

Molecular basis of LFER: theoretical study of polar substituent effect in aliphatic series

Robert Ponec^{1*} and Sofie Van Damme²

¹Institute of Chemical Process Fundamentals, Czech Academy of Sciences, 165 02 Prague 6, Suchdol 2, Czech Republic

²Department of Inorganic and Physical Chemistry, Ghent University, Krijgslaan 281, B-9000, Belgium

Received 28 February 2007; revised 26 April 2007; accepted 16 May 2007



ABSTRACT: The nature of inductive substituent effect on the gas phase acidity of several series of aliphatic carboxylic acids with rigid molecular skeletons was analyzed using the recently proposed quantum chemical approach based on the theory of proton affinity proposed by Longuet-Higgins. The results of the analysis suggest that the substituent induced variation of the acidity is in all series due to electrostatic field-effect which in the gas phase can reasonably be characterized by Kirkwood–Westheimer theory. Copyright © 2007 John Wiley & Sons, Ltd.

Supplementary electronic material for this paper is available in Wiley InterScience at <http://www.mrw.interscience.wiley.com/suppmat/0894-3230/suppmat/>

KEYWORDS: nature of inductive effect; field-effect

INTRODUCTION

The nature of polar substituent effect in aliphatic series, classified according to the classical English school^{1,2} as inductive effect, has been and still is the subject of continuing discussions.^{3–15} While all the available experimental data point to the decrease of the magnitude of the effect with increasing distance between the substituent and the reaction center, the main issue of discussions concerns the actual mechanism of the propagation of the effect along the molecular skeleton. One of the traditionally considered theories is the so-called sigma inductive effect theory^{1,3,12,13} which assumes that the effect propagates by the successive polarization of the bonds between the substituent and the reaction center. This theory does not make any assumption about the physical nature of the interaction, it only explains the observed falloff of the effect with increasing distance between the substituent and the reaction center using the empirical quantity called attenuation factor f , which characterizes the weakening of the effect transmitted through each of n intervening bonds.

$$\log\left(\frac{K}{K_0}\right) = \rho_I \sigma_I \sum f^n$$

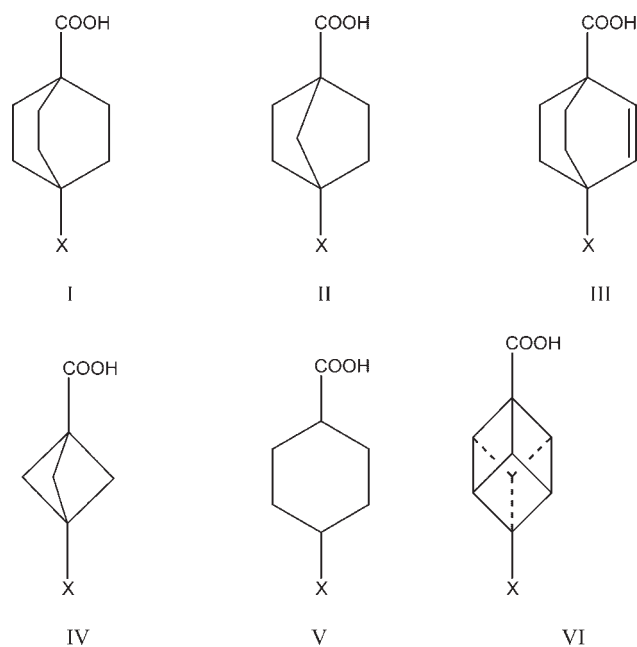
*Correspondence to: R. Ponec, Institute of Chemical Process Fundamentals, Czech Academy of Sciences, 165 02 Prague 6, Suchdol 2, Czech Republic.

E-mail: rponec@icpf.cas.cz

The most serious drawback of this theory is that it is inherently unable to explain the observed angular dependence of the effect^{7,9,10,16,17} – the phenomenon which, in turn, is correctly described by the alternative field-effect theory. This theory is more deeply rooted in physics and assumes that the inductive effect is primarily governed by the electrostatic interactions of charges and dipoles in the molecule. This approach is best exemplified by the Kirkwood–Westheimer theory of the dissociation equilibria of aliphatic carboxylic acids.^{18,19} Within this approach the dissociation of the acids is assumed to be dominated by the electrical work required to remove the proton from the molecule of the acid in the electrostatic field created around the acid by the charged and/or dipolar substituent.

$$\log\left(\frac{K}{K_0}\right) = \frac{1}{(4\pi\epsilon_0\epsilon_{\text{eff}})} \frac{e\mu \cos\theta}{2.303kTr^2}$$

Despite its sound theoretical basis, the practical application of the Kirkwood–Westheimer equation often meets with only moderate success. Part of the existing discrepancies can be certainly attributed to the uncertainties concerning the actual values of the parameters involved in the theory as, e.g., the quantity ϵ_{eff} which represents the ‘effective’ permittivity of the molecule represented by the cavity model,^{18–20} but the other deviations reported for ingeniously designed model series suggest that the reduction of the substituent effect to electrostatic interactions of localized charges and dipoles is not apparently realistic enough and that the



Scheme 1

modification of the original Kirkwood–Westheimer electrostatic theory would be needed.¹¹

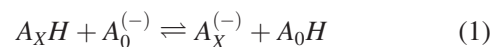
Although the approximate character of the Kirkwood–Westheimer theory is now widely recognized, much less consensus exists so far in the question of along what lines the more realistic theory of inductive effect should be formulated.

Our aim in this study is to contribute to the existing debate concerning the nature of inductive effect by the systematic study of gas phase proton transfer equilibria in the series of substituted carboxylic acids I–VI (Scheme 1). Our approach relies on the application of recently proposed quantum chemical approach^{21,22} based on the theory of proton affinity originally proposed by Longuet-Higgins.²³ Within this approach it is possible to partition the total proton affinity into two contributions which can be regarded as the theoretical counterparts of the classical concepts of field- and sigma inductive effect. The main goal of our systematic study of the substituent induced variation of the acidity in the series of the above acids is to evaluate the differences in the transmission of the substituent effect through the individual molecular skeletons and contribute thus to the understanding of the factors responsible for the propagation of the inductive effect.

