Molecular Basis of Linear Free Energy Relationships. The Nature of Inductive Effect in Aliphatic Series†

Robert Ponec*

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

Xavier Girones and Ramon Carbó-Dorca

Institute of Computational Chemistry, University of Girona, Campus Montilivi, 17071 Girona, Spain

Received June 30, 2001

The nature of inductive substituent effect on the acidity of aliphatic carboxylic acids was analyzed in terms of a quantum chemical model based on the Longuet-Higgins theory of proton affinity. It has been shown that the effect is generally composed of two additive components, the electrostatic one and the polarization one. The relative weights of these components depend in any given case on the type of the reaction series. Thus, for example, the substituent-induced variation of gas-phase acidity in a series of 4-substituted bicyclo-[2.2.2]octane-1-carboxylic acids is due to the electrostatic component classically described by the Kirkwood−Westheimer theory. On the other hand, the gas-phase basicity in a series of aliphatic amines is primarily determined by the polarization term that in traditional description corresponds to the concept of inductive effect.

INTRODUCTION

Concepts are a vital and inescapable part of our thought processes, and their formulation is thus one of the most important steps in the buildup of science. Chemistry is not an exception, and there is a wealth of examples where various empirical and often ill-defined concepts have played and still play an important role in the systematic classification of chemical phenomena. An example in this respect is the concept of substituent effect. The accumulated experimental evidence has made it apparent, however, that this effect is not an invariant property of substituents, but that its manifestations depend on the structure of the substituted molecules. On the basis of this observation, the substituent effects in organic chemistry are generally interpreted as being composed of several components (inductive, resonance, steric, etc.), and the appropriate scales of substituent constants for individual components have been determined. Although this approach is certainly satisfactory for the characterization of substituent effect in terms of appropriate correlation equations, the detailed understanding of the nature of these effects lies beyond the reach of this phenomenological description. This is also the case of the concept of inductive effect, whose nature was and still is the focus of numerous studies.[1−14] The term "inductive effect" describes the operation of polar substituent effect in aliphatic series, and the main issue of long-lasting discussions is to decide between two traditionally considered theories that specify the propagation or the transmission of this effect within molecules.

One of the traditionally considered theories is the so-called electrostatic or field effect theory, according to which the inductive effect is basically governed by the electrostatic interaction of charges and dipoles in the molecule. This theory is best exemplified by the Kirkwood−Westheimer equation for the dissociation of aliphatic carboxylic acids.[14] The alternative sigma inductive effect theory[1,2,7] assumes that the effect propagates by the successive polarization of bonds by a dipolar or charged substituent between the substituent and the reaction center. This theory correctly predicts the successive falloff of substituent effect with the length of the chain of intervening bonds, but its main disadvantage is that it is inherently unable to describe the angular dependence of substituent effect, the phenomenon that is well described by the electrostatic theory.[7] However, as the agreement between the experimental data and the predictions of Kirkwood−Westheimer theory is often only moderate, the final decision between the alternative theories still has not been adopted and the problem of the nature of inductive effect is repeatedly addressed.[6−9,11−13] Although it is generally accepted that the main problem of the electrostatic theory is the approximate character of the Kirkwood−Westheimer equation, much less consensus exists in the question of along what lines the more realistic theory of inductive effect should be formulated.[8,9,12,13]

Our aim in this study is to show that, despite recently expressed prudent pessimism,[10] it is possible to propose a simple quantum chemical model, in terms of which the nature of inductive effect on the ionization equilibria could be explained both qualitatively and quantitatively. In the following section the theoretical background underlying this model will be reported.

THEORETICAL SECTION

The traditional approach to the study of inductive effects is based on the investigation of the dissociation equilibria

† Dedicated to Professor A. Balaban on the occasion of his 70th birthday.

* Corresponding author phone: 420 2 20390271; e-mail: rponec@icpf.cas.cz.

10.1021/ci0100651 CCC: $22.00 © 2002 American Chemical Society
Published on Web 01/19/2002

in a series of aliphatic carboxylic acids. Thus, for example, the well-known scale of inductive substituent constants σ_I was derived from the study of dissociation constants in a series of 4-substituted bicyclo[2.2.2]octane 1-carboxylic acids,[15−17] and the theoretical analysis of the equilibrium process (1) in a series of aliphatic carboxylic acids has also served as a basis for the electrostatic theory of inductive effect exemplified by the Kirkwood−Westheimer equation.[14]

$$A_XH + A_0^{(-)} \rightleftharpoons A_0H + A_X^{(-)} \tag{1}$$

As one of the main goals of this study is to propose a more realistic, quantum chemically based theory of inductive effect, we first remind the basis ideas of the existing theories. For this purpose let us start with the brief summarization of Kirkwood−Westheimer theory. This theory starts from the exact thermodynamic formula for the ratio of dissociation constants of two carboxylic acids A_XH and A_0H

$$\log \frac{K_X}{K_0} = \frac{\Delta G_0^\circ - \Delta G_X^\circ}{2.303RT} = \frac{\delta \Delta G^\circ}{2.303RT} \tag{2}$$

and its main goal is to approximate the standard free enthalpies ΔG_0° and ΔG_X°, which characterize the dissociation of individual acids, by electrostatic work Δw required to remove the proton from the acid A_XH and to transfer it to the anion A_0^-.

