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Review Commentary

The inductive effect: theory and quantitative assessment

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ABSTRACT: The concept of the inductive effect is defined in terms of thermodynamics and its quantitative estimation is reviewed. The electrostatic (through-space) and sigma-inductive (through-bond) theories are confronted and experimental proofs evaluated, with the result that both theories are very approximate and neither is in principle correct. The inductive effect in isolated molecules (acids, bases, anions, cations) is estimated separately by means of isodesmic reactions. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: inductive effect; field effect; electrostatic theory; effective permittivity

INTRODUCTION

The inductive effect was one of the fundamental concepts of the classical English school.[1] Together with the other substituent effects, it should approach to the complex question of how the individual parts of a molecule influence each other. Further development of this concept proceeded mainly along two lines.[2,3] On the one hand, inductive effects of individual substituents were quantitatively estimated[4–6] and expressed in terms of constants of various types (σ^*, σ_I, σ_F). On the other hand, the mode of transmission was discussed[7–10] in terms of two alternative theoretical concepts, usually called 'transmission through bonds' and 'transmission through space'. Although in the opinion of some workers the dilemma has been resolved, the view was also offered[8] that the problem is poorly formulated and neither of the two theories is correct. Further contributions to this problem appeared recently[11–19] so that a new review may appear appropriate. Parallel reviews in this issue deal mainly with the above question of transmission[20] or with the quantitative prediction.[21] In the present paper, we shall attempt to treat the problem from a more general point of view. The reasoning presented previously[8] should not be repeated, merely attention should be focused on the most general problems and on new results.

DEFINITION

Ingold[1] originally defined the inductive effect in terms of electron density which is merely descriptive and not acceptable from the point of view of rigorous quantum chemistry. The classical example is chloroacetic acid (p*K* 2.86), which is stronger than acetic acid (p*K* 4.76), supposedly owing to the inductive effect of chlorine. This example can be used for a kind of operational definition:[2] the inductive effect is defined as a difference of a measurable quantity between a substituted and an unsubstituted molecule. In a more detailed description, one has to divide a molecule into three parts:[2,5] substituent which is changed, functional group on which an observable quantity is localized and a skeleton connecting both. This definition has an exact physical meaning but is fairly general and can describe a substituent effect of any kind. We can define further that the substituent effect is called 'inductive' when the connecting skeleton has a particular structure: it must not contain any double bonds (or at least not a conjugated system) and should be sufficiently large to eliminate any direct steric effect (van der Waals interaction). Particularly convenient is the skeleton of bicyclo[2.2.2]octane[22] but it has been proved[5] that in almost all cases even a single methylene group is sufficient, as in the mentioned case of chloroacetic acid. While we can be satisfied with the definition, the term 'inductive' is not satisfactory in connection with the mentioned discussion[8,9] about the two possible mechanisms. Although it was suggested that both through-bond and through-space transmission might be designated as inductive,[23] in common sense the word inductive would be connected with the former. At present we have no better term; also, replacement of such a common term would hardly be feasible. Therefore, we shall retain here the term 'inductive effect' in a general

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sense, without connecting it with any assumed mechanism.

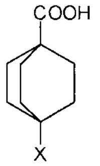
Also, the term 'measurable quantity' may be defined with more precision. The original content of the theory was reactivities, which means either equilibrium or rate constants in various reactions, mostly proceeding in solution. Recently, great attention has been given to NMR shifts,[15,24–26] mainly of ^{19}F and ^{13}C nuclei. However, these quantities are governed at least in some molecules by different laws, and doubts were offered[27] as to whether they can be explained in terms of the inductive effect (or by a combination of inductive and mesomeric effects). In this review, attention is focused on reactivities, i.e. on the values of ΔG° and $\Delta G^{\neq}$, or say ΔH° and $\Delta H^{\neq}$. Particularly important are equilibrium quantities in water[28] and in the gas phase[29,30] since in this case the substituent effect has a direct physical meaning. Thus in the mentioned case of chloroacetic acid, the inductive effect of chlorine is given by the value of ΔG° of the reaction

$$\begin{aligned}&\mathrm{ClCH_2COOH(aq) + CH_3COO^-(aq)}\\ &\quad = \mathrm{CH_3COOH(aq) + ClCH_2COO^-(aq)} \qquad (1)\\ &\qquad \Delta G^\circ{}_1 = -10.78\ \mathrm{kJ\ mol^{-1}}\end{aligned}$$

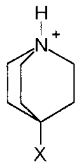
According to this definition, the inductive effect has an exact meaning from the thermodynamic point of view but nothing is said about its nature or mode of propagation.

QUANTITATIVE ESTIMATION

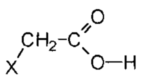
The inductive effect of individual substituents can be quantitatively evaluated and expressed in terms of substituent constants. It is sufficient to select a model system in which the necessary compounds are synthetically available and the observable quantity can be measured with acceptable accuracy. For these reasons, ionization constants appear particularly suitable. Of several models,[4,5,22,31–34] 4-substituted bicyclo[2.2.2]-octane-1-carboxylic acids[22] (**1**) or 4-substituted quinuclidines[31,32] (**2**) are best suited from the theoretical point of view, since any direct steric interaction is excluded.