THEORETICAL

The traditional approach to the study of inductive effect is based on the investigation of the substituent induced variation of experimental dissociation constants characterizing the equilibrium (1), in which the proton is

transferred from a substituted acid (A_XH) to the unsubstituted conjugated base ($A_0^{(-)}$) and vice versa.



The above equilibrium can be quantitatively characterized by Eqn (2), which relates the ratio of the dissociation constants to the differences in the values of the Gibbs free energies of the proton transfer between the acid and the conjugated anion for unsubstituted and substituted acids, respectively.

$$\log \left(\frac{K_X}{K_0} \right) = \frac{\Delta G_0^0 - \Delta G_X^0}{2.303RT} = \frac{\delta \Delta G^0}{2.303RT} \quad (2)$$

Most of the experimental data on the substituent induced variation of the proton transfer equilibria are available in solution and in fact the study of the dissociation of 4-substituted bicyclo [2,2,2] octane 1-carboxylic acids in 50% ethanol²⁴ was used for the introduction of the inductive substituent constants σ_I . Despite considerable progress in the quantum chemical description of acid–base dissociation constants pK in solution,^{25–27} the majority of contemporary theoretical approaches to the study of the inductive effect is based on the comparison of calculated values of Gibbs free energies and/or the reaction energies characterizing the proton transfer equilibrium (1) or other ingeniously designed isodesmic reactions in the gas phase.^{13,15,28–31} In addition to this, other theoretical approaches to the study of the inductive effect have also recently been used and reviewed.^{32–38} Despite undeniable progress which these studies contributed to the elucidation of the nature and the propagation of the inductive effect, the disadvantage of the straightforward computational approaches is that they often yield just numbers but do not provide the necessary insight into the origin of the observed effects as offered by simple qualitative models. In order to remedy the above drawback we have recently proposed the new theoretical approach^{21,22} which combines the advantage of realistic quantum chemical description with the simplicity and attractiveness of the qualitative models. As the whole procedure, which is based on the theory of proton affinity proposed originally by Longuet-Higgins²³ is sufficiently described in the original studies, we consider it possible to remind briefly only the basic ideas to the extent necessary for the purpose of this study.

The first and in fact the only approximation used in our approach consists in replacing the standard Gibbs free energies ΔG_0^0 and ΔG_X^0 in Eqn (2) by the corresponding differences in the total energy (3).

$$\log \left(\frac{K_X}{K_0} \right) \approx \frac{\Delta E_0^0 - \Delta E_X^0}{2.303RT} = \frac{\delta \Delta E^0}{2.303RT} \quad (3)$$

As the vibrational (ZPE) and thermal contributions which cause the difference between ΔE and ΔG are

generally quite small, the use of this approximation in the series of structurally related molecules is entirely plausible and widely accepted. The close parallel between ΔG and ΔE is advantageously used also in our study as the energy differences ΔE_0^0 and ΔE_X^0 are the crucial quantities in the theory of proton affinity.²³ According to this theory, the proton affinity is identified with the work required to transfer the proton in the electric field of the molecule (in our case anion) from infinity to its final position r_0 that characterizes the length of OH bond in the acid. This work can be expressed in the form of the integral (4)

$$\Delta W = \int_{\infty}^{r_0} \frac{\partial E}{\partial r} dr \quad (4)$$

This approximation is in fact similar to that used by Kirkwood and Westheimer,^{18,19} but while these authors concentrated only on the electrostatic part of the work, the formula (4) involves all possible types of electrical work. In the case of the isodesmic process characterizing the proton transfer equilibrium (1), the total energy change we are dealing with is given by Eqn (5)

$$\delta \Delta E = \Delta W_0 - \Delta W_X \quad (5)$$

where ΔW_0 and ΔW_X represent the proton affinities (4) for the non-substituted and substituted acid, respectively.

The key step of the Longuet-Higgins theory consists in rewriting the general formula (4) in the alternative form (6)

$$\Delta W = \int_{\infty}^{r_0} \frac{\partial E(\rho, 0)}{\partial \rho} d\rho + \int_0^1 \frac{\partial E(r_0, \lambda)}{\partial \lambda} d\lambda \quad (6)$$

Within such an approach the proton transfer is separated into two steps of which the first step corresponds to the transfer from infinity to the position r_0 of the vacant orbital localized on the hypothetical particle with the core charge $\lambda=0$. The charge of this hypothetical particle is then, in the second step, continuously increased from 0 to 1. The above two-step process allows one to rewrite the quantity ΔW as a sum of two terms (7)

$$\Delta W = \Delta \varepsilon + \Delta \eta \quad (7)$$

The first term eliminates from the total work the part due to the difference in the basis set between the protonated and nonprotonated molecule. This term, which is in fact equivalent to the well-known counterpoise correction for the elimination of basis set superposition error (BSSE),³⁹ is generally very small. Dominant contribution to ΔW thus comes from the second term $\Delta \eta$, which describes the charging process and whose values characterize the total electrical contribution to the work associated with the proton transfer. Using the partitioning (7), the original Eqn (3)

can be rewritten in the form (8)

$$\begin{aligned} \log\left(\frac{K_X}{K_0}\right) &\approx \frac{\delta \Delta E^0}{2.303RT} = \frac{\Delta W_0 - \Delta W_X}{2.303RT} \\ &= \frac{\Delta \varepsilon_0 - \Delta \varepsilon_X + \Delta \eta_0 - \Delta \eta_X}{2.303RT} \\ &= \frac{\delta \Delta \varepsilon + \delta \Delta \eta}{2.303RT} \end{aligned} \quad (8)$$

