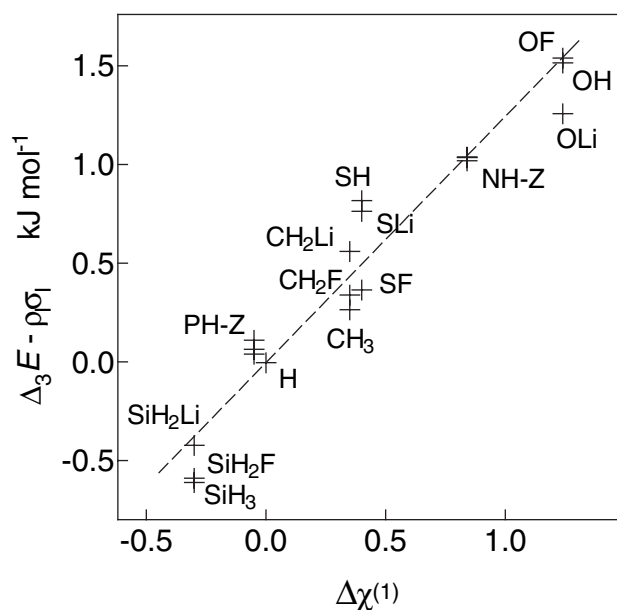


Figure 2. Significance of the two terms of Eqn (4): Reaction energies Δ_3E (with $Y = F$) without the subtracted first term of Eqn (4) have been plotted against $\Delta\chi^{(1)}$; substituents X are noted at the points

plotted against $\chi^{(1)}$. The dependence is evident, in particular one sees clearly that the electronegativity term is controlled only by the first atom of the substituent: there is no difference between the substituents NH_2 , NHF , NHTLi and only insignificant difference between OH , OF , and OLi . The dependence only on the first atom is thus the most remarkable property of Eqn (4). When this test was reversed, the second term of Eqn (4) (a smaller correction) was subtracted from Δ_3E and plotted against σ_1 . We got a closer regression (Fig. 3) since the term with σ_1 is more important; particularly impressive is the difference between substituents OF and OLi —the inductive effect depends sensitively also on the more remote atoms of the substituent. In our opinion, the importance of the electronegativity term is revealed very clearly in this way. As far as we know, common two-parameter equations have never been checked by this very sensitive test.

Dependence of the substituent effects on the distance

We examined the dependence on the distance on bicyclo[1.1.1]pentane derivatives **3** and on ethane derivatives **4** with the fixed conformation *ap*; the fixed substituent $Y = F$ was chosen since its electronegativity is extreme and its effect should be very marked. The substituent effects are represented by the reaction energies Δ_5E and Δ_6E , Eqns (5) or (6), respectively (Table 3). Their correlation with the two-parameter equation, Eqn (4), is described in Table 1, lines 20 and 21. Compared to similarly substituted bicyclo[2.2.2]octanes

Table 3. Calculated energies and some bond lengths of substituted bicyclo[1.1.1]pentanes **3** and 1,2-disubstituted ethanes **4**