1
$r = 6.44$ Å
$\theta = 0°$
$n_{cf} = 4$



2
$r = 4.46$ Å
$\theta = 0°$
$n_{ef} = 2$



3
$r = 3.40$Å (X = Cl)
$\theta = 57°$
$n = n_{ef} = 3$

The pK values can be measured in 50% ethanol or in water; the substituent inductive effect is expressed by the substituent constant σ_I and defined by Eqns[5] (2) and (3), respectively:

$$(\log K - \log K^\circ)_{\mathrm{BCO,50A}} = 1.56\sigma_I \qquad (2)$$

$$(\log K - \log K^\circ)_{\mathrm{QUIN,w}} = 5.28\sigma_I \qquad (3)$$

However, it was proved in a convincing manner[5] that simple substituted acetic acids furnish the same scale of σ_I while pK can be measured in water with better accuracy. Steric effects or hydrogen bonds could come into play only for large substituents and even then seem to be negligible in water solution. In the definition of Eqn. (4) the large proportionality constant is of advantage:

$$(\log K - \log K^\circ)_{\mathrm{ACET,w}} = 4.05\sigma_I \qquad (4)$$

Of course, the most important question is whether the constants σ_I defined according to Eqns (4)–(6) are identical within the assumed accuracy, or even valid also for other compounds. Comparison of several model systems[6,35] and systematic statistical analysis of practically all available data of many model systems[5] confirmed this. Direct statistical comparison[35] of the model systems **2** and **3** with 20 substituents gave a correlation coefficient $R = 0.989$ and standard deviation (SD) 0.033 σ units; these values can give a measure of accuracy of the whole approach. Even some physical quantities gave the same sequence of substituent inductive effects provided that the structural requirements are met. The ^{19}F substituent-induced NMR shifts in *meta*-substituted fluorobenzenes[36] served to determine σ_I on empirical grounds, although a conjugated system is present. However, the accuracy is lower[35] ($R = 0.941$, $SD = 0.068$ σ units) and the deviation of the point for hydrogen is significant.[37] In a recent principal component analysis[38] which included also physical quantities, 98% of variance was explained by the first component. The last approach is to calculate σ_I by quantum chemical procedures.[35,39,40] These procedures are related to the assumption that the inductive effect changes the charge on a given place in the molecule but they should be viewed merely as empirical and justified only by their correlation with experimental quantities.

In conclusion, there is good evidence that many observable quantities y, including all available values of log K or log k, are with good precision linearly related to each other and hence also to the inductive constant σ_I according to Eqn. (5). The only precondition is a structure as was defined above.

$$y - y^\circ = \rho_I\sigma_I \qquad (5)$$

This general applicability is characteristic only for the inductive effect.[2] Any reasonable explanation of this fact must refer to the principle of similarity.[41] When the observable quantities are so different, and the structures of molecules are also different, there must be an essential similarity in the very principle.[37]

Note that some authors[6,29,39] have replaced the symbol σ_I by σ_F for the reasons discussed in the next section, which are in our opinion not convincing. The change is purely formal and without consequences for the validity of Eqn. (5).

TRANSMISSION THROUGH BONDS OR THROUGH SPACE

Theoretical concepts

According to Eqn. (5), unknown values of the observable quantity can be predicted provided that both σ_I and ρ_I are known. This means that the respective substituent has already been investigated in a standard reaction (to obtain σ_I) and the respective reaction under the specified conditions has been investigated using some standard substituents (to obtain ρ_I). When this evidence is not available, two approximate theories can be helpful. Their recent detailed analysis[8] can be recapitulated as follows.

In the theory called here 'electrostatic,' the inductive effect is calculated as the interaction energy between the charge in the anion (cation) and the substituent.[42,43] In the case of a dipolar substituent, the energy is given by the relationship

$$\log(K/K^{\circ}) = \frac{Z_1 e \mu \cos\theta}{2.303\, k\, T\, r^2\ (4\pi\varepsilon_o\varepsilon_{ef})} \qquad (6)$$

This calculation concerns the substituted ion on the right-hand side of Eqn. (1). On its left-hand side, a similar interaction is possible between the substituent dipole and the dipole of the functional group (say COOH). This is usually omitted as negligible.

When the substituent bears a charge, a pole–pole interaction takes place and the equation has the form

$$\log(K/K^{\circ}) = \frac{Z_1 Z_2 e^2}{2.303\, k\, T\, r\ (4\pi\varepsilon_o\varepsilon_{ef})} \qquad (7)$$

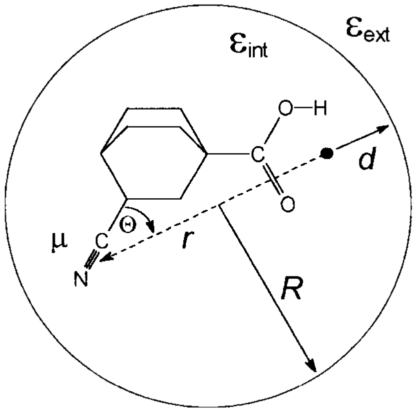
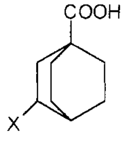
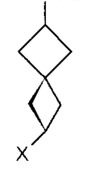


Figure 1. Representation of an acid molecule within the framework of the electrostatic theory. Shown are the conventional position (Ref. 44) of the hydrogen atom ●, the dipole μ, geometrical parameters *r* and *θ*, a spherical cavity with the radius *R* and the distance *d* of the charge from the cavity surface