This formula, which still represents the exact transcription of the formula (3), can be further simplified for proton transfer equilibria in the series of structurally closely related molecules. In this case, namely, the BSSE $\Delta \varepsilon$ is not only negligibly small, but also its values practically do not vary within the series so that the terms $\Delta \varepsilon_0$ and $\Delta \varepsilon_X$ practically cancel each other. The Eqn (8) thus reduces to the form (9) which implies that the substituent effect on the proton transfer equilibria is dominated by electrical interactions.

$$\log\left(\frac{K_X}{K_0}\right) \approx \frac{\Delta E_0^0 - \Delta E_X^0}{2.303RT} \approx \frac{\delta \Delta \eta}{2.303RT} \quad (9)$$

Such a conclusion is in fact reminiscent of the original ideas of Bjerrum⁴⁰ and Kirkwood,^{18,19} but in contrast to these authors who concentrated only on the electrostatic part of the work, for which approximate analytical expressions could be derived, the exact Eqn (9), based on the quantum chemical calculations takes into account all possible kinds of electrical interactions. Besides describing more realistically possible interactions, another advantage of the above approach is that it brings more detailed insight into the nature of these interactions by further partitioning of the term $\Delta \eta$ into contributions characterizing electrostatic and polarization part of the electrical work (Eqn 10).

$$\Delta \eta = \Delta W^{\text{elstat}} + \Delta W^{\text{polar}} \quad (10)$$

Using this additional partitioning, the Eqn (10) can be rewritten in the form (11) which suggests that the polar substituent effect is generally composed of two components and the final manifestation of the effect thus may depend on which of the terms is in a given case responsible for the observed substituent induced variation of the acidity.

$$\log\left(\frac{K_X}{K_0}\right) \approx \frac{\delta \Delta W^{\text{elstat}} + \delta \Delta W^{\text{polar}}}{2.303RT} \quad (11)$$

Thus, e.g., in the series of 4-substituted bicyclo [2,2,2] octane 1-carboxylic acids,²² the polarization term was found to be roughly constant. The substituent induced variation of the acidity of the corresponding acids is thus primarily due to the electrostatic term approximately considered by the Kirkwood–Westheimer theory.^{18,19} On the other hand the analysis of the gas phase basicity in the series of ammonia, methylamine, dimethylamine, and trimethylamine in the same study²² revealed that in this case it is the electrostatic contribution which is constant,

so that the substituent effect is primarily due to polarization term which is consistent with the expectations of the classical inductive effect theory.

This implies that the interpretation of the field- and sigma inductive effect as two mutually exclusive mechanisms of the propagation of polar effects is not appropriate because the final classification crucially depends on the particular type of the analyzed reaction series. With this in mind we report in this study the application of the above approach to the series of substituted carboxylic acids I–VI.

COMPUTATIONAL

The analysis reported in this study required several types of calculations. In the first step it was necessary to calculate the energy changes characteristic for the proton transfer equilibria that characterize the substituent effect on the gas phase acidity in all the studied series of the acids. For the sake of elimination of the problems with the eventual conformational ambiguity, the studied set of substituents *X* involved only simple groups with axial symmetry (*X* = H, Br, Cl, F, CH₃, CF₃, CN, and NO₂).

These calculations were performed using Gaussian 03⁴¹ at B3LYP/6-31+G(d) level of the theory. The geometries of all the structures were completely optimized at the above level and the final energy-optimized structures were checked by vibrational analysis to correspond to true minima on the corresponding PE hypersurfaces. The resulting protonation energies were in the second step subjected to the reported analysis so as to identify the dominant contributions to the substituent effect. For this purpose it was first necessary to eliminate the BSSE $\Delta\varepsilon$ defined as the difference between the energy of the anion and the energy of the same anion whose Hamiltonian was, however, modified by the presence of the ghost orbital localized at the dummy atom with zero core charge in the position corresponding to the position of the proton in the neutral acid (Eqn 12).

$$\Delta\varepsilon = E^0(A^{(-)}) - E^0(A^{(-)}(\text{ghost})) \quad (12)$$

Once the BSSE is eliminated, the total electrical work associated with the proton transfer is given by Eqn (13)

$$\Delta\eta = \Delta E - \Delta\varepsilon \quad (13)$$

The resulting values of $\Delta\eta$ are then, in the last step, partitioned into electrostatic and polarization components. Such a partitioning is straightforwardly possible because the electrostatic part of the work is numerically equal to the value of the electrostatic potential at the position of the ghost orbital,^{21,22,42} which is straightforwardly available in the Gaussian package. The complementary polarization term is then calculated simply as a difference (Eqn 14).

$$\Delta W^{\text{polar}} = \Delta\eta - \Delta W^{\text{elstat}} \quad (14)$$

The calculated values of total energy differences, together with the quantities $\Delta\varepsilon$, ΔW^{elstat} , and ΔW^{polar} resulting from the reported partitioning for all the reaction series I–VI are summarized in Tables 1 and 2.

RESULTS AND DISCUSSION

The traditional approach to the discussion of the nature of inductive effect is based on the systematic study of the

Table 1. Calculated values of total energy differences and the components of their partitioning according to the theory of proton affinity for the studied series of acids I–VI. Values in kcal/mol

