JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. **12**, 283–288 (1999)

Review Commentary

Inductive substituent effects

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Received 24 March 1998; revised 4 August 1998; accepted 7 August 1998

ABSTRACT: A brief description and analysis of the history of and modern situation in the field of inductive effects, methods for its quantitative determination and prospects are presented, including a discussion of the underlying mechanism. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: inductive substituent effects

INTRODUCTION

The relationship between the structure and reactivities of organic and organoelement compounds is a fundamental problem in modern chemistry. The overall interaction of a substituent with a reaction center is usually considered to consist of inductive, resonance and steric components. The inductive effect is one of the most fundamental intramolecular interactions and plays an extremely significant role in organic reactivity. In our mind, when we refer to inductive effects, the following questions arise: (1) the nature of the inductive effect and the mechanism of its transfer; (2) methods for the quantitative determination of the inductive effect and their reliability and perspectives; and (3) the problem of a unified scale of inductive constants. Let us consider these questions in this order.

THE NATURE OF THE INDUCTIVE EFFECT AND THE MECHANISM OF ITS TRANSFER

Although there is still no rigorous mathematical description of the inductive effect, the concept is generally clear and reduces to the classical view that electron density flows from an atom with a lower electronegativity to an atom with a higher electronegativity. Two possible mechanisms for the propagation of this effect are discussed in the literature, both having their pros and cons and their adherents and opponents. Because both of these alternative mechanisms are considered in detail in other reviews in this issue,[1,2] there is no need to delve excessively into this old debate. We only recall that the first mechanism, described long ago by Lewis, suggests that the influence is transmitted along the bonds by their consecutive polarization, i.e. by a mechanism similar to electrostatic induction.[3,4]

An alternative mechanism of the transfer of the inductive effect, proposed for the first time by Ingold,[3] involves the interaction of functional groups through space. This induction mechanism, later called the ‘field effect,’ is purely electrostatic in nature. It has been assumed to occur via electrostatic ion–ion, ion–dipole and dipole–dipole interactions, the intensity of which is described by various functions of the distance r^{-n} ($n = 1$–4).[1,2,4–6]

In recent years, preference has been given to the field mechanism; an increasing number of scientists prefer to consider inductive interactions in terms of the electrostatic concept.[2,4,6] Swain and Lupton[7] even introduced a special scale of field/inductive constants F, which was later developed and enlarged by Hansch *et al.*[6] Our own results concerning the mechanism of inductive effect transfer, based on the inductive effect model which we suggested (see below), are also in good agreement with the field theory, but the mathematical dependences obtained are not simple enough to correspond to any single physical law. We consider the inductive effect as a complicated phenomenon, which reflects correctly the real electron-donating and electron-withdrawing properties of atoms and groups and which must be accepted as it is, without forcing it to pass under the control of any simple and well known physical law.

On the other hand, the transmission of the inductive influence ‘along bonds’ and ‘through space’ should not necessarily be regarded as alternative mechanisms. Whereas the field theory accounts well for the very fact of the Coulomb stabilization of charges arising in a molecule, the nature of their appearance, i.e. the mechanism of the intramolecular redistribution of the electron density, still remains obscure. In any case,

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electron density redistribution can hardly be conceived without the participation of molecular orbitals. In this connection, it seems to be more correct to judge the Coulomb interactions, dependent on direct intramolecular distances, to be only the means of charges stabilization. Of course, this influences also the amount of charge: a smaller distance corresponds to more possible charge. However, the mechanism of stabilization (even if very effective) is still not the mechanism of transmission. On the simplest level, such a situation may be compared with an electric condenser (now we study this analogy more deeply), where a smaller distance between plates also leads to more charge. However, in this case nobody considers that the charge is transferred through space.