$$\log \frac{K_X}{K_0} \approx \frac{N\Delta w}{2.303RT} \tag{3}$$

This work depends, of course, on the medium in which the proton transfer takes place and the well-known Kirkwood−Westheimer equation (4)

$$\log \frac{K_X}{K_0} = \frac{e\mu \cos \vartheta}{4\pi\epsilon_0\epsilon_{eff} 2.303kTr^2} \tag{4}$$

was obtained from the original formula (3) under two additional simplifying assumptions. One of them is the assumption that the electrostatic work is dominated by the interactions between the moving proton and the dipolar substituent X in the acid. In the gas phase this interaction energy (per molecule) is given by

$$\Delta w(g) = \frac{e(\vec{\mu}\cdot\vec{r})}{4\pi\epsilon_0 r^3} \tag{5}$$

where $\vec{\mu}$ is the bond moment of the bond C−X in the molecule of the acid A_XH and $\vec{r}$ is the vector characterizing the distance from the midpoint of the bond moment of the bond C−X to the carboxylic proton.

Within this approximation the formula (2) can be rewritten in the form

$$\log \frac{K_X}{K_0} = \frac{Ne\mu \cos \vartheta}{4\pi\epsilon_0 (2.303RTr^2)} \tag{6}$$

The second simplifying assumption of Kirkwood−Westheimer theory concerns the consideration of the effect of the medium. This effect was taken into account using a cavity model,[14] but for practical applications this model is often being replaced by a much cruder approximation, where the solvent is characterized by the effective value of the dielectric constant ϵ_{eff} entering into the formula (4). These two simplifying assumptions represent in fact the weakest point of Kirkwood−Westheimer theory, and the main reasons for often observed deviations from this theory certainly have their origin in the crudeness and questionable justification of these simplifying assumptions.

In contrast to theoretically well justified electrostatic theory, the alternative sigma inductive effect theory has much less background in physics, and in fact it can provide only a phenomenological description of the propagation of the effect. According to this theory, the effect is transmitted by the successive polarization of the bonds separating the substituent and the reaction center. Each of the bonds is assumed to attenuate the effect by a constant ratio called transmission factor f and the final response is described by

$$\log \frac{K_X}{K_0} = \rho_I^\circ \sigma_I \sum f^n \tag{7}$$

where n denotes the number of intervening bonds and the summation runs over all bond paths through which the substituent effect can be transmitted.

Having recalled the basic ideas and approximations of the existing theories of inductive effect, let us attempt, in the following, the introduction of a new approach based on a quantum chemical model of dissociation equilibria.

Strictly speaking, contemporary quantum chemistry is able to describe the dissociation equilibrium (1) exactly, since the free enthalpies appearing in the strict thermodynamic formula (2) are readily available from existing quantum chemical programs. Moreover, such calculations are available not only for gas-phase processes, but due to progress in the quantum theory of solvent effects,[18] the necessary free energies can be obtained even for processes in solution and the calculation of absolute pK values thus becomes a realistic perspective.[19,20] Despite the unquestionable importance of such a straightforward computational approach, it is true, however, that this approach lacks the transparency of qualitative models and for this reason it can hardly provide a convenient framework for qualitative understanding and predictions. Fortunately, the straightforward numerical calculation of thermodynamic parameters is not the only way to the quantum chemical analysis of the equilibrium process (1). Our aim in this study is to propose a new procedure that combines the advantage of realistic quantum chemical description with the simplicity and attractiveness of the qualitative models. In the following the basic idea of our approach will be reported.

The first and in fact the only approximation we adopt concerns the simplification of the exact formula (2), by replacing the thermodynamic quantities ΔG_0° and ΔG_X° by the corresponding differences of total energies. Within this approximation, which is equivalent to the neglect of vibrational (ZPE) and thermal contributions responsible for the difference between the energy and the free enthalpy, the original exact formula (2) transforms to

$$\log \frac{K_X}{K_0} \approx \frac{\Delta E_0^\circ - \Delta E_X^\circ}{2.303RT} = \frac{\delta \Delta E^\circ}{2.303RT} \tag{8}$$

where $\Delta E_0°$ and $\Delta E_X°$ represent the difference of total energies between the anion and the associated acid for the acids A_0H and A_XH, respectively. This approximation is not too serious, and the fact that the error introduced in this way is usually negligible is well demonstrated by extensive examples reported in the literature.[21,22] This result is certainly very useful, but from a practical point of view the replacement of one calculated quantity ($\Delta G_X°$) by another one ($\Delta E_X°$) does not help too much and the basic criticism of the lack of transparency of this purely computational approach still remains valid. The main advantage that our approach offers compared to the straightforward computational procedure is that it allows partitioning of the calculated ΔE values into contributions that can be attributed a clear physical meaning. Such partitioning is based on the theory of proton affinity proposed some time ago by Longuet-Higgins.[23] According to this theory, the proton affinity, defined as the reaction heat of the gas-phase process (9)

$$A + H^+ \rightleftharpoons AH^+ \tag{9}$$

is identified with the work required to transfer the proton in the electric field of the molecule A from infinity to its final position r_0 that characterized the length of newly formed bond in the protonated molecule. This work can be expressed in the form of integral (10)

$$\Delta W = \int_{\infty}^{r_0} \frac{\partial E(A)}{\partial r}\, dr \tag{10}$$