In Eqns (6) and (7), Z_1 and Z_2 are the charges on the reaction center and on the substituent, respectively: they have usually the value ± 1. The vector μ is the substituent dipole (considered as a point vector on a proper place) and the vector *r* is the distance from the substituent (charge or point dipole) to the reaction center; usually it is measured up to the ionizable hydrogen atom.[42–44] The angle *θ* is the angle between these two vectors. The geometrical parameters are illustrated in Fig. 1 and some examples of their values are given in formulas **1**–**5**. They were calculated with the standard geometry for X = Cl; the negative charge was placed between the two carboxylate oxygen atoms[42–44] and the substituent dipole into the middle of the C—Cl bond. All these assumptions may seem rather arbitrary but they do not affect the result very much and do not represent the main problem. The main problem lies in the quantity[43–45] ε_{ef}, representing any 'effective' relative permittivity. This has no other physical meaning than of an artificial constant which meets the experimental results according to Eqn. (6) or (7). This means that the electrostatic approach cannot work in practice without an auxiliary theory yielding a value of ε_{ef} for a given molecule. This value must lie between the bulk permittivity of solvent (e.g. ε_{ext} = 78 for water) and the internal permittivity of the solute molecule (usually the value of ε_{int} = 2 is taken[44–46]; this interval is very large and the result of calculation is sensitive to the parameters used and to computational details. The popular cavity model of Kirkwood and Westheimer places the molecule into a spherical[44] or ellipsoidal[45] cavity: this surface separates the spaces with ε_{ext} and ε_{int} (Fig. 1). The proper choice of parameters (radius of the sphere *R*, or semiaxes of the ellipsoid) was discussed in detail,[8] and also the extended and more sophisticated cavity models. The most important modification[46] requires a constant value of *d*, the difference between



4
r = 5.72 Å
θ = 54°
n_{ef} = 4.11



5
r = 7.57Å
θ = 28°
n_{ef} = 5

(X = Cl)

the radius of the sphere R and the distance r (Fig. 1). In conclusion, the whole treatment is rather flexible and can be accommodated to various experimental results.

The alternative theory,[47–49] called most properly sigma-inductive, does not allow the inductive effect to be calculated explicitly. It only describes its dependence on structure for a given substituent and a given reaction center; in terms of Eqn. (5) it can help to estimate the reaction constant ρ_I. For this purpose, it assumes that the effect is weakened by every bond in the same ratio, called the attenuation factor, ε. This can be expressed by the following dependence on the number of bonds n:

$$\log(K/K^\circ) = \rho_I{}^\circ \sigma_I \Sigma \varepsilon^n \tag{8}$$

where σ_I is the normalized substituent effect as in Eqn. (5) and $\rho_I{}^\circ$ is the extrapolated reaction constant for $n = 0$ (usually compounds with $n = 0$ cannot be included into the model). In further discussion, σ_I and $\rho_I{}^\circ$ may be simply viewed as adjustable parameters characterizing the substituent and reaction, respectively: any solvent effect is included into $\rho_I{}^\circ$. The summation in Eqn. (8) extends over all possible paths (when there are more such paths in the molecule, for instance in **1** or **2** there are three). This treatment[22] is in fact an extension of the original theory and is not quite consequent. In the molecules such as **4** or **5** the number of paths and their length are not evident and this is a serious drawback since similar somewhat exotic molecules played a relatively great role in attempted experimental decisions between the two theories. Therefore, an improvement of the sigma-inductive theory was suggested[50] in which the molecule is compared to an electric network.[8] If each bond had a resistance of 1 Ω and an electromotive force of 1 V was applied to the two terminals (substituent and ionizable group), the resistance of the whole network could be calculated by applying the Kirchhoff laws. In the case of a straight-chain compound, this resistance equals the number of bonds. For any other compound, it can be called the effective number of bonds, n_{ef}, and introduced into Eqn. (8) instead of n to give Eqn. (9). The improvement is considerable (Fig. 2 in Ref. 8). Of course, the model lacks any actual physical meaning. It was created[50] with the intention of comparing the two theories at similar levels of sophistication.

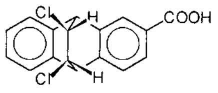
$$\log(K/K^\circ) = \rho_I{}^\circ \sigma_I \varepsilon^{n_{ef}} \tag{9}$$

Note also that the sigma-inductive theory [Eqn. (8) or (9)] is compatible with the $\rho\sigma$ approach [Eqn. (5)] whereas the electrostatic theory [Eqn. (6)] is not[33] since the geometrical parameters, r and θ, are variable for different substituents and cannot be included in the constant ρ valid for all substituents. However, as approximate relationships, all the named equations may be valid simultaneously. In a recent approach,[17,21] constants σ_I of composite substituents were calculated on the principle of Eqn. (6) but the constant ρ remains as an empirical parameter, in principle incompatible with this equation.

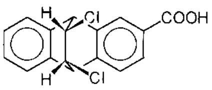
Experimental decision

Both theories are evidently far from a true picture. When a quantum chemical description is replaced by the electrostatic approach, it is viewed in theoretical chemistry as the zero-order approximation. Reduction to the electrostatic energy is also incompatible with the principle of bond energies:[8] Eqn. (6) assumes that the O—H bond energies on the two sides of Eqn. (1) are equal. Even when this approximation is accepted, it is certain that the electrostatic field is very inhomogeneous. The question is whether this field can be approximated as homogeneous with a uniform ‘effective’ permittivity as in Eqn. (6), or described better in topological terms as in Eqn. (8) or (9). Regardless of any theory, one can view these equations as two relationships within the framework of correlation analysis. Then the meaningful question is which of them works better in practice. A statistically significant answer would require the selection of a large sample of ‘typical’ compounds, calculation of the ΔpK values according to either theory and comparison with experiments; from the result, no conclusions can be drawn about the ‘nature’ of the inductive effect or its ‘transmission’. There are two principal difficulties in this procedure. First, the two theories are of different predictive power. Equation (6) or (7) predicts an actual value of ΔpK provided that ε_{ef} is calculated according to a complementary theory but Eqn. (8) has two empirical constants ρ_I and σ_I and is only able to predict relative pK values for compounds with the same substituent and the same functional group. In this way, the number of possible model systems will be very restricted. The second problem is still more general:[51] how to imagine the population of ‘typical’ compounds from which the statistical sample should be withdrawn. No such definition is satisfactory and is not even realizable, e.g. acidic compounds of all possible structures, all compounds with acidity in the given limits, all compounds the acidity of which has been reported or has been reported with a given precision, etc. Consequently, correct statistical investigations of this kind do not seem feasible.