QUANTITATIVE METHODS FOR THE EVALUATION OF THE INDUCTIVE EFFECT

The methods that permit a quantitative description of each of the constituents of the overall influence of substituents on the reaction center (inductive, resonance and steric) can be divided conventionally into three main groups. Empirical approaches according to which the influence of a substituent is inferred from data on the reactivities or the physical properties of molecules have found the widest application. The second group of methods is based on quantum-chemical calculations or on the use of fundamental characteristics of atoms, groups or molecules that obey particular empirical relationships. Methods that involve the construction of formal models of the corresponding interactions based, as a rule, on fairly simple physical laws should also be assigned to this group. Finally, a separate group includes topological approaches, which occupy an intermediate position between the methods belonging to the first and second groups.

Empirical methods. Inductive interaction constants

Experimental methods for the evaluation of the influence of substituents are based on the principles of linearity of free energy (LFE) and polylinearity (PL), which make it possible to perform a mathematical formalization of the problem of the relationship between structure and reactivities.[5,8]

Quantitative evaluation of the inductive influence of substituents became possible for the first time within the framework of the approach developed by Hammett, who proposed a well known empirical equation to describe the ionization of substituted benzoic acids:[8]

$$\log(K/K_0) = \rho\sigma$$

For aliphatic compounds, the Hammett relation, as a rule, did not hold. Taft[9] suggested that in this case the steric substituent effects are significant and should be separated. He accomplished this task on the basis of standard reaction series of the alkaline (A) and acid (B) hydrolysis of alkyl carboxylates:

$$\sigma^* = 1/2.48[\log(k/k_0)_\mathrm{B} - \log(k/k_0)_\mathrm{A}]$$
$$\log(k/k_0)_\mathrm{A} = E_\mathrm{S}$$

where σ^* is a substituent constant depending only on its inductive influence and E_S is the substituent constant reflecting its steric influence. The Taft inductive scale is now one of the most reliable and widespread.

Another model, which permits the direct determination of the inductive influence of substituents, was proposed by Roberts and Moreland in 1953.[10] The σ^I (σ_I, σ') constants, which are based on the dissociation of a series of bicyclooctanecarboxylic acids, reflect only the inductive influence of the corresponding substituents.

The σ constants, free from a contribution due to direct polar conjugation, are also used as a measure of the inductive influence of substituents.[11,12]

A large number of inductive constants for hundreds of diverse substituents have been determined; these constants form more than a dozen of the most extensively used scales. As a rule, they correlate well with one another. Thus, we can say with confidence that the empirical inductive constants, based on standard reaction series, properly reflect the electron-donating and electron-withdrawing properties of substituents and can be adequately used in quantitative organic chemistry. A wide series of different inductive constants have been presented, for example, in monographs[13,14] and reviews.[15,16]

It is also noteworthy that the approach developed by Hammett and Taft for the analysis of organic compounds proved applicable to the reactivities of organoelement compounds.[16–18]

Thus, the data accumulated to date make it possible to conclude that empirical inductive constants are fairly versatile, at least in classical organic chemistry, and that they apparently reflect adequately the inductive influence of substituents.

It should be noted that the methods for the determination of the empirical inductive constants are not at all restricted to the approaches based on consideration of quantitative data on reactivities. Innumerable examples of correlations of σ constants with diverse physical properties, which are associated in one way or another with the electron density distribution, have been found.[4,19] Based on these correlations, a large number of extensively used empirical scales of substituent constants have been developed.[15] Characteristics obtained by NMR,[4,6] NQR,[4,20] IR,[4,21] and photoelectron spectroscopy[4] and data on dipole moments and polarizabilities of molecules[4,22] are most frequently used for this purpose. Thus, the inductive and other substituent constants can adequately describe both the reactivities and the physical properties of diverse organic and organoelement compounds.