Substituent X	3 Y = H		3 Y = F		$\Delta_5 E$ (kJ mol ⁻¹)	4 Y = H		4 Y = F		$\Delta_6 E$ (kJ mol ⁻¹)
	<i>E</i> (DFT) a.u.	<i>E</i> (DFT) a.u.	C–F (Å)	<i>E</i> (DFT) a.u.		<i>E</i> (DFT) a.u.	<i>E</i> (DFT) a.u.	C–F (Å)		
H	–195.3260086	–294.6091466	1.365		0	–79.8627823	–179.1348672	1.399	0	
CF ₃	–532.5037902	–631.7836297	1.357		8.66	–417.0386334	–516.3055717	1.392	13.51	
CN	–287.6004703	–386.8798750	1.354		9.80	–172.1327732	–271.4005771	1.388	11.24	
NH ₂	–250.7056680	–349.9845254	1.362		11.24	–135.2317644	–234.5020277	1.396	4.78	
NO ₂	–399.9077293	–499.1830962	1.352		20.40	–284.4406164	–383.7050675	1.386	20.04	
OH	–270.5821744	–369.8581638	1.358		18.77	–155.1069780	–254.3751881	1.393	10.17	
SH	–593.5522917	–692.8312538	1.362		10.96	–478.0817317	–577.3504439	1.394	8.86	
F	–294.6091466	–393.8821189	1.354		26.69	–179.1348672	–278.4005875	1.391	16.71	
Cl	–654.9624672	–754.2377295	1.357		20.68	–539.4912073	–638.7591344	1.394	10.92	
O [–]	–269.9938256	–369.2806961	1.401		43.70	–135.5920858	–234.8458580	1.369	48.08	
NH ₃ ⁺	–251.0660367	–350.3325316	1.332		–9.80	–154.4932381	–253.7759421	1.439	–27.88	
Li	–202.2107143	–301.5056316	1.407		–30.93	–86.7415299	–186.0282479	1.447	–38.42	

2 (line 19), the overall correlation is less precise but the electronegativity term is statistically significant. With **3**, this term is increased and even more important than the inductive term, with **4** it is smaller and just at the limit of statistical significance.

To get a better survey of the dependence on the distance, we present in Table 4 the relative values of the coefficients ρ_1 and ζ (Eqn (4)) for the compounds **2**, **3**, and **4**. As expected ρ_1 decreases steeply and regularly as reported many times^{4a,9} for the classical inductive effect (i.e., when charged groups are involved). The decrease was related either to the geometric parameters^{19a,27,30} or to the number of bonds;^{31,32} the problem of which mathematical model is better was discussed extensively^{7,9,10,27} and will not be repeated here. Our scarce data of ρ_1 would be compatible with both theories. Our ratio of ρ_1 of **3** an **2** (1.35) agrees with the ratio from the experimental gas-phase acidities of the corresponding carboxylic acids^{29b} (1.295).

The electronegativity effect was expected to drop with the distance still more steeply, just because it is controlled by the first atom of the substituent. This has not been confirmed. In **3** it is much greater than in **2** but in **4** it is again smaller. It evidently does not depend only on the

Table 4. Dependence of the inductive effect on the distance of the substituent^a

Equations	Compounds	ρ^a	ζ^a	$r^{b\text{Å}}$
3	Bicyclo[2.2.2]octanes 2 Y = F	1	1	3.278
5	Bicyclo[1.1.1]pentanes 3 Y = F	1.35	10.9	2.512
6	Ethanes 4 Y = F	2.37	3.8	1.874

^aRelative values of the regression coefficients of Eqn (4) when it is applied to the reaction energies $\Delta_3 E$, $\Delta_5 E$, and $\Delta_6 E$ of the reactions of Eqns (3), (5), and (6).

^bThe distance from the center of the C–F bond to the C atom bearing the variable substituent X.

distance but also on the geometry and on bonds present in the molecule between the two interacting groups. We shall return to this question in the next section. A remarkable mention in the older literature³³ assumed that the inductive effect can be different in cyclic and acyclic systems but the evidence was not convincing.

Some relationship with the electronegativity

For the time being we are unable to offer any physical explanation of the second term in Eqn (4); the problem is already in the definition of electronegativity, particularly for groups.²⁶ Dependence on the electronegativity was claimed^{34,35} for some NMR shifts observed in our compounds: ¹³C in³⁴**2** with Y = CH₃, ¹⁹F in³⁵**2** with Y = F, ¹⁹F in^{36,37}**3** with Y = F, respectively. Some correlations were excellent, the other poor but the electronegativity was defined in a different way and sometimes even not quite unambiguously. The shifts in **2** were correlated with an equation formally similar to Eqn (4) but the electronegativities used³⁵ (denoted ι) were taken from the older paper of Inamoto and Masuda³⁸ neglecting the newer values.^{26b} (Note that even the original definitions^{26b,38} were not quite clear.) Also the values of σ_1 used^{34,35} were specially derived³⁹ from NMR shifts of a similar system but they were nearly proportional to the common scale. In the correlations of **3**, the electronegativities were replaced³⁶ by the electronegativity parameters σ_x defined on a very simple quantum chemical model.⁴⁰ Later this model was improved³⁷ using a larger basis set but the new values were rather different. According to our experience,⁴¹ a larger basis set need not give better results with these oversimplified models.