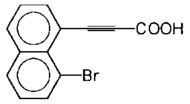
Actually, the decision between the two theories has been attempted many times in another way: specially tailored molecules were synthesized which would yield sufficiently different results according to Eqns (6) and (8). Usually it was necessary to compare two molecules or two systems. Attention was focused particularly on the two following features. First, in Eqn. (6) the angle θ is involved whereas in Eqn. (8) it is not. According to Eqn. (8), substituent effects in stereoisomers should be equal, which is evidently not the case. Stereoisomers such as fumaric and maleic acid are not completely convincing since they contain conjugated double bonds and do not belong into the model of the pure inductive effect. However, series of sophisticated molecules have been synthesized with different values of this angle; they have been listed in reviews[8–10] and new examples added.[19] A particularly convincing example are the compounds[52] **6** and **7**, whose pK values differ dramatically, or compound **8**, in which the bromine substituent has an acid weakening effect,[53] in agreement with $\theta > 90°$.



6
ΔpK ·· -0.47 (50% EtOH)

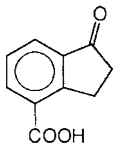


7
ΔpK = -0.02 (50% EtOH)

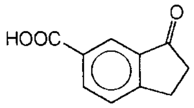


8
ΔpK = +0.47 (80% MCS)

These facts were commonly interpreted[9,10] as meaning that the electrostatic theory is 'correct' and the sigma-inductive theory is 'wrong'. There is certainly no doubt that the substituent effect depends on the angle θ but there are also good proofs[8] that its effect is overestimated by Eqn. (6). In compounds **9** and **10**, the values calculated according to Eqn. (6) overestimate badly[54] the influence of the angle θ. Note that also calculation of ε_{ef} is very uncertain. Curiously, Eqn. (9) with $\varepsilon_{ef} = 0.36$ predicts the ratio of pK values with reasonable accuracy.[8] It has happened several times that for very sophisticated compounds no theory is satisfactory; examples have been discussed.[8–10]

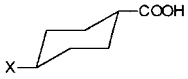


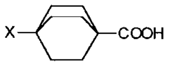
9
$r = 6.76$ Å
$\theta = 7°$
$n_{ef} = 4.76$
ΔpK -0.88 (50% EtOH)

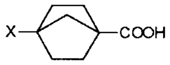


10
$r = 6.53$ Å
$\theta = 66°$
$n_{ef} = 4.97$
ΔpK -0.77 (50% EtOH)

In the second approach, attention was given to molecules of similar shape but differing in the number of paths. The most important example[8,10] is compounds **11**, **1** and **12**. The observed relative Δ pK values are fairly close in spite of the difference in the number of paths, but introducing ε_{ef} according to Eqn. (9) brings a significant improvement. When the relative effects are compared,







	11	**1**	**12**
ΔpK rel.	0.71	1	1.17
calc.[10] eq. (6)	0.84	1	1.26
calc. eq. (9)	0.60	1	1.15

we cannot agree with the conclusion[10] that the electrostatic model is good and the inductive model bad. Note also some arbitrariness in the electrostatic calculations (ε_{ef}) and still more in the experimental values obtained in different solvents; the values given here are ratios of carefully calculated ρ_I in the same solvent.[5]

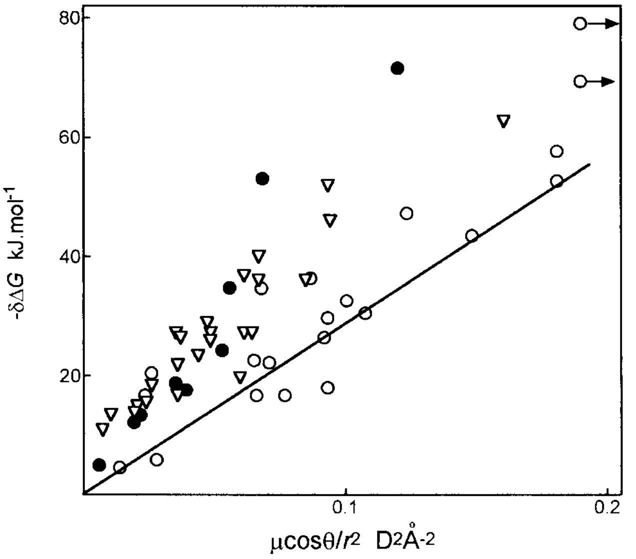


Figure 2. Test of the electrostatic theory on the ionization equilibria in the gas phase, a plot of $\delta\Delta G°$ vs $\mu\cos\theta/r^2$ according to Eqn. 6, Tanford spherical cavity (Ref. 46). ▽, Substituted carboxylic acids (**3, 1, 4**, bicyclooctenecarboxylic, propionic, 3- and 4-methylbenzoic, adamantanecarboxylic, cubanecarboxylic acids); ○, substituted ammonium ions (**2**, trimethylammonium, methylammonium, bicyclooctylammonium); ●, protonated substituted nitriles. (bicyclooctanecarbonitriles, acetonitriles, 3- and 4-methylbenzonitriles); substituents Cl, CN, F, CF_3, CO_2Me, OMe, Br, exceptionally CCl_3, OH, NO_2 and SMe. The straight line has the theoretical slope $\varepsilon_{ef} = 1$. Experimental data from Refs 11, 12, 18, 29, 55 and 56