This approximation is in fact similar to that used by Kirkwood and Westheimer,[14] but in contrast to these authors, who concentrated only on the electrostatic part of the work, the formula (10) involves also all other possible contributions. In calculating the integral (10), one can use the fact that its value does not depend on the actual integration path. As a consequence, the process of the proton transfer can be formally separated into two independent steps. In the first, one transfers from infinity to r_0 the vacant orbital(s) localized at a hypothetical particle carrying the core charge $\lambda = 0$. In the subsequent step, this hypothetical particle is being charged in such a manner (r_0 is kept fixed) that its charge continuously varies between 0 and 1. Within this model, the energy E can be considered as a function of two variables $E = E(r,\lambda)$and the above two-step integration can be schematically described by

$$\Delta W = \int_{\infty}^{r_0} \frac{\partial E(\rho,0)}{\partial \rho}\, d\rho + \int_0^1 \frac{\partial E(r_0,\lambda)}{\partial \lambda}\, d\lambda \tag{11}$$

Based on this equation, the total work ΔW necessary to perform the proton transfer can be separated into two contributions, of which each can be attributed a clear physical meaning.

$$\Delta W = \Delta\epsilon + \Delta\eta \tag{12}$$

The first contribution $\Delta\epsilon$ equals the difference between the energy of the "ordinary" molecule A and the energy of the same molecule modified by the presence of ghost vacant orbital(s) localized on a hypothetical particle with the core charge $\lambda = 0$ at the position r_0. This term thus in fact corresponds to the well-known counterpoise correction introduced by Boys et al.,[24] and its physical meaning consists of the elimination from the total work the part due to the difference in the basis set between the protonated and nonprotonated molecule. The second term $\Delta\eta$ then describes the charging process, and its value characterizes in any given case the total electrical contribution to the work associated with the proton transfer.

Applying now the same approach to the dissociation equilibrium (1), the total work required to transfer the proton from one acid to another is given by (13)

$$\Delta W = \int_{\infty}^{r_0} \frac{\partial E(A_0^-)}{\partial r}\, dr - \int_{\infty}^{r_0} \frac{\partial E(A_X^-)}{\partial r}\, dr \tag{13}$$

$$\Delta W = (\Delta\epsilon_0 + \Delta\eta_0) - (\Delta\epsilon_X + \Delta\eta_X) \tag{14}$$

Based on this equation, the original formula (8) can be rewritten in the form

$$\log \frac{K_X}{K_0} = \frac{\delta\Delta\epsilon + \delta\Delta\eta}{2.303RT} \tag{15}$$

where

$$\delta\Delta\epsilon = \Delta\epsilon_0 - \Delta\epsilon_X$$
$$\delta\Delta\eta = \Delta\eta_0 - \Delta\eta_X \tag{16}$$

This equation, which still represents the exact transcription of the formula (8), can be further simplified in the case that the studied acids form a structurally related homogeneous series. In this case, namely, the basis set correction term $\Delta\epsilon$ is often more or less constant within a whole series so that the terms $\Delta\epsilon_0$ and $\Delta\epsilon_X$ roughly cancel each other. The formula (15) transforms to the form (17) that attributes the differences in the dissociation constants in the series of structurally related acids to the variation of electrical work required to transfer the proton between the acids in the equilibrium (1).

$$\log \frac{K_X}{K_0} = \frac{\delta\Delta\eta}{2.303RT} \tag{17}$$

This result is very interesting, since the same idea of attributing the substituent effect to the electrical interactions was proposed many years ago by Bjerrum[25] and it was also used by Kirkwood.[14] However, while these authors concentrated only on the electrostatic part of the work, for which the approximate analytical expressions could be derived, the formula (17) based on the above quantum chemical model takes into account all possible kinds of electrical interactions. To get more insight into the composition of the term $\Delta\eta$, it is possible to profit from the possibility of its further partitioning.