Series	<i>X</i>	ΔE	$\Delta\varepsilon$	ΔW^{elstat}	ΔW^{polar}
I	H	346.960	-9.223	178.538	177.646
	Br	340.131	-9.309	171.439	178.001
	CF ₃	340.548	-9.321	172.339	177.530
	Cl	340.544	-9.339	172.134	177.749
	CN	338.112	-9.212	169.645	177.679
	F	341.740	-9.313	173.791	177.262
	CH ₃	346.467	-9.267	177.845	177.889
	NO ₂	337.459	-9.245	169.257	177.447
II	H	347.362	-9.242	179.162	177.442
	Br	340.080	-9.485	171.470	178.095
	CF ₃	340.174	-9.345	172.224	177.295
	Cl	340.577	-9.449	172.350	177.676
	CN	337.573	-9.208	169.266	177.515
	F	342.077	-9.307	174.490	176.894
	CH ₃	347.095	-9.211	178.578	177.728
	NO ₂	336.870	-9.411	169.083	177.197
III	H	344.390	-9.597	175.491	178.497
	Br	337.525	-9.730	168.460	178.795
	CF ₃	337.652	-9.735	169.050	178.337
	Cl	337.957	-9.790	169.112	178.635
	CN	335.123	-9.580	166.157	178.546
	F	339.220	-9.666	170.766	178.120
	CH ₃	343.959	-9.637	174.877	178.720
	NO ₂	334.503	-9.377	166.474	177.406
IV	H	346.011	-8.571	177.261	177.321
	Br	335.937	-9.958	167.197	178.698
	CF ₃	337.456	-8.827	169.060	177.222
	Cl	337.095	-9.663	168.904	177.854
	CN	334.889	-7.853	164.913	177.829
	F	339.440	-9.272	171.816	176.897
	CH ₃	346.580	-8.674	177.511	177.744
	NO ₂	332.839	-8.645	163.842	177.642
V	H	347.932	-9.025	180.842	176.115
	Br	341.503	-9.218	174.294	176.428
	CF ₃	341.779	-9.118	174.912	175.985
	Cl	341.749	-9.283	174.785	176.247
	CN	339.574	-9.102	172.416	176.260
	F	342.808	-9.226	176.257	175.777
	CH ₃	347.470	-9.120	180.200	176.390
	NO ₂	338.371	-9.250	171.317	176.304
VI	H	346.601	-8.615	175.157	180.059
	Br	340.137	-8.726	168.468	180.395
	CF ₃	339.362	-8.723	168.044	180.041
	Cl	340.590	-8.728	169.133	180.185
	CN	337.010	-8.524	165.241	180.292
	F	341.956	-8.708	171.169	179.495
	CH ₃	346.580	-8.657	174.774	180.463
	NO ₂	336.016	-8.586	164.273	180.330

Table 2. Values of $\delta\Delta E$, and of its components $\delta\Delta\varepsilon$, $\delta\Delta\eta$, δW^{elstat} , and δW^{polar} calculated according to the theory of proton affinity for the studied series of acids I–VI. Values in kcal/mol

Series	X	$\delta\Delta E$	$\delta\Delta\varepsilon$	$\delta\Delta\eta$	δW^{elstat}	δW^{polar}
I	H	0.00	0.00	0.00	0.00	0.00
	Br	6.83	0.09	6.74	7.10	-0.35
	CF ₃	6.41	0.10	6.31	6.20	0.12
	Cl	6.42	0.12	6.30	6.40	-0.10
	CN	8.85	-0.01	8.86	8.89	-0.03
	F	5.22	0.09	5.13	4.75	0.38
	CH ₃	0.49	0.04	0.45	0.69	-0.24
II	H	0.00	0.00	0.00	0.00	0.00
	Br	7.28	-0.24	7.04	7.69	-0.65
	CF ₃	7.19	-0.10	7.09	6.94	0.15
	Cl	6.79	-0.21	6.58	6.81	-0.23
	CN	9.79	0.03	9.82	9.90	-0.07
	F	5.29	-0.07	5.22	4.67	0.55
	CH ₃	0.27	0.03	0.30	0.58	-0.29
III	H	10.49	-0.17	10.32	10.08	0.24
	Br	6.86	-0.13	6.73	7.03	-0.30
	CF ₃	6.74	-0.14	6.60	6.44	0.16
	Cl	6.43	-0.19	6.24	6.38	-0.14
	CN	9.27	0.02	9.28	9.33	-0.05
	F	5.17	-0.07	5.10	4.73	0.38
	CH ₃	0.43	-0.04	0.39	0.61	-0.22
IV	H	9.89	0.22	10.11	9.02	1.09
	Br	0.00	0.00	0.00	0.00	0.00
	CF ₃	10.07	1.39	8.69	10.06	-1.38
	Cl	8.56	0.26	8.30	8.20	0.10
	Cl	8.92	1.09	7.82	8.36	-0.53
	CN	11.12	-0.72	11.84	12.35	-0.51
	F	6.57	0.70	5.87	5.44	0.42
V	CH ₃	-0.57	0.10	-0.67	-0.25	-0.42
	NO ₂	13.17	0.07	13.10	13.42	-0.32
	H	0.00	0.00	0.00	0.00	0.00
	Br	6.43	-0.19	6.24	6.55	-0.31
	CF ₃	6.15	-0.09	6.06	5.93	0.13
	Cl	6.18	-0.26	5.93	6.06	-0.13
	CN	8.36	-0.08	8.28	8.43	-0.15
VI	F	5.12	-0.20	4.92	4.59	0.34
	CH ₃	0.46	-0.09	0.37	0.64	-0.28
	NO ₂	9.56	-0.22	9.34	9.53	-0.19
	H	0.00	0.00	0.00	0.00	0.00
	Br	6.46	0.11	6.35	6.69	-0.34
	CF ₃	7.24	0.11	7.13	7.11	0.02
	Cl	6.01	0.11	5.90	6.02	-0.13
	CN	9.59	-0.09	9.68	9.92	-0.23
	F	4.64	0.09	4.55	3.99	0.56
	CH ₃	0.02	0.04	-0.02	0.38	-0.40
	NO ₂	10.58	-0.03	10.61	10.88	-0.27

substituent effect on the acidity of aliphatic carboxylic acid in various, often ingeniously designed reaction series. This is also the case of the series I–VI for which the experimental data on the substituent induced variation of dissociation constants are available.^{4–6,43–45} Most of these experimental data were, however, obtained from the measurements in various solvents and although the results