Statistical tests

Our conclusion from these examples and from some others is that the problem cannot be solved by the synthesis of special model compounds, and less so by calculation of systems of atoms which are not molecules;[8] every particular case can be explained with a certain effort and every disagreement with experiment can be considered as more or less acceptable. More decisive could be statistical tests based on larger sets of compounds. As mentioned above, a random selection from all organic compounds is not feasible. However, even a test summarizing the results on special model compounds is much more efficient than the result from a single compound. A very important test can be obtained from recently measured[29,55,56] ionization equilibria in the gas phase. Under these conditions, any cavity theory is of little importance since ε_{ef} in Eqn. (6) is near to unity:[57] as the highest possible the value of 1.5 was considered.[58] All

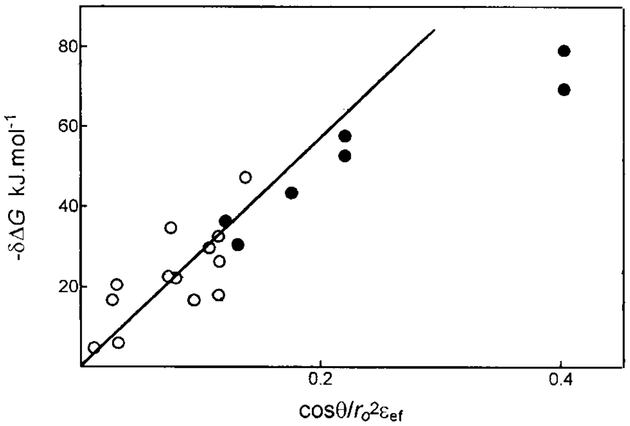


Figure 3. Test of the electrostatic theory in the gas phase restricted to ammonium ions with the distance r_0 taken only to the nitrogen atom. ○, Quinuclidines and bicyclooctylamines; ●, methylamines and trimethylamines. The straight line has the theoretical slope $\varepsilon_{ef} = 1$. Experimental data from Refs 11, 29 and 55

experiments with various substituents and various skeletons can be presented in one test. On the other hand, polarizability effects appear in the gas phase in which any substitution contributes to the stability of both anions and cations.[29,30] These effects can be accounted for by choosing the reference compound (to which $K°$ relates) with the substituent CH_3 instead of H. In Fig. 2 we have collected available data on molecules with a rigid skeleton or at least with an estimatable conformation. Particularly in the case of benzene *meta* derivatives e.g. 3-chloromethylbenzoic acid), the two possible positions were taken with the same probability. Attention was focused on the substituents with an appreciable inductive effect. Figure 2 reveals that compounds with different functional groups behave differently. While ammonium ions are predicted with reasonable precision, carboxylic acids and protonated nitriles exhibit increased effects which cannot be accounted for within the framework of the electrostatic theory since it would require $\varepsilon_{ef} < 1$. We must conclude that in the case of ions with delocalized charge the preconditions of Eqn. (6) are not fulfilled. Since most of the experimental evidence was based on carboxylic acids, all of these results are somewhat in doubt. When the test is restricted to ammonium ions (Fig. 3), the agreement with theory is improved when the distance r is measured only to the nitrogen atom, not to the hydrogen as usual [42,44] Even so, there is a considerable scatter which cannot be explained by imprecise geometry or uncertain conformation. Even a correction for finite dipole length[59] has a small effect. An efficient comparison with the alternative theory, Eqn. (8) or (9), is not possible since it would require more experimental results with the same substituent and the same reaction center. For instance, with X = Cl we have at our disposal only three data on substituted amines and three further can be obtained indirectly from other substituents using Eqn. (1); plots of these data according to Eqn. (6), (9) or (10) are equally scattered (not shown).