For this purpose let us introduce, in keeping with Longuet-Higgins,[23] a potential ϕ defined by

$$\int_0^{\lambda} \frac{\partial E(r_0,x)}{\partial x}\, dx = \lambda\phi(r_0,\lambda) \tag{18}$$

In terms of this potential, the term $\Delta\eta$ can be rewritten in the form

$$\Delta\eta = \int_0^1 \phi(r_0,\lambda)\,\mathrm{d}\lambda + \int_0^1 \lambda \frac{\partial\phi}{\partial\lambda}\,\mathrm{d}\lambda \tag{19}$$

To interpret the physical meaning of individual terms of the partitioning (19), let us express the potential $\phi(r_0,\lambda)$ in the form of Taylor series (20)

$$\phi(r_0,\lambda) = \phi(r_0,0) + \left(\frac{\partial\phi}{\partial\lambda}\right)_0 \lambda + \ldots \tag{20}$$

The first term on the right-hand side of (20) describes the electrostatic potential of the fixed charge distribution of the molecule A at a point r_0. This potential is thus reminiscent of the electrostatic potential introduced some time ago by Tomasi et al.,[26] but despite this formal similarity, the meaning of the term $\phi(r_0,0)$ is slightly different. The difference is that the potential $\phi(r_0,0)$ was not derived from the charge distribution of the "ordinary" molecule but from the molecule whose charge distribution is modified by the presence of ghost vacant orbital(s) localized at the position r_0. The second and higher terms describe the distortion of the electron cloud; i.e., they characterize the polarizability of the molecule. Substituting (20) into (19), one obtains the expression

$$\Delta\eta = \int_0^1 \phi(r_0,0)\,\mathrm{d}\lambda + 2\int_0^1 \lambda\left(\frac{\partial\phi}{\partial\lambda}\right)_0 \mathrm{d}\lambda + \ldots \tag{21}$$

The first term in (21) can be, in light of the above discussion, identified with the electrostatic part of the work associated with the proton transfer, and it is perhaps worth mentioning that in atomic units this electrostatic work is numerically equal to the value of the potential $\phi(r_0,0)$.

$$\Delta W^{\mathrm{elstat}} = \int_0^1 \phi(r_0,0)\,\mathrm{d}\lambda \tag{22}$$

The second term represents the first approximation to the polarization part of the electrical work. The total polarization contribution includes, of course, also all remaining terms due to second and higher derivatives of the potential, but fortunately their knowledge is not necessary since the total polarization term can be simply calculated from

$$\Delta W^{\mathrm{polar}} = \Delta\eta - \Delta W^{\mathrm{elstat}} \tag{23}$$

Using this equation, the formula (17) can be rewritten in the form

$$\log\frac{K_X}{K_0} = \frac{\delta\Delta W^{\mathrm{elstat}} + \delta\Delta W^{\mathrm{polar}}}{2.303RT} \tag{24}$$

where

$$\delta\Delta W^{\mathrm{elstat}} = \Delta W^{\mathrm{elstat}}(A_0) - \Delta W^{\mathrm{elstat}}(A_X)$$

$$\delta\Delta W^{\mathrm{polar}} = \Delta W^{\mathrm{polar}}(A_0^-) - \Delta W^{\mathrm{polar}}(A_X^-) \tag{25}$$

This result is very interesting since (24) implies that the substituent effect on the dissociation of carboxylic acids is composed of the same two components (the electrostatic and polarization) that are considered in traditional theories of inductive effect. The only difference is that while in traditional description these theories are considered as two mutually exclusive alternatives, (24) suggests that both contributing mechanisms operate simultaneously and both of them have to be considered if really quantitative agreement between the experimental data and theoretical prediction is required. The fact that according to (24) the inductive effect is generally composed of two components does not exclude, however, that under certain circumstances the situation can be simpler. This is indeed the case, and long-lasting discussions concerning the nature of inductive effect only demonstrates that the reaction series can be found in which the traditional interpretation can be, at least qualitatively, plausible.

Table 1. Experimental and Calculated Values of Thermodynamic Characteristics of the Gas-Phase Dissociation Equilibria in a Series of 4-Substituted [2.2.2] Bicyclooctane-1-carboxylic Acids (All Values in kcal/mol)[a]

substituent	$\Delta E_X°$	$\delta\Delta E_X°$	$\delta\Delta G_X°$
H	363.23	0.0	0.0
Br	356.01	7.22	6.9
CF_3	355.22	8.01	6.5
Cl	355.37	7.86	6.2
CN	353.57	9.66	8.6
F	357.29	5.94	5.6
CH_3	362.99	0.24	1.0
NO_2	351.29	11.94	8.8

[a] Experimental values taken from ref 27.

The theoretical explanation of this reduction is straightforward. It is evident, namely, that due to the additive nature of (24) the simplified description of the effect can result in the situation where one or the other component of the effect is in a given series roughly constant, so that the substituent-induced variation of the observed quantity (p*K*) is necessarily due to the variation of the complementary component. Such a situation can to a considerable extent be influenced by an ingenious choice of the reaction series, and in the following section an example of such a series, consisting of a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, will be analyzed in detail. In order to not complicate the analysis by the problem of solvent effect, the analysis was applied to the gas-phase acidity data reported in ref 27.

CALCULATIONS

The quantum chemical calculations in this study were of two types. In the first, the geometry of all the studied molecules (series of 4-substituted [2.2.2] bicyclooctane-1-carboxylic acids and their anions) was completely optimized at the ab initio Hartree−Fock level of the theory in 3-21G* basis using the Gaussian 98 program.[28] These differences of the total energies characterizing the gas-phase acidity of individual acids were calculated and the corresponding values are summarized, together with experimental values of $\Delta G°$ in Table 1.