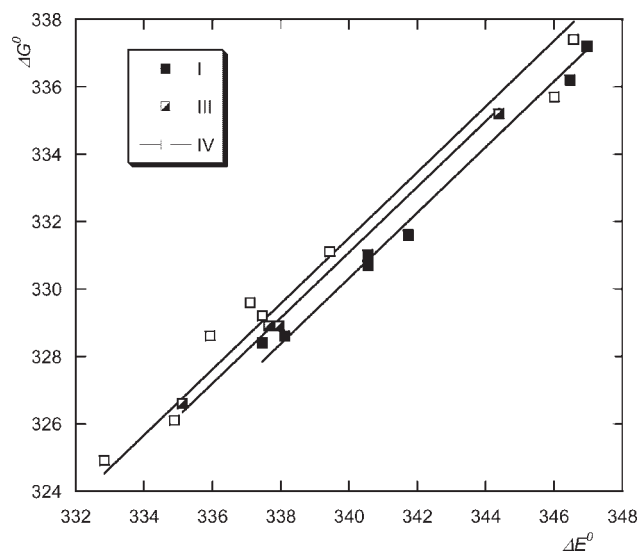


Figure 1. Dependence of experimental Gibbs free energies ΔG^0 for the gas phase acidities of the acids I, III, and IV on the variation of the total energies ΔE^0 characterizing the proton transfer equilibrium (1). (R^2 for the series (I), 0.993; series (III), 0.998; series (IV), 0.979)

within individual series are generally consistent with the idea of the field-effect, the crudeness of Kirkwood–Westheimer model makes it difficult to evaluate whether or to what extent the observed results reflect the inherent structural effects or whether they can be due to interference with the specific solvent effects.

In order to eliminate the above uncertainties we report in this paper systematic theoretical study of inherent structural effects on the substituent induced variation of gas phase acidity in the series of substituted acids I–VI. As the first step of such analysis we first compared the calculated values of reaction energies ΔE , with the experimental values of ΔG which are available for the reaction series I, III, and IV.^{46,47} Such a comparison is shown in Fig. 1. Given the close parallel shown in the figure it seems entirely plausible to assume that the calculated values of ΔE correctly reflect the trends in the gas phase acidity also in the series for which the experimental gas phase data are not available and, consequently, these values can be used to reliably monitor the substituent induced variation of the inductive effect in remaining series II, V, and VI. The efficiency of individual skeletons to transmit the substituent effect in the ideal conditions of the gas phase can be characterized by the values of the transmission factor z_J obtained from the correlation of the calculated values of $\delta\Delta E$ for each particular series J relative to the bicyclooctane series.

$$\delta\Delta E_J = z_J \delta\Delta E_I \quad (15)$$

The above correlation is in fact nothing but the theoretical counterpart of the approach known as the

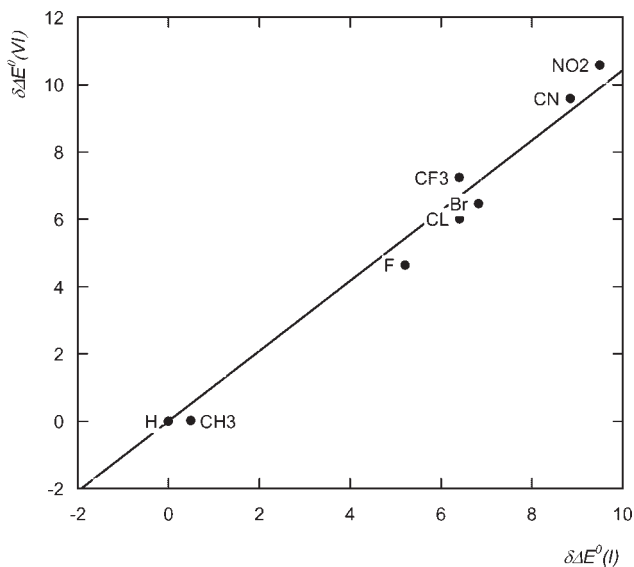


Figure 2. The calculated dependence of substituent-induced variation of reaction energies $\delta\Delta E^0$ for the series of cubane carboxylic acids (VI) on the corresponding energy difference in the series of bicyclo-[2,2,2]-carboxylic acids (I). ($R^2 = 0.975$)

so-called ρ - ρ technique,^{8,48}

$$\frac{\log\left(\frac{K_X}{K_0}\right)_J}{\log\left(\frac{K_X}{K_0}\right)_I} \simeq \frac{\rho_J}{\rho_I} = z_J \quad (16)$$

which was used as a general tool for the determination of the transmission factors of various aliphatic skeletons using experimental solution pK values.

An example of the correlation (15) for the series of substituted cubane carboxylic acids is given in Fig. (2), but similar, equally good correlations are observed for all the studied series. The statistical parameters of such correlations for the entire set of acids are summarized in the Table 3. The inspection of the table shows that in the majority of cases the substituent effect is in the gas phase transmitted through individual skeletons with comparable efficiency as in bicyclooctane. The only exception is the series of bicyclo [1,1,1] pentane-carboxylic acids

(IV), and our value 1.35 fairly well agrees with the value 1.29 determined from the comparison of experimental gas phase acidities and a similar value 1.34 was also reported in the study by Wiberg.⁴⁹

In order to get more detailed insight into the nature of the observed substituent effect let us first focus on the decomposition of the calculated values of $\delta\Delta E$ according to the theory of protonaffinity²³ (Table 2). The inspection of this table shows that because of negligibly small and practically constant values of the BSSE $\Delta\varepsilon$, the substituent effect in each of the studied series is dominated by the term $\delta\Delta\eta$ which reflects the electrical work connected with the proton transfer between substituted and non-substituted acids. As, however, this total electrical work has two basic components, it was of interest to evaluate the role of these components in each particular reaction series. The general conclusion which straightforwardly follows from the inspection of the Table 2 is that the values of the polarization term ΔW^{polar} within each of the series remain practically constant so that the substituent-induced variation of the acidity is in all series predominantly due to the electrostatic effect.