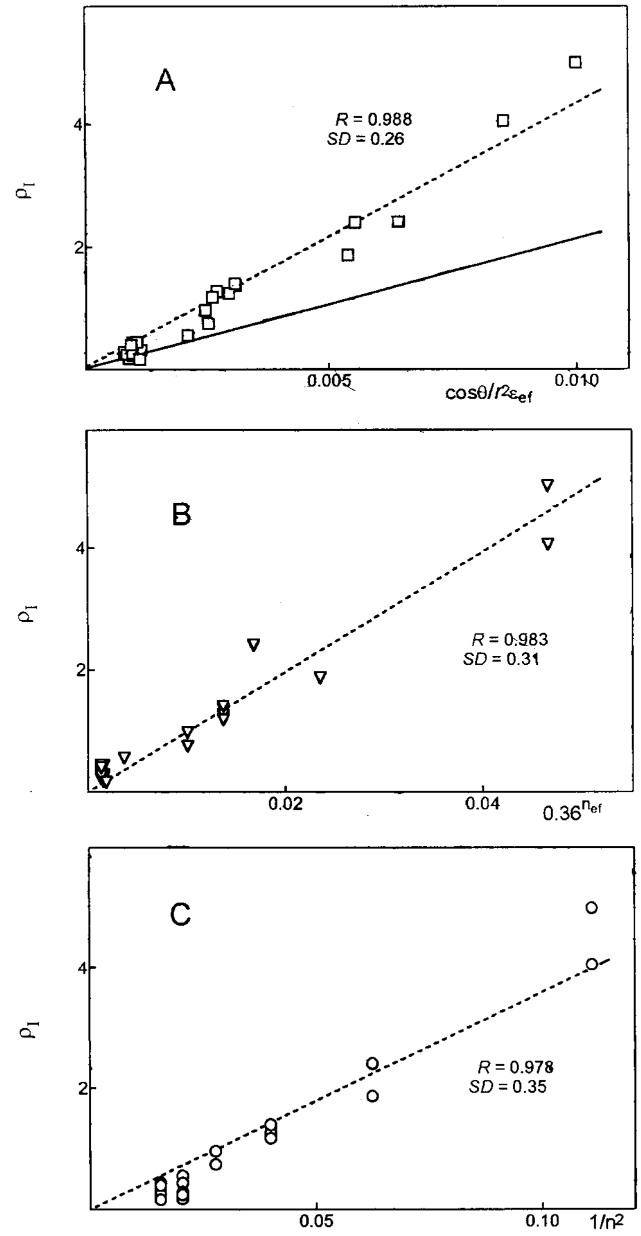


Figure 4. Plot of the inductive reaction constants ρ_I (≡*L*, Ref. 14) in terms of different theories: (A) electrostatic theory, Eqn. 6, Tanford's (Ref. 46) spherical cavity; (B) refined inductive model, Eqn. 9; (C) simplified field model, Ref. 14, Eqn. 10. The full line is theoretical from Eqn. 6 with $\varepsilon_{ef} = 1$; broken lines are regression lines

From the solution data, large sets are available in terms of the constant ρ_I. In this way even conjugated molecules such as benzene derivatives can be included since ρ_I is believed to measure only the inductive effect. In a statistical test, Eqn. (6) was simplified by neglecting both ε_{ef} and cos θ (for θ <45°); as a measure of the distance r

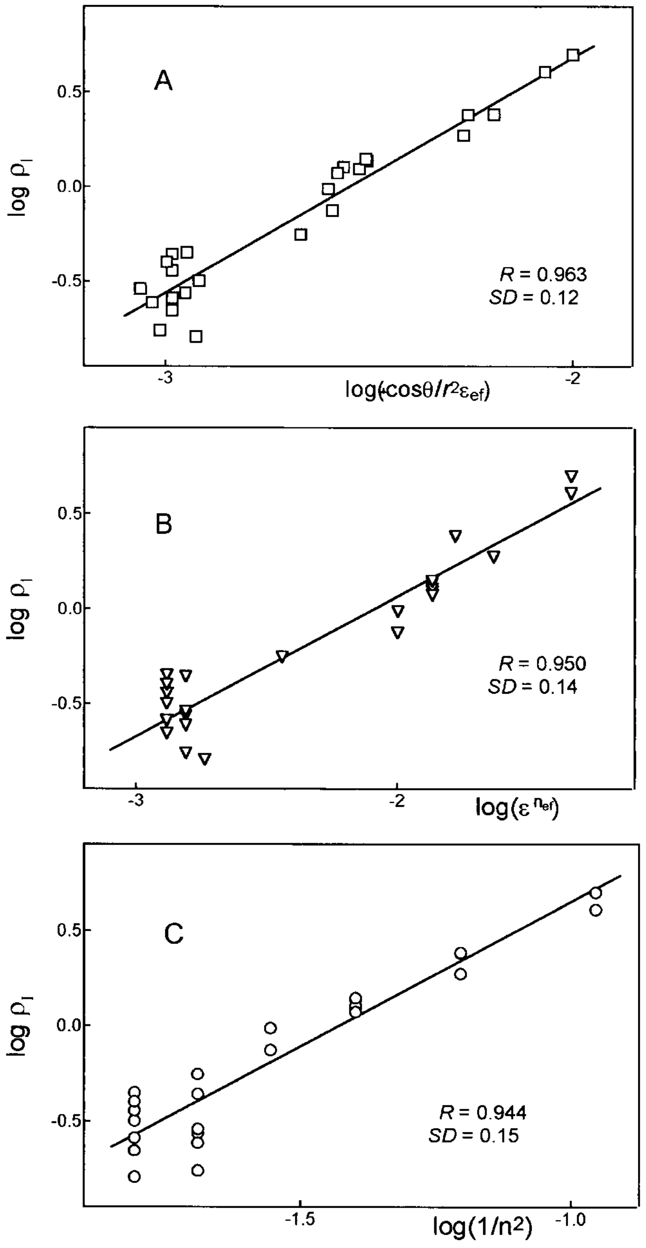


Figure 5. The same plots as in Fig. 4 on a logarithmic scale

the number of bonds n was substituted.[14] The resulting equation takes the form

$$\log(K/K^{\circ})\ (\text{or}\ \rho_{\text{I}}) = C/n^{m} \qquad (10)$$

The best value of m was 2 as expected. In our opinion, this model could be designated as 'modified electrostatic'. It is in a certain sense intermediate between the Eqns (6) and (8); nevertheless, it was taken as a proof for transmission through space. The fit achieved is shown here in Fig. 4 concerning the fundamental reaction series, carboxylic acids in water. Equations (6), (9) and (10) appear to be of comparable accuracy and a statistically significant decision is not possible. Although Eqn. (6) would give the best fit in a regression, the slope of the regression line differs from the theoretical slope, showing the insufficiency of calculating ε_{ef}; at best ε_{ef} can be accepted as an adjustable parameter.