However, the dependences obtained are not necessarily suitable for the determination of new substituent parameters, although they often provide information on the spatial structures of molecules and on the nature and mechanisms of various intramolecular interactions. In recent years, an increasing number of new, complex substituents have appeared in organic and, especially, in organoelement chemistry. These substituents have not been described and some of them cannot in principle be described quantitatively within the framework of empirical methods. Besides, some substituents can display specific effects when evaluating their empirical inductive constants, conditioned by a concrete procedure. For instance, strong electron-withdrawing groups (such as CCl_3, CN, NO_2 and others), disposed near an electrophilic reaction center, may block the attack of negatively charged nucleophiles owing to electrostatic repulsion, leading to reduction of their effective σ values calculated from this reaction series. Such an 'electrostatic umbrella effect,' noted earlier by Pal'm,[5] is, for example, briefly demonstrated in S_N2 reactions of chloromethylphosphine oxides.[23] Analogously, all other experimental methods which are used for the estimation of σ constants may provide their own specific errors.

Moreover, none of the empirical approaches claims or can claim to be a physical model, capable of revealing the nature and mechanism of the transmission of the inductive influence. In addition, none of the approaches described above possesses a versatile mathematical technique establishing the quantitative relationship between the structure and reactivities of organic and organoelement compounds. Therefore, it is no wonder that interest in the quantitative evaluation of substituent effects based on non-empirical and semi-empirical methods has grown so sharply in recent years.

Non-empirical methods for the evaluation of the inductive effect

Among non-empirical methods for the evaluation of the inductive influence of substituents, the quantum-chemical approach should undoubtedly be considered the most rigorous. The quantum theory permits the calculation of molecular energies and charges on atoms (the electron density distribution). Thus, consideration of the calculated parameters over a reaction series with variation of a substituent, precluding the conjugation effect, provides a direct path to the description of inductive interactions.

The simplest approach involves the separation of the contributions of the inductive and resonance constituents to the variation of the reaction free energies found by quantum-chemical calculations to a good approximation. Another method involves correlation of the σ_I basic set with the quantum-chemical characteristics of the charge distribution in the molecules incorporating the corresponding substituents.[4]

For various mechanisms of transmission of the inductive influence, different quantum-chemical calculation models are chosen. For example, *ab initio* calculations carried out under the assumption that the inductive influence are transmitted 'along bond,' result in uniform attenuation in *n*-alkyl radicals of the electron density variations caused by the substituent.[4,14]

In recent years, the method of 'isolated molecules' has been widely used for the modeling of the field effect.[24] This approach served as the basis for the introduction of a new scale of 'theoretical field' constants of substituents T_F, determined from the charge variation on the β-hydrogen atom in *para*-substituted styrenes.[25]

Among recent work devoted to quantum-chemical calculations of σ constants, that of Exner *et al.*[26] should be mentioned.

However, the extensive use of quantum-chemical calculations in the analysis of substituent effects is hampered by the insufficient level of their development and by a number of other objective factors. In particular, the use of various approximations sometimes leads to results that disagree with one another or are even fundamentally contradictory.[4,24]

Hence it is not surprising that attempts are sometimes made to develop formal non-quantum-chemical models for intramolecular electrostatic interactions.[4,16,27]

It should be noted that all models based on the electrostatic theory suggest that the charges and dipoles are constant, the electron displacements remaining beyond their consideration.

Semi-empirical methods for the evaluation of inductive effects

Methods based on the formal analysis of a structure with the aim of identifying the correlation between the structure and a property (topological methods) have been used in theoretical organic chemistry for a long time. The development of the topological approach is largely associated with the application of the methods of graph theory.[28] The use of graph theory within the framework of the global 'structure–property' problem frequently leads to adequate results. However, the use of topological indices suffers from obvious drawbacks. Not all the characteristic features of molecular structure are taken into account (for example, the conformation is ignored) and, more important, the physical meaning of these indices is obscure. Despite the fact that in some cases the topological indices correlate with electronic parameters (ionization potential, electron affinity, polarizability, chemical shifts in NMR spectra, optical density, etc.),[16,29,30] one cannot speak of the serious application of graph theory to the evaluation of electronic effects of substituents.