We carried out the correlations of these ¹³C and ¹⁹F shifts^{34–36} with Eqn (4), using our defined scale of σ_1 and

Table 5. Statistics of correlations of the bond lengths and NMR shifts of the model compounds **2**, **3**, **4** with Eqn (4)

Compound	Quantity	ρ_1^a	ζ^a	R^b	s^b	N^b	α^c
1	3 Y = F C–F bond length	–0.0168(17)	–0.0030(7)	0.980	0.0010	9	0.005
2	4 Y = F C–F bond length	–0.0164(26)	—	0.924	0.0016	9	—
3	2 Y = CH ₃ ¹³ C NMR shift	–1.14(33)	–0.79(13)	0.889	0.25	19	<0.001
4	2 Y = F ¹⁹ F NMR shift	–3.4(14)	–4.0(6)	0.922	0.98	15	≪0.001
5	3 Y = F ¹⁹ F NMR shift	—	–43(5)	0.923	4.2	16	—

^aRegression coefficients of Eqns (1) or (4); Eqn (4) used only when the second term was significant at least at $\alpha = 0.05$; standard deviations are given in parentheses.

^bCorrelation coefficient R (R_{ZX} in the simple regression or $R_{Z,XY}$ in the multiple regression as the case may be), standard deviation from the regression s and number of data N , respectively.

^cSignificance level of the second term (F -test).

$\Delta\chi^{(1)}$ of Allred,²⁴ to obtain a reference excluding any ambiguity: any group electronegativities were avoided and various scales for atoms are numerous but little different from each other.²³ The electronegativity term was always highly significant; with ¹³C and ¹⁹F of **2** it was more important than the inductive term (Table 5, lines 3 and 4), with ¹⁹F of **3** it was the only significant (line 5). However, the overall fit was bad as seen from the correlation coefficients $R < 0.93$. We are of the opinion that the NMR shifts are influenced by electronegativity but affected also by some specific effects; their detailed interpretation is rather complex.³⁷

The most striking property of Eqn (4) is that the second term depends only on the first atom of the substituent; one can imagine something as direct interaction of the bonds C–X and C–Y in **2–4**, or say any interaction of the pertinent orbitals. We examined the dependence of the C–F bond length in **3** and **4** on the substituent X. Eqn (4) holds only for **3** and the second term is significant at $\alpha = 0.005$ (Table 5, line 1). Evidently the interaction depends not only on the distance but also on the detailed geometry. One remembers the old theory of interaction of distant localized orbitals;^{42,43} the interaction was strongly dependent on symmetry and strengthened by the bonds situated between the interacting orbitals. We chose the molecules **3** with the symmetrical substituents X = H, CN or F, and investigated the orbitals contributing to the sigma frame. The most interesting are the orbitals No. 13 (X = H), No. 16 (X = CN) and No. 15 (X = F), which are shown in detail in Figures S1–S3, Supplementary Material. With the first two molecules, when there is a great difference in the electronegativity of X and Y, we found direct bonding interaction between the orbital located on the substituent and orbitals on the bonds of the parent skeleton. With X = F, that is, when X and Y are identical, we found no orbital with the same properties. This result could be qualitatively in accord with the mentioned theory^{42,43} but does not say more for the quantitative explanation. Another interpretation can be attempted in terms of repulsion of the carbon orbitals in the bridgehead

positions⁴⁴ but this explanation can apply only to **2** and **3**, not to **4**.