Consistent with the above-reported theory, these global values have been further partitioned into individual components that are summarized in Table 2.

The partitioning is described by

$$\Delta E_X° = E°(A_X^-) - E°(A_XH) = \Delta\epsilon_X + \Delta\eta_X \tag{26}$$

The correction for the basis set superposition error $\Delta\epsilon_X$ is given as a difference of the energy of "ordinary" anion and the energy of the same anion with the Hamiltonian modified by the presence of ghost orbital(s) localized on a hypothetical

Table 2. Calculated Contributions of Total Energy Differences in a Series of of 4-Substituted [2.2.2] Bicyclooctane-1-carboxylic Acids (All Values in kcal/mol)

substituent	$\Delta\epsilon_X$	$\Delta\eta_X$	ΔW_X^{elstat}	ΔW_X^{polar}
H	−6.42	369.65	211.57	158.08
Br	−6.84	362.85	203.90	158.95
CF_3	−6.77	362.00	203.90	158.10
CN	−6.68	360.25	201.89	158.36
Cl	−6.84	362.21	203.75	158.46
F	−6.63	363.92	205.97	157.95
CH_3	−6.44	369.43	211.02	158.41
NO_2	−6.85	358.14	199.93	158.21

particle with core charge $\lambda = 0$ at the position r_0 characteristic of the equilibrium position of the carboxylic hydrogen in the molecule of the acid.

$$\Delta\epsilon_X = E_X^\circ(A_X^-) - E_X^\circ(A_X^-(\text{ghost})) \qquad (27)$$

The possibility of such a modification is now incorporated into a Gaussian, and the resulting values of the contributions for each acid/anion pair are summarized in Table 2.

The remaining term $\Delta\eta_X$, characterizing the work of electrical forces associated with proton transfer, is simply given by (28), and its values are again summarized in Table 2.

$$\Delta\eta_X = \Delta E_X^\circ - \Delta\epsilon_X \qquad (28)$$

To get a more detailed insight into the composition of this term, the quantities $\Delta\eta_X$ were further decomposed into electrostatic and polarization contributions ΔW^{elstat} and ΔW^{polar} and the values of these individual components are also summarized in Table 2.

RESULTS AND DISCUSSION

Having reported the theoretical background as well as technical details of the new unified theory of inductive effect, let us discuss, in the following, the results of the practical application of the approach. As already stressed above, the most straightforward approach to the study of substituent effect on the dissociation equilibria consists of replacing the experimental values of standard free enthalpies in the formula (2) by their theoretical counterparts generated using contemporary quantum chemical methods. Unfortunately, this straightforward computational approach has the disadvantage of the lack of transparency of qualitative chemical models in terms that chemists use to rationalize the observed phenomena. To transform this straightforward computational approach into a form more suitable for chemists, it is necessary to adopt a series of simplifying assumptions. The first of such simplifications consists of approximating the values of free enthalpies ΔG° of individual species participating in the equilibrium (1) by the corresponding total energies ΔE° (eq 8). The quality of the approximation replacing the calculated standard free enthalpies ΔG° by the corresponding energy differences can be convincingly demonstrated by the existence of a tight linear correlation between experimental ΔG° values and the corresponding ΔE° terms. In the particular case of bicyclo[2.2.2]octane-1-carboxylic acids, this correlation is described by (29) and in graphical form is displayed in Figure 1, but similar correlation equations were also reported in the literature[21,22,29] for other dissociation equilibria.

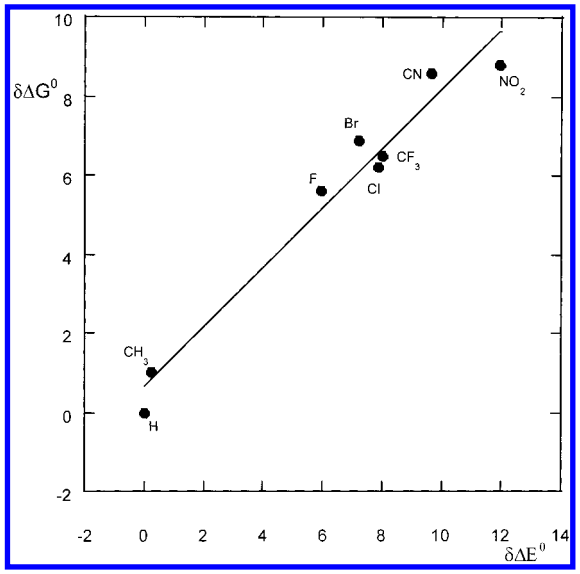

Figure 1. Dependence of experimental gas-phase acidities in a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids on the variation of total energies characterizing the proton-transfer equilibrium (1).

$$\delta\Delta G^\circ = 0.76\delta\Delta E^\circ + 0.65 (n = 8, r = 0.982, \sigma = 0.667) \qquad (29)$$