The dominant role of the electrostatic field-effect is also clearly corroborated by the existence of the correlation between the calculated total energy differences $\delta\Delta E$ and the electrostatic terms $\delta\Delta W^{\text{elstat}}$. An example of such a correlation involving the data for all the series of substituted acids I–VI is shown in Fig. (3). In addition to this straightforward demonstration, the decisive role of the electrostatic field-effect as the dominant component of the inductive substituent effect in the studied series of acids can be also independently demonstrated by the comparison of the transmission factors z_J (Eqn. 15, Table 3) with the analogous quantities ω_J derived from the correlation of pure electrostatic terms (17).

$$\delta\Delta W_J^{\text{elstat}} = \omega_J \delta\Delta W_I^{\text{elstat}} \quad (17)$$

As it is possible to see from the values summarized in the Table 4, the agreement between both sets of quantities is practically quantitative. This result is very important since the near equality of the transmission factors z_J and

Table 3. Comparison of theoretical values of transmission factors z_J of individual skeletons calculated according to Eqn (15) with the available experimental data

Series	z_J	R^2	Std. Dev.	Experimental transmission factors from various solvents
I	1.00	1.000	—	1.00 ^a
II	1.09 ± 0.01	0.996	0.234	1.17 ^a
III	1.03 ± 0.01	0.998	0.151	1.07 ^b
IV	1.35 ± 0.04	0.981	0.692	1.51 ^c
V	0.97 ± 0.01	0.997	0.176	0.76 ^a
VI	1.04 ± 0.03	0.975	0.618	0.92 ^a

^a Taken from Reference [12].

^b Taken from Reference [7].

^c Calculated from the pK values determined in H₂O.⁴⁷

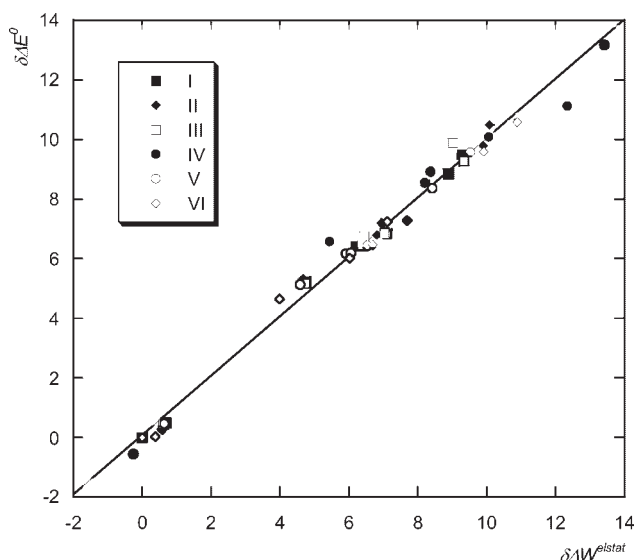
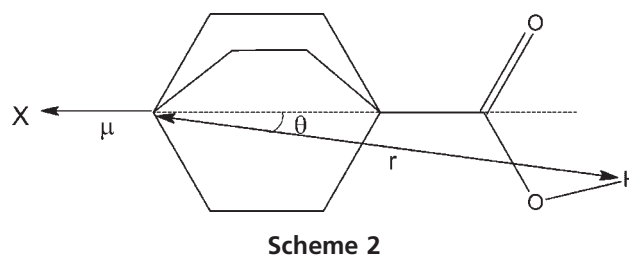


Figure 3. Dependence of the total reaction energies $\Delta\Delta E^0$ of the proton transfer equilibria (1) in the series of acids I–VI on the electrostatic component $\Delta\Delta W^{\text{elstat}}$ calculated according to theory of proton affinity. ($R^2 = 0.990$)

ω_j implies that the propagation of the inductive effect in all the studied molecules is indeed due to the electrostatic interactions. Although such a conclusion is very reminiscent of the conclusions of many earlier experimental^{4–11} and also more recent theoretical studies^{29,35–38} in which the dominance of the field (through-space) effect as the primary mechanism of the propagation of inductive effect was repeatedly advocated, the quantitative agreement of the calculated transmission factors puts the above conclusions on much safer theoretical footing. The reason is that in contrast to the approximate Kirkwood–Westheimer model, the above approach is free of any imperfections because the electrostatic component of the substituent effect ΔW^{elstat} is determined directly from the quantum chemical analysis of the calculated reaction energy. This deep rooting in the theory is indeed very important since it opens the way to much more realistic analysis of the inductive substituent effects and especially to its confrontation with the existing theories, i.e., both with the classical Kirkwood–Westheimer theory and the sigma inductive effect theory.

Table 4. Theoretical values of transmission factors ω_j of individual skeletons calculated from the electrostatic components of the substituent effect according to Eqn (17)

Series	ω_j	R^2	Std. Dev.
I	1.00	1.000	0.000
II	1.09 ± 0.02	0.996	0.234
III	1.01 ± 0.01	0.996	0.214
IV	1.37 ± 0.04	0.981	0.703
V	0.97 ± 0.01	0.994	0.255
VI	1.06 ± 0.04	0.963	0.767



In order to throw some new light on the above problems let us focus first on the confrontation of the quantum chemically calculated electrostatic component of the effect with the classical Kirkwood–Westheimer theory. For this purpose we compare the quantum chemically calculated electrostatic energies ΔW^{elstat} for each individual series with the parameter ξ (Eqn 18)

$$\xi = \frac{\mu \cos \theta}{r^2} \quad (18)$$

defined in terms of quantities characterizing the Kirkwood–Westheimer model. The values of these parameters were determined as follows. The dipole μ characterising the substituent X was approximated by the calculated dipole moment of the molecule CH_3X , and the distance r and the angle θ were taken in each individual case from the real optimized geometry of the molecule (Scheme 2).