Inductive effect in the gas phase and in solution

In the course of this investigation, the substituents were always characterized by constants measuring the inductive effect in isolated molecules or in the gas phase. These were obtained either from the defining reaction²⁰ Eqn (2) or statistically from several reactions;²³ subsequently they were scaled to resemble the best known scale² of constant σ_1 determined from data in water solution. In this paper further values were estimated in an indirect way from literature data.²⁹ We collected all values available, giving preference to the values derived from the standard defining reaction, Eqn (2). It turned out that they are slightly smaller than the standard σ_1 in solution. Therefore, we rescaled our σ_1 values with the factor of 1.023 determined on seven selected substituents and we present the rescaled values in Table 2, column 4. In our opinion they are the best values for isolated molecules available to date. They differ from the previous values²⁰ only by the mentioned factor; hence all correlations described earlier retain their validity.

There is a rather close resemblance of σ_1 determined for isolated molecules and in water solution² ($R = 0.965$), taking into account both the experimental uncertainty and the imperfection of the theoretical model. However, some differences exceed clearly this uncertainty and are worth mention (Table 2). In general, one expects that substituents that are able to join into the system of hydrogen bonds will make the value of σ_1 in water greater. This is evidently the case with F, while with NH₂ the effect is smaller and with OH and COOH negligible. It is particularly difficult to understand why σ_1 of the alkylated groups OCH₃, COOCH₃ and N(CH₃)₂ are significantly raised in water compared to OH, COOH, and NH₂. On the opposite, substituent breaking the structure of water should possess smaller or negative σ_1 . The effect of CH₃

and $C(CH_3)_3$ is small but the strong effect of SO_2CF_3 and CH_2Cl can be understood in this way. A more exact investigation would evidently need a more efficient model in water solution.

CONCLUSIONS

The classical inductive effect is certainly the best defined and best supported phenomenon in the area of correlation analysis. Its broad applicability and transferability from one system to another was proven on the experimental gas-phase equilibria^{3,15,16a} and on the calculated energies^{11,18,19} with a greater precision than it was possible formerly on reactivities in solution.^{2,17,28} In our opinion, the calculated energies are as dependable as the experimental values: Any artifact of the method can be excluded with respect to the diverse character of the compounds within each series; in addition calculations and experiments were many times closely correlated.

The more complex character of the inductive effect was discovered only recently²³ and was confirmed here on further systems, partly also on the independent literature data.³⁰ The principle is that a simple transferable inductive effect can be observed only on the interaction with a charged (or strongly polar) group; when both interacting groups are less polar, the effect must be expressed by two terms. The second term depends only on the first atom of the substituent and decreases with the distance more steeply. Its physical meaning is still unclear; the relation to the electronegativity cannot be simply interpreted. Note that this term is small. Its significance was proven by statistical tests with all possible dependability but its experimental confirmation would be almost impossible, for instance the accuracy of the enthalpies of formation would not be sufficient. Some confirmation was obtained here from the NMR shifts but these quantities are evidently still more complex in character.

CALCULATIONS

DFT calculations were performed at the levels B3LYP/6-311++G(3df,3pd)//B3LYP/6-311++G(3df,3pd) (series of compounds **3** and **4**) or B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) (several additional compounds to the series **1**). The Gaussian 03 program⁴⁵ was used; no corrections for the zero-point energy were introduced. No symmetry conditions were presumed. Several possible conformations of the functional group were always taken into consideration; the resulting minimum-energy conformation was always the same in bifunctional and monofunctional compounds. All minimum-energy structures were checked by the vibrational analysis and were found to represent energy minima. In the case of compounds **4**, we started from a conformation on the

C—C bond near to *ap* and let the optimization proceed. The conformation has never changed during the calculation. What we obtained, was a stable conformer, checked also by the vibrational analysis; we have only not examined whether this conformer is more or less stable than the second conformer *sc*.

The energies of compounds **3** and **4** are listed in Table 3 together with reaction energies Δ_5E and Δ_6E of the isodesmic reactions, Eqns (5) and (6), respectively.

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