In Figure 4 both the slopes and fits are too strongly affected by the remote points for substituted acetic acids and acrylic (on the right). This defect is removed in logarithmic plots (Fig. 5). The fit has been worsened in all cases: any decision in favour of one theory was not achieved.

Previously, we carried out similar tests based mainly on pK values in 50% ethanol[8] but the significance of the data obtained is mixed solvents has been generally challenged.[60] Nevertheless, the result (Figs 5 and 6 in Ref. 8) was partly similar to Fig. 2: while carboxylic acids gave a reasonable trend, ammonium ions deviated badly. One has to assume that in the calculation of ε_{ef} there is an arbitrariness suitable just for carboxylic acids. A Further important plot was for the pK of **2** in water against the substituent dipole μ (Fig. 4 in Ref 8); a rough dependence was obtained for simple substituents but for more complex groups the influence of θ was overestimated. The dependence on solvent is in our opinion particularly important since only in the dependence on solvent is Eqn. 6 apparently superior to Eqn. 8. However, the plot of calculated vs experimental pK for one compound (Fig. 7 in Ref. 8) represents a complete failure of the theory, for both mixed and pure solvents.

A different approach assumes the electrostatic and sigma-inductive effects to be two independent phenomena which could be expressed by different substituents constants, σ_{I} and ι, respectively.[61] The reactivity data correlated better with σ_{I} but this is in our opinion self-evident since the constants σ_{I} were derived just from the reactivities.

Conclusions drawn from the NMR shifts will not be discussed here since the structural dependence of these shifts is insufficiently known; conclusions have been claimed in favor of both through-space transmission[24,25] and through-bond transmission.[15] Note that the terms through-bond and through-space transmission as discussed here have little in common with the same terms used for the interaction of separated orbitals, e.g. in 1,4-diazabicyclo[2.2.2]octane. The latter problem was reviewed[62] and extended to further atoms with lone-pair orbitals.[63] In this case, through-bond transmission was considered to be deciding.

INDUCTIVE EFFECT IN ISOLATED MOLECULES

In the above examples the inductive effect was always observed as a difference between two molecules: an acid and its anion, a base and the conjugated cation or a ground state and a transition state. Another complication is due to measurement in water or other aqueous solvents which involves unknown solvent effects. As mentioned in the preceding section, the second problem may be solved by measuring acid–base equilibria in the gas phase. General methods are available,[18,29,30] although not all compounds can be investigated in this way[64] (low volatility, rapid decomposition of ions, unknown site of protonation). In the gas phase, instead of Eqn. 1 we have

$$\begin{aligned} &ClCH_2COOH(g) + CH_3CH_2COO^-(g) \\ &\quad = CH_3CH_2COOH(g) + ClCH_2COO^-(g) \qquad (11) \\ &\Delta G^\circ{}_{11} = -46.1 \text{ kJ mol}^{-1} \end{aligned}$$

Relative values $\Delta G^\circ{}_{11}$ or $\Delta H^\circ{}_{11}$ (mostly equal) can be determined with reasonable accuracy, although the absolute values of $\Delta G^\circ{}_{acid}$ and $\Delta G^\circ{}_{base}$ are very large and rather uncertain. More essential is the separation of the effects in neutral molecules and in ions. A possible way was suggested[37] based on isodesmic reactions.[65–68] For the example of chloroacetic acid, the isodesmic reaction reads

$$\begin{aligned} &CH_3CH_2COOH(g) + ClCH_3(g) \\ &\quad = ClCH_2COOH(g) + C_2H_6(g) \qquad (12) \\ &\Delta H^\circ{}_{12} = +16.2 \text{ kJ mol}^{-1} \end{aligned}$$

Its reaction enthalpy can be considered as a measure of interaction of the two functional groups Cl and COOH, or say the inductive effect of Cl on the COOH group or *vice versa*. As mentioned in the previous section, an inductive effect in the gas phase is accompanied by an effect of polarizability, usually less intense;[29,35] for this reason, we used in Eqns (11) and (12) as reference propionic acid and not acetic acid. In this particular case the difference is minute; in larger molecules it can be neglected. As a sum of Eqns (11) and (12) we obtain Eqn. (13) expressing the inductive effect in the anion:

$$\begin{aligned} &CH_3CH_2COO^-(g) + ClCH_3(g) \\ &\quad = ClCH_2COO^-(g) + C_2H_6(g)(13) \qquad (13) \\ &\Delta H^\circ{}_{13} = -29.9 \text{ kJ mol}^{-1} \end{aligned}$$