The next step in the buildup of a unified theory of inductive effect consists of the partitioning of the calculated ΔE° values into contributions $\Delta\epsilon$ and $\Delta\eta$ (eq 12). The values of these contributions are summarized in Table 2. Inspection of this table shows that the correction for basis set superposition error ($\Delta\epsilon$) is relatively very small compared to ΔE° itself and, moreover, its values in a series of substituted acids are more or less constant. This implies that the substituent-induced variation of dissociation constants is completely due to the second term $\Delta\eta$, which characterizes the electrical work associated with the proton transfer in the equilibrium (1). The correctness of this conclusion is also straightforwardly supported by the existence of tight linear correlation (eq 30, Figure 2), whose statistical parameters are comparable to the previous correlation with the primary quantity ΔE°.

$$\delta\Delta G^\circ = 0.78\delta\Delta\eta + 0.67 (n = 8, r = 0.982, \sigma = 0.671) \qquad (30)$$

This result is very important since it clearly confirms the correctness of early studies by Bjerrum[25] and Kirkwood[13] and more recently by Charton,[13] who attributed the substituent effect on the dissociation of carboxylic acids to electrical interactions in the molecule. The only difference compared to early theories[13,25] is that their authors concentrated only on the electrostatic component of the work, while the above quantum chemical approach inherently includes also all other possible contributions. The dominant component of this additional electrical work is due to polarization, and the advantage of the above quantum chemical model is that the additional partitioning of the term $\Delta\eta$ allows one to estimate the relative role of electrostatic and polarization components of the inductive substituent effect in each particular case. These values are summarized in Table 2, and the inspection

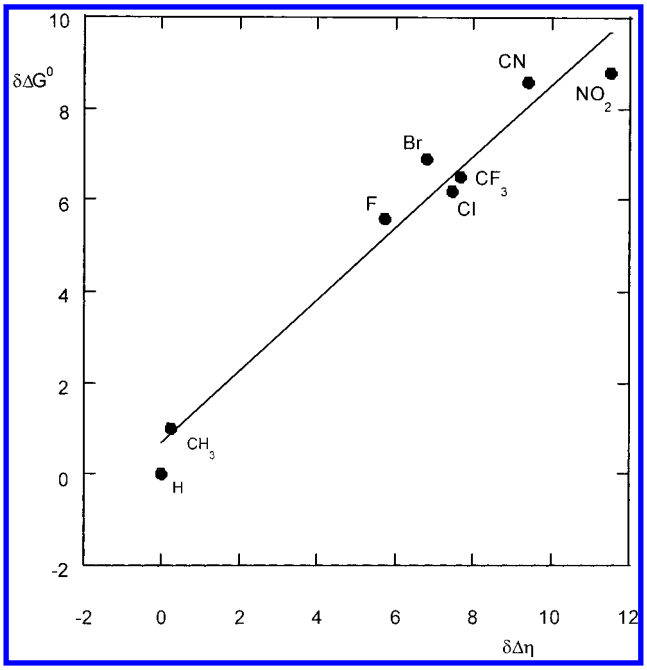

Figure 2. Dependence of experimental gas-phase acidities in a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids on the variation of the term $\Delta\eta$ describing the electrical component of the work associated with the proton transfer in the equilibrium (1).

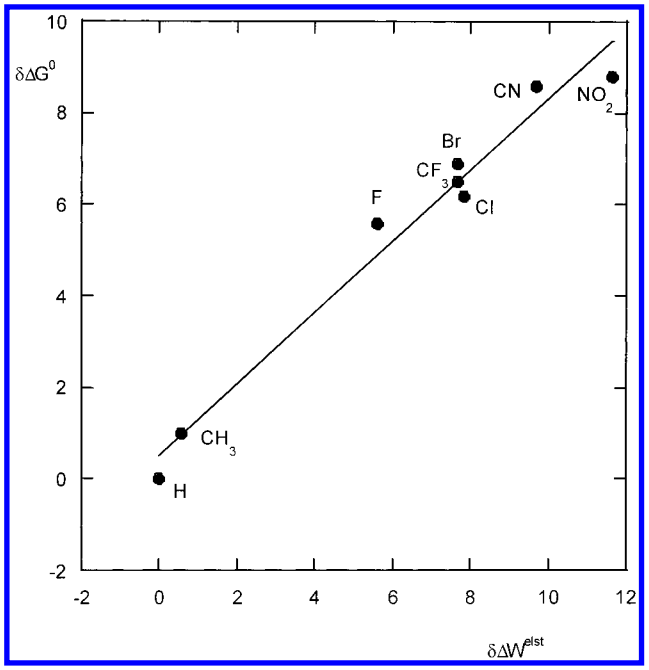

Figure 3. Dependence of experimental gas-phase acidities in a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids on the variation of electrostatic component of the total electrical work associated with the proton transfer (1).