The parameters of the correlation described by Eqn (19) are summarized in Table 5.

$$\Delta W^{\text{elstat}} = a\xi + b \quad (19)$$

The inspection of this table shows that although the actual correlation lines slightly depend on the type of the reaction series, the differences are not too dramatic and in view of the crudeness of the assumptions adopted for the determination of the parameter ξ , the agreement is really satisfactory. Given the estimated confidence intervals of the regression parameters, the differences of the slopes for the most closely related series I–III and also for bicyclo [1,1,1] pentane series IV are practically negligible. Slightly higher difference is thus observed only for the cyclohexane and cubane series (V and VI) but even in these cases, the deviations are not too dramatic. This

Table 5. Statistical parameters of the correlation of the exact quantum chemically calculated electrostatic component of the substituent effect ΔW^{elstat} with the parameter ξ derived from the Kirkwood–Westheimer model

Series	a	b	R^2	Std. Dev.
I	-80.43 ± 6.69	177.65 ± 0.460	0.960	0.745
II	-81.89 ± 7.11	178.31 ± 0.530	0.957	0.863
III	-81.96 ± 6.21	174.63 ± 0.42	0.967	0.690
IV	-86.65 ± 8.77	176.71 ± 0.80	0.942	1.291
V	-94.72 ± 7.32	180.10 ± 0.42	0.965	0.681
VI	-94.66 ± 7.33	174.80 ± 0.50	0.965	0.803

result is very interesting since it suggests that no dramatic modifications of Kirkwood–Westheimer theory are apparently needed if it is used to describe the inductive effect in the gas phase.

The most important qualitative expectation that can be deduced from the classical Kirkwood–Westheimer model is the inverse dependence of the inductive (field) effect on the (square of the) distance between the substituent and the reaction center and as it will be shown the calculated differences in the sensitivity of individual skeletons to the transmission of substituent effect (Table 4) do indeed correspond to what the classical field-effect predicts. Simple inspection of geometrical parameters of the series of acids I–VI shows, namely, that the distance between the substituent and reaction centre is considerably shorter in the case of bicyclo-[1,1,1] pentane series (IV) than in the remaining ones and the increased sensitivity of the skeleton IV thus can straightforwardly be attributed just to the above simple proximity effect.

The situation, can be, however, slightly more difficult in the case of the transmission factors calculated from experimental solution data. The importance of the solvent effect on the transmission factors can be estimated from the comparison of the experimental data also summarized in Table 3 with the gas phase z_J values. The inspection of this table shows that although the general trends expected on the basis of gas phase data are also more or less reflected in the experimental solution data, some non-negligible discrepancies are also nevertheless clearly evident. The most important of such discrepancies concerns the series of bicyclo [1,1,1] pentane carboxylic acids (IV), for which the transmission factor estimated from the experimental pK values in water⁴⁷ is considerably higher than the analogous factor derived from the gas phase data. Another higher numerical discrepancy can also be found in the case of the cyclohexanes series (V) where, however, the solvent effect contributes to the reduction of the transmission factor. These differences are certainly interesting and deserve further analysis but we are afraid that because of uncertainties in the values of the effective permittivity of the molecule in the solvent cavity, the Kirkwood–Westheimer model can hardly provide more than a kind of approximate phenomenological description. Really convincing and satisfactory explanation of the solvent effect on the protonation equilibria will thus have to wait for the elaboration of reliable procedures of direct inclusion of the solvent into quantum chemical description.

Although the results of our study clearly identify the field-effect as the dominant mechanism of the propagation of polar substituent effect on the gas phase acidities of the studied series of acids, we nevertheless consider it useful to compare the predictions of the electrostatic theory also with the expectations derived from the alternative sigma inductive effect theory. The reason is that this theory is still occasionally considered and especially the predictions of the improved model by

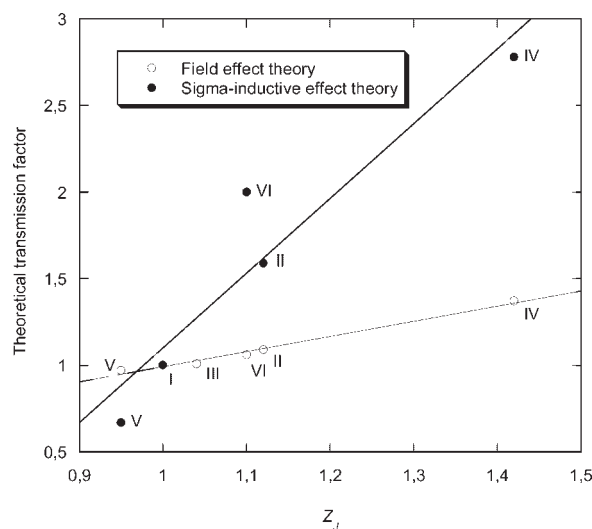


Figure 4. Comparison of transmission factors of individual skeletons in the series of acids I–VI with the predictions of the field- and sigma inductive effect theory

Exner and Fiedler¹² were interesting enough to keep the sigma inductive effect theory still in the play. The straightforward comparison of both the alternative theories of inductive effect is available via the confrontation of transmission factor ω_J derived from the electrostatic component of the total energies (Eqn 17) and/or from the refined Exner¹² model of sigma inductive effect with theoretical transmission factor z_J determined from the calculated total energy differences according to Eqn (15). Such a comparison is shown in Fig. 4. As it is possible to see, the agreement with the electrostatic theory is nearly quantitative while the sigma inductive theory, although it also correctly describes the general trends, is much less precise from the quantitative point of view and its predictions of the extent of the effect are strongly overestimated. In connection with this result it is, nevertheless important to realize, that despite providing plausible, albeit less precise description of the propagation of the substituent effect, the sigma inductive theory is clearly inferior to the field-effect theory because of its lack of a sound physical background. The importance of this aspect can be best demonstrated on the observed deviations of the transmission factors derived from the solutions data in the case of bicyclo-[1,1,1]-pentane and cyclohexane series. While the field-effect theory is still able to provide at least phenomenological explanation via the appropriate choice of effective permittivity of the molecule in the solvent cavity, the complete lack of such a flexibility in sigma inductive theory makes its use for the interpretation of the solvent data really questionable.