Evaluation of $\Delta H^\circ{}_{12}$ was based on the known enthalpies of formation $\Delta_f H^\circ$; the primary experimental quantities were the enthalpies of combustion. Determination of the latter quantity is cumbersome and only a limited number of data are available.[69,70] Therefore, we attempted to calculate these data by quantum chemical methods at a reasonably high level (HF/6–31G** and MP2/6–31G** with a complete geometry optimization). (O. Exner, P. Nauš and P. Čársky, unpublished work). The model compounds were, in addition to chloroacetic acid, particularly derivatives of bicyclooctane (**1**, X = F; 4-cyanobicyclo[2.2.2]octyl-l-amine) and **2** (X = CN), 2,2,2-trifluoroethanol, 1,4-dicyanobicyclo[2.2.2]octane and 2-cyanoethyldimethylamine, and comparison was made also with some unsaturated compounds in which the effect is predominantly inductive, such as 3-nitrophenol, 3-nitroaniline and 3-cyanopyridine. The result was that the values of $\Delta H^\circ{}_{12}$ are appreciable and positive for smaller molecules as in Eqn. 12; for larger molecules they are mostly less than 5 kJ mol^{-1}. Their dependence on structure has nothing in common with the known inductive effect. Non-additive effects of two functional groups on $\Delta_f H^\circ$ in the simple molecules were observed and interpreted in a complex way by two independent modes of interaction of which only one was inductive in character.[71] The resulting equation has not been tested further and no explanation is known. In any case, the conclusion is safe that the inductive effect is at least in some classical examples only partly due to enhanced stability of the anion but partly also to the lowered stability of the acid. From this point of view, it is hopeless to calculate the effect only from the structure of the ion as in Eqn. (6).

INDUCTIVE EFFECT IN CONFORMATIONAL EQUILIBRIA

In most of the preceding reactions, charged particles were involved, which caused a larger inductive effect and allowed it to be calculated in terms of Eqn. (6). In conformational equilibria the effects between uncharged particles are smaller similarly as in Eqn. (12): electrostatic calculations may proceed either in terms of point dipoles or each dipole may be represented by two point charges. The calculations and results obtained have been reviewed in detail.[8] The dilemma of through-space or through-bond effects has never appeared since suitable model compounds for the sigma-inductive model are hardly possible. Results for the electrostatic model sometimes seemed not too bad.[8] Note, however, that this model would predict for all compounds the conformer with the lowest dipole as the most stable. This is not valid in many cases.[72,73]

INDUCTIVE EFFECT IN UNSATURATED SYSTEMS

In a skeleton containing isolated double bonds, the inductive effect is transmitted over this bond with just a slightly enhanced intensity than if this bond were single. An example is substituted bicyclo[2.2.2]octene-1-carboxylic acids[12] with ρ_I in the gas phase of 14.3 compared with $\rho_I = 13.4$ for the saturated acids **1**; also in solution the difference is very small.[74] In terms of sigma-inductive theory, a special value of ε can be given for transmission through any kind of bond. In terms of the electrostatic theory, the difference must by accounted for by slight changes in geometry.

In molecules with a conjugated system of multiple bonds, an influence of resonance (mesomerism) cannot be doubted but there is also no reason why the inductive effect should be absent. Commonly accepted theory[75] assumes that inductive effect and mesomerism (resonance) can be expressed as a sum; in terms of constants σ this is written as

$$y - y^{\circ} = \rho_I\sigma_I + \rho_R\sigma_R \tag{14}$$

A well known example is *meta* and *para* derivatives of benzene; variable blends of inductive and resonance components are expressed by variable values of ρ_I and ρ_R. This interpretation was accepted generally for donor substituents whereas for acceptors it was observed[76] that effects in the *meta* and *para* positions are proportional for a large series of substituent groups (NO_2, CN, CF_3, CH_2X, SO_2X, SF_5) according to the equation

$$\log K_p - \log K^{\circ} = \lambda(\log K_m - \log K^{\circ}) \tag{15}$$

Our simple conclusion was that the named substituents (viz. all substituents without a lone electron pair in the α-position) act by one mechanism.[76,77] It is only a question of terminology whether this mechanism is called simply the inductive effect. This conclusion was much opposed,[5,75,78–82] a resonance effect was considered to be present in principle and assumed to be simply proportional to the inductive effect, and an explanation was also sought in solvent effects and still more complex models were suggested.[83] On the other hand, the same proportionality was observed recently even for protonation equilibria in the gas phase.[18] Arguments from other sources are also available[18,84] that the resonance is negligible in substituted benzenes with the named acceptor substituents. In the particular case of the nitro group, all pros and cons were summarized in a review.[84]

The correct question is not whether there is conjugation but whether the conjugation is strong enough to be seen in a given observable quantity. We consider as proven at least that there is a fundamental difference between the behavior of common donors and acceptors in simple aromatic derivatives.[85] While donors are conjugated differently, some of them very strongly, with the benzene ring, common acceptor groups are conjugated very little and with respect to certain observable quantities we may say not at all. ‘Nature has endowed us with a variety of donors whereas the common acceptors form a group with less discriminating abilities.’[86] These conclusions would be strongly supported if an actually strongly conjugated acceptor were found. Attention was focused on the group BBr_2 with a sextet on boron, but owing to its instability experimental proofs are only available from dipole moments.[87]

CONCLUSIONS

The inductive effect is an important concept in the approach to the general problem of how the individual parts of a molecule influence each other. It deserves more attention than is given in standard textbooks.[88–90] Concerning the dilemma of transmission through bonds or through space, the question is not well formulated, even for the reason that bonds are also parts of the space. A direct translation of the problem into quantum chemical terms seems impossible[3] since quantum chemistry starts from different fundamental principles.

For the time being, we do not see a good reason for changing the well tried term inductive effect and its symbol σ_I. When the task is to predict the inductive effect on the ionization equilibria, quantum chemical calculations gave incomparably better results (O. Exner, P. Nauš and P. Čársky, unpublished work)[91] than Eqn. (6) for the gas-phase values. For solution values, Eqn. (6) is also of little value (see Fig. 7 in Ref 8). For the first orientation or for text-book purposes, the statement is sufficient that a more remote substituent has a smaller effect; even the simple rule[47–49] that it is reduced to one third by any further bond is still valid.

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