of this table shows that although both contributions are quite comparable in absolute value, the polarization term remains more or less constant within the whole series. This, however, is just the situation favorable for the simplified classical description, and quite in keeping with the expectation, the observed substituent-induced variation of acidity of the studied acids is practically completely due to the variation of electrostatic term approximately considered in the Kirkwood−Westheimer field theory[14] (eq 31, Figure 3).

$$\delta\Delta G^\circ = 0.78\delta\Delta W^{\mathrm{elstat}} + 0.52 (n = 8, r = 0.986, \sigma = 0.582) \quad (31)$$

On the other hand, there are other reaction series in which the substituent effect will be similarly dominated by a polarization term that qualitatively corresponds to what classical chemistry describes as sigma inductive effect theory. An example of such a series was reported some time ago in a study[30] dealing with the substituent effect in aliphatic amines. It was found that the electrostatic contribution to total electrical work in a series ammonia, methylamine, dimethylamine, and trimethylamine is more or less constant so that the observed variation of gas-phase basicity of these amines in this case must be due to polarization term. As, however, the study[30] was performed only at semiempirical CNDO level of the theory which does not meet contemporary computational standards, we have reconsidered the same reaction series and performed the above analysis at the HF/3-21G* level of the theory. The results of the calculations are summarized in Tables 3 and 4, from which it is evident that the conclusions of the original semiempirical analysis that attributed the variation of gas-phase basicity of a series of the above amines to the polarization component of the inductive effect were correct. The relation of both quantities is described by the correlation equation (32).

Table 3. Experimental and Calculated Values of Thermodynamic Characteristics of the Gas-Phase Basicity in a Studied Series Aliphatic Amines (All Values in kcal/mol)[a]

molecule	$\Delta E_X°$	$\delta\Delta E_X°$	$\delta\Delta G_X°$
NH_3	226.9	0	0
CH_3NH_2	234.9	8.0	10.7
$(CH_3)_2NH$	243.5	16.6	17.7
$(CH_3)_3N$	247.9	21.0	21.7

[a] Experimental values taken from ref 27.

Table 4. Calculated Contributions of Total Energy Differences in a Studied Series of Aliphatic Amines

molecule	$\Delta\epsilon_X$	$\Delta\eta_X$	$\Delta W_X^{\mathrm{elstat}}$	$\Delta W_X^{\mathrm{polar}}$
NH_3	+3.7	223.2	89.6	133.6
CH_3NH_2	−0.7	235.6	89.9	145.7
$(CH_3)_2NH$	−0.2	243.7	89.4	154.3
$(CH_3)_3N$	−0.9	248.8	86.2	162.6

$$\delta\Delta G^\circ = 0.76\delta\Delta W^{\mathrm{polar}} + 0.76 (n = 4, r = 0.993, \sigma = 1.38) \quad (32)$$

This result is very interesting since it suggests that traditional discrimination between field and sigma inductive effect theories of inductive effect is in fact possible only in ingeniously designed reaction series in which the apparent dominance of one particular mechanism is due to the constancy of the other component. If this basic condition is not satisfied, the strict unambiguous classification of inductive effect is impossible and both electrostatic and polarization contributions must be considered simultaneously. Such a consideration is straightforwardly possible using the above-reported general quantum chemical model, and in this respect (17) and (24) represent the example of unified general theory of inductive effect whose need was repeatedly expressed by various authors.[7,13]

CONCLUSIONS

On the basis of the above results, it is possible to conclude that the inductive effect in aliphatic series is due to electrical interactions in the molecule quantitatively described by (17). The more detailed analysis of this equation shows that this effect can be generally decomposed into two basic components, the electrostatic one and the polarization one, that correspond to two traditionally considered theories of inductive effect. However, the relative weight of these components depends on the actual reaction series and the traditional discrimination between field and sigma inductive effect theories is thus possible only for ingeniously designed systems in which one of the contributions is roughly constant.

ACKNOWLEDGMENT

This study was supported by a grant from the Czech Ministry of Education, No. D0.20. R.P. gratefully acknowledges this support. X.G. acknowledges the University of Girona for a predoctoral fellowship covering his stay at ICPF Prague.