Together with the purely topological method for the evaluation of the influence of the structure of molecules on their properties, which does not reflect the distribution and redistribution of the electron density, there are a number of approaches which take into account to a certain extent the mutual arrangement of atoms and groups.

The modeling of interactions based on the structural characteristics and geometric parameters in relation to the inductive effect has been accomplished by various procedures. The best known is the Dewar method, developed for naphthalene derivatives. Several modifications of this method exist. In terms of one of them, the Hammett constant is described by a two-parameter equation:[4,31]

$$\sigma = F_{\mathrm{D}}/r + M_q$$

where F_D is the substituent field (inductive) constant, r is the distance from this substituent to the reaction center expressed in terms of the aromatic carbon–carbon bond lengths, M is the mesomeric constant and q is excess charge. The first term describes the field effect and the second term corresponds to conjugation.

The method of additive determination of inductive constants suggested by Taft, who was the first to introduce the additivity principle for the inductive influence, can be regarded as being ‘conventionally topological’. According to this method, the overall inductive influence of a complex substituent is determined by the inductive effects of fragments incorporated in it.[4,5]

The Dewar approach and the Taft method share the common property that they are based on the analysis of substituent constants themselves, i.e. they can be classified as semi-empirical methods. In addition, both approaches take into account in a certain way the geometry and the electronic structures of molecules. The key feature which distinguishes semi-empirical from empirical methods is that the constants can be calculated theoretically rather than found directly from correlations with the physico-chemical properties or reactivities data.

Thus, neither non-empirical approaches nor the construction of electrostatic interaction models, based on concrete physical laws, currently provide a universal description of the inductive effect; therefore, these approaches cannot compete with empirical methods for the determination of inductive constants. In turn, experimental approaches based on data on the reactivities and physical properties of compounds do not allow one to reveal comprehensively the physical nature of intramolecular interactions and so do not possess sufficient prognostic potential.

The problem of a unified scale of inductive constants

The diversity of approaches to the evaluation of inductive effects in the description of reactivities of organic and organoelement compounds points to a need for the development of a universal scale of inductive constants, which would be suitable for use in any field of organic and organoelement chemistry. Three approaches to the solution of this problem can be suggested: (1) the use of several scales in various fields, according to their maximum efficiency; (2) the search for a universal scale with several parameters; and (3) the calculation of the total energy of the system in each particular case.

The first approach reflects the current situation in chemistry: numerous scales of various constants of substituents are currently in use, their success being as a rule difficult to predict, especially in the chemistry of organoelement compounds. Furthermore, a strategy for choosing a particular scale does not exist, and one can hardly be expected in the near future.

The calculation of the total energy of a system is, of course, the most universal method to account for the inductive effect and also other effects. However, as noted above, the wide use of molecular mechanics and quantum chemistry for the quantitative evaluation of reactivities still seems not to be realizable in the near future.

At present, the second approach, namely, the search for a universal scale having a clear physical meaning, is the optimum method. The interrelations of the existing scales and numerous examples of their use in organic and organoelement chemistry, which indicate the common nature of substituent effects, serve as prerequisites for this approach. The universal scale should be based on structural calculations, since empirical scales depend too much on the particular conditions and on the accuracy of experiments. Finally, the universal character of this scale should be based on extensive experimental verification; in other words, it should describe the maximum possible number of experimental data, a high quality of correlation being maintained.

We have tried to develop such an approach in the framework of an elaborated additive model of the inductive effect.[16,32,33] According to this approach, the inductive effect of a substituent is determined by the sum of the inductive influences of the atoms contained within it:

$$\sigma^* = \sum_{i=1}^{n} (\sigma_{\mathrm{A}})_i / {r_i}^2 \qquad (1)$$

where σ^* is the Taft inductive constant of the substituent, n is the number of atoms in the substituent and r_i is the distance from a particular atom to the reaction center.