Acknowledgements

This study was supported by the grant of the Czech Academy of Sciences (AVOZ 407 20504). This support

is appreciated by the author R.P. S.v.D. also thanks the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen) for its support.

REFERENCES

- Ingold CK. *Structure and Mechanism in Organic Chemistry*, Chapter II. Cornell University Press: Ithaca, NY, 1953.
- Taft RW. *J. Phys. Chem.* 1960; **64**: 1805–1815.
- Hine J. *Physical Organic Chemistry*, Chapter 2, 2nd edn. Mc Graw Hill: New York, 1962.
- Baker FW, Parish RC, Stock LM. *J. Am. Chem. Soc.* 1967; **89**: 5677–5685.
- Golden R, Stock LM. *J. Am. Chem. Soc.* 1966; **88**: 5928–5929.
- Wilcox CF, Leung C. *J. Am. Chem. Soc.* 1968; **90**: 336–341.
- Stock LM. *J. Chem. Educ.* 1972; **49**: 400–404.
- Bowden K. *Can. J. Chem.* 1963; **41**: 2781–2793.
- Bowden K. *J. Chim. Phys.* 1992; **89**: 1647–1659.
- Bowden K, Grubbs EJ. *Chem. Soc. Rev.* 1996; 171–177.
- Charton M. *J. Phys. Org. Chem.* 1999; **12**: 275–282.
- Exner O, Fiedler P. *Coll. Czech. Chem. Commun.* 1980; **45**: 1251–1268.
- Böhm S, Exner O. *Coll. Czech. Chem. Commun.* 2004; **69**: 984–995.
- Exner O, Friedl Z. *Prog. Phys. Org. Chem.* 1993; **19**: 259–294.
- Exner O. *J. Phys. Org. Chem.* 1999; **12**: 265–274.
- Bowden K, Grubbs JE. *Progr. Phys. Org. Chem.* 1993; **19**: 183–224.
- Roberts JD, Carboni RA. *J. Am. Chem. Soc.* 1955; **77**: 5554–5558.
- Kirkwood JG, Westheimer FH. *J. Chem. Phys.* 1938; **6**: 506–512.
- Kirkwood JG, Westheimer FW. *J. Chem. Phys.* 1938; **6**: 513–517.
- Orttung W. *J. Am. Chem. Soc.* 1978; **100**: 4369–4375.
- Ponec R, Kučera J. *Chem. Scripta* 1984; **22**: 152–154.
- Ponec R, Gironés X, Carbó-Dorca R. *J. Chem. Inf. Comp. Sci.* 2002; **42**: 564–570.
- Longuet-Higgins HC. *Rec. Trav. Chim.* 1956; **75**: 825–835.
- Roberts JD, Moreland TW. *J. Am. Chem. Soc.* 1953; **75**: 2167–2173.
- Cramer Ch, Truhlar DG. *Chem. Rev.* 1999; **99**: 2161–2200.
- Silva CO, da Silva EC, Nascimento NA. *J. Phys. Chem. A* 2000; **104**: 2404–2409.
- Schurmann G, Cossi M, Barone V, Tomasi J. *J. Phys. Chem. A* 1998; **102**: 6706–6712.
- Wiberg KB. *J. Org. Chem.* 2002; **76**: 1613–1617.
- Exner O, Böhm S. *Chem. Eur. J.* 2003; **9**: 4718–4723.
- Exner O, Böhm S. *J. Phys. Org. Chem.* 2006; **19**: 393.
- Exner O, Böhm S. *J. Phys. Org. Chem.* 2004; **17**: 124.
- Exner O, Böhm S. *Curr. Org. Chem.* 2006; **10**: 763–778.
- Krygowski TM, Stepien BT. *Chem. Rev.* 2005; **105**: 3482–3512.
- Liu L, Fu Y, Li RQ, Guo QX. *J. Chem. Inf. Comp. Sci.* 2004; **44**: 652–657.
- Nolan EM, Linck RG. *J. Am. Chem. Soc.* 2000; **122**: 11497–11506.
- Nolan EM, Linck RG. *J. Phys. Chem. A* 2001; **105**: 7297–7307.
- Nolan EM, Linck RG. *J. Phys. Chem. A* 2002; **106**: 533–543.
- Campanelli AR, Domenicano A, Ramondo F. *J. Phys. Chem. A* 2006; **110**: 10122–10129.
- Boys SF. *Mol. Phys.* 1970; **19**: 553–566.
- Bjerrum NJ. *Z. Phys. Chem.* 1923; **106**: 219–242.
- Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani M, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JP, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski W, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi K, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill MPW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA. Gaussian 03, Revision B.05. Gaussian, Inc., Pittsburgh, PA, 2003.
- Scrocco E, Tomasi J. *Top. Curr. Chem.* 1973; **42**: 95–167.
- Charton M. *Prog. Phys. Org. Chem.* 1981; **13**: 119–251.
- Siegel S, Komarmy JM. *J. Am. Chem. Soc.* 1960; **82**: 2547–2553.
- Cole TW, Mayers C, Stock LM. *J. Am. Chem. Soc.* 1974; **96**: 4555–4557.
- Koppel IA, Mishima M, Stock LM, Taft RW, Topsom RD. *J. Phys. Org. Chem.* 1993; **6**: 685–689.
- Adcock W, Baran Y, Filipi A, Speranza M, Trout NA. *J. Org. Chem.* 2005; **70**: 1029–1034.
- Palm VA. *Osnovy kolichestvennoi teorii organicheskikh reakcii*, Chapter VII. Izdatelstvo Khimiya: Leningrad, 1967;
- Wiberg KB. *J. Org. Chem.* 2002; **67**: 1613–1617.