REFERENCES AND NOTES

(1) Branch, J. G.; Calvin, M. *The theory of organic chemistry*; Prentice Hall, New York, 1941; p 201.
(2) Taft, R. W. Sigma values from reactivities. *J. Phys. Chem.* **1960**, *64*, 1805−1815.
(3) Ehrenson, S. Theoretical Interpretation of the Hammett and Derivative Structure−Reactivity Relationships. *Prog. Phys. Org. Chem.* **1964**, *2*, 195−251.
(4) Stock, L. M. The Origin of Inductive effect. *J. Chem. Educ.* **1972**, *49*, 400−404.
(5) Bowden, K. The transmission of Polar Effects. *Can. J. Chem.* **1963**, *41*, 2781−2793.
(6) Bowden, K. The electrostatic field-inductive effect controversy. *J. Chim. Phys.* **1992**, *89*, 1647−1659.
(7) Bowden, K.; Grubbs, J. Through-bond and Through-space Models for Interpreting Chemical Reactivity in Organic Reactions. *Chem. Soc. Rev.* **1996**, *25*, 171−177.
(8) Friedl, Z.; Hapala, J.; Exner, O. Electrostatic effects in ionization equilibria. 3-substituted bicyclo[2,2,2]octane-1-carboxylic acids. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2929−2945.
(9) Exner, O.; Fiedler, P. A refined empirical model of the sigma-inductive effect. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1251−1267.
(10) Exner, O. The inductive effect: theory and quantitative assessment. *J. Phys. Org. Chem.* **1999**, *12*, 265−274.
(11) Exner, O.; Friedl, Z. Transmission of Substituent Effects: The through Space and Through Bond Models and Their Experimental Verification. *Prog. Phys. Org. Chem.* **1993**, *19*, 259−294.
(12) Exner, O.; P. Naus: Reevaluation of the inductive effect in isolated moecules and in solution. *J. Phys. Org. Chem.* **2000**, *13*, 693−698.
(13) Charton, M. The nature of electrical effect transmission. *J. Phys. Org. Chem.* **1999**, *12*, 275−282.
(14) Kirkwood, J. G.; Westheimer, F. H. The electrostatic Influence of Substituentsd on the Dissociation Constants of Organic Acids. I. II. *J. Chem. Phys.* **1938**, *6*, 506−512, 513−517.
(15) Roberts, J. D.; Moreland, T. W. Electrical Effects of Substituted Groups in saturated Systems. Reactivities of 4-substituted Bicyclo[2,2,2]octan-1-carboxylic Acids. *J. Am. Chem. Soc.* **1953**, *75*, 2167−2173.
(16) Charton, M. Electrical Effect Substituent Constants for Correlation Analysis. *Prog. Phys. Org. Chem.* **1981**, *13*, 119−251.
(17) Baker, E. W.; Parish, R. C.; Stock, L. M. Dissociation Constants of Bicyclo[2,2,2]oct-2-ene-1-carboxylic acids, Dibenzobicyclo[2,2,2]octa-2,5-diene-1-carboxylic acids and Cybanecarboxylic Acids. *J. Am. Chem. Soc.* **1967**, *89*, 5677−5685.
(18) Cramer, Ch. J.; Truhlar, D. G. Implicit Solvation Models: Equilibria, Structure, Spectra and Dynamics. *Chem. Rev.* **1999**, *99*, 2161−2200.
(19) Silva, C. O.; da Silva, E. C.; Nascimento, N. A. C. Ab initio Calculations of Absolute pK_a Values in Aqueous Solution II, Aliphatic Alcohols, Thiols and Halogenated carboxylic Acids. *J. Phys. Chem. A* **2000**, *104*, 2404−2409.
(20) Schuurmann, G.; Cossi, M.; Barone, V.; Tomasi, J. Prediction of pK_a of Carboxylic Acids Using the ab initio Continuum-Solvation Model PCM-UAHF. *J. Phys. Chem. A* **1998**, *102*, 6706−6712.
(21) Taft, R. W. Perspectives on structural effects in organic chemistry. *J. Chim. Phys.* **1992**, *89*, 1557−1566.
(22) Adcock, W.; Anvia, F.; Butt, G.; Cook, A.; Duggan, P.; Grob, C. A.; Marriott, S.; Rowe, J.; Taagepera, M.; Taft, R. W.; Topsom, R. D. The nature of field effects and their fall-off with distance: The acidity of substituted quinuclidium and bicyclooctylammonium ions. *J. Phys. Org. Chem.* **1991**, *4*, 353−360.
(23) Longuet-Higgins, H. C. Proton affinities. *Recl. Trav. Chim.* **1956**, *75*, 825−835.
(24) Boys, S. F.; Bernardi, F. The calculation of small molecular interactions by the differences of total energies. Some procedures with reduced errors. *Mol. Phys.* **1970**, *19*, 553−566.
(25) Bjerrum, N. Dissoziationskonstanten von mehrbasischen Säuren und ihre Anwendung zur Berechnung molekularer Dimensionen. *Z. Phys. Chem.* **1923**, *106*, 219−242.
(26) Scrocco, E.; Tomasi, J. The Electrostatic Potential as a Tool for Interpretation of Molecular Properties. *Top. Curr. Chem.* **1973**, *42*, 95−167.
(27) Koppel, A.; Mishima, M.; Stock, L. M.; Taft, R. W.; Topsom, R. D. Acidities of 4-substituted benzoic, bicyclo[2,2,2]oct-1-yl and bicyclo-[2,2,2]oct-2-enyl carboxylic acids. *J. Phys. Org. Chem.* **1993**, *6*, 685−689.
(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.
(29) Böhm, S.; Kuthan, J. An ab initio LCAO-MO study of the Substituent Effect in Benzenoid Systems: Meta- and Para Substituted Benzoic Acids. *Int. J. Quantum Chem.* **1994**, *26*, 21−33.
(30) Ponec, R.; Kučera, J. Proton Affinity. *Chem. Scr.* **1984**, *22*, 152−254.

CI0100651