The empirical parameter $(\sigma_{\mathrm{A}})_{\mathrm{i}}$, which we introduce here, determines the capability of the ith atom to exert the inductive effect and depends on the chemical nature of the element and on its valence state. The atomic constants σ_A have been calculated for a wide range of elements in various valence states by substituting empirical 'tabulated' σ^* constants in Eqn. (1) and solving it for σ_A.

This additive approach, which is purely semi-empirical, makes it possible to describe with a relatively high degree of accuracy the inductive constants of diverse substituents, i.e. of virtually all substituents for which the σ^* constants are available.

$$\sigma^*_{\text{calc}} = (-0.031 \pm 0.012) + (0.991 \pm 0.006)\sigma^*_{\text{exp}}$$
$$N = 427\ ,\ R = 0.9910\ ,\ S = 0.130$$

Investigation of the physical meaning of elemental σ_A constants, carried out by the method of regression analysis for a broad selection of elements, led to a high-quality correlation with the difference between the electronegativities of a given element and carbon (reaction center) and with the square of the covalent radius (R) of the element in the corresponding valence state:

$$\sigma_A = 7.840\ \Delta\chi R_{\text{cov}}{}^2 \qquad (2)$$

Combination of Eqns (1) and (2) gives the following final expression for a Taft inductive constant:

$$\sigma^* = 7.840\ \Sigma\Delta\chi_i R_i{}^2/r_i{}^2 \qquad (3)$$

where $\Delta\ \chi_i$ is the difference between the electronegativities of the ith atom in the substituent and the reaction center, R_i is the covalent radius of the ith atom and r_i is the distance from this atom to the reaction center.

This equation (and the model as a whole) permits the direct calculation of the Taft inductive constant of any substituent at any reaction center from the fundamental characteristics of atoms, and is in good agreement with both the magnitude and sign of inductive constants. In addition, it allows one to solve some other interesting theoretical questions connected with the problem of the inductive effect (inductive influence of substituents at heteroatomic reaction centers, the problem of the inductive effect of alkyl groups, etc.; see Ref. 16 and references cited there in), which, however, exceed the limits of this short review. We can add only that the model suggested, owing to its accessibility and relatively simple mathematics, could be useful in the everyday practical work of chemists who deal with quantitative organic chemistry and correlation analysis.

The relationships obtained evidently correspond to the field theory of the inductive effect, underlining the importance of Coulomb interactions and direct intramolecular distances. However, such an accordance is actually formal, and can say nothing concerning the real mechanism of inductive influence transmission. It can neither confirm nor deny any of alternative transmission mechanisms ('through space' or 'along bonds'); moreover, both of them alone may be incorrect.[34] To our mind, it would be more worthwhile to imagine a united mechanism of inductive effect transmission as follows. Owing differences in atomic electronegativities (driving force), the redistribution of electron density is occurring along bonds, but only to such a degree that the charges arising can be effectively stabilized (through space) by Coulomb interactions. Such a concerted mechanism seems us to be the most real and acceptable.

CONCLUSION

In conclusion, we must once again return to the fundamental question of what we should understand by the inductive effect' and its measure. As seen above, the inductive effect is a complicated phenomenon, which cannot be fully described by any simple physical law. That is why the numerous attempts to find a direct relationship between the inductive constants and some known physical parameters characterizing in one way or another the ability of an atom to attract electrons, such as electronegativity,[35,36] ionization potential,[35] electron affinity,[35] dipole moment[4,16] and degree of ionic character of the bond,[4,31] were in general unsuccessful. However, one would hardly expect that any one parameter alone would be sufficient to describe the inductive effect quantitatively. Even if this were the case, the dependence obtained would be far from simple. This is demonstrated, in particular, by Eqn. (3). It is not surprising, therefore, that up to now the experimental inductive scales remain the most reliable, and provide firm ground for further theoretical investigations. From this point of view, it would be most correct and efficient to understand by the inductive effect just those electronic interactions which are described by empirical constants, and to try on this basis to make clear its physical meaning.

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