

A REFINED EMPIRICAL MODEL OF THE SIGMA-INDUCTIVE EFFECT

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The classic theory of the sigma-inductive effect fails in the case of more complex polycyclic molecules since it is not possible to define unambiguously the "number of paths" to be introduced into Eq. (2a). Therefore, three more sophisticated procedures were suggested and tested: 1) a model based on the charge distribution according to Smith-Eyring, or, 2) according to Del Re, and 3) a simple generalization of the classic description — Eq. (7). All the models meet some basic requirements, *viz.* they are compatible with the Taft equation and predict transmission of the inductive effect in either direction with the same intensity. If tested on experimental dissociation constants of carboxylic acids in mixed aqueous solvents, the third model appears to be the most satisfactory. The fit is actually better than expected for a purely topological approach, nevertheless it is impaired by solvent effects, in particular when polycyclic and open-chain acids are compared. In addition, the precision would be ultimately restricted if topologically equivalent but sterically different molecules were confronted.

It follows that previous reasoning in favour of the through-space transmission of substituent effects is invalidated by our improved model. On the other hand, our results do not allow to claim the through-bonds transmission as the only process operating.

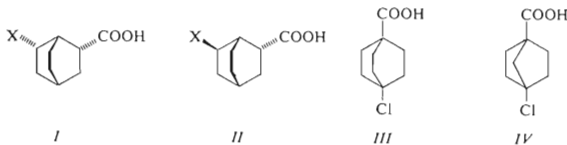
There is a continuous discussion about the nature of substituent effects in saturated molecules¹⁻⁴. According to the electrostatic theory the effect is caused by the difference of coulombic interactions in the initial and final (or transition) state, respectively; it is transmitted directly through space according to the laws of electrostatics (the field effect). The sigma-inductive theory does not make any assumption about the nature of the interaction, it describes only its transmission from the substituent to the reaction site in such a manner that it is weakened by each bond in a constant ratio (the sigma-inductive effect). A classic experimental quantity, still mostly referred to in either theory, is the relative dissociation constant of carboxylic acids. Within the framework of the electrostatic theory it is expressed^{5,6} as a function of the dipole (μ) of a dipolar substituent, its distance (r) from the ionizable proton, the angle of these two vectors (θ) and the effective permittivity ϵ_{ef} :

$$\log(K/K^0) = \frac{e\mu \cos \theta}{2 \cdot 303 k T r^2 \epsilon_{ef}} \quad (1)$$

According to the sigma-inductive theory the relevant quantity⁷⁻⁹ is the number of intervening C—C bonds (n), while the transmission coefficient ϵ and the constants characterizing the substituent (σ_1) and the reaction conditions (ϱ_1^0) are purely empirical quantities:

$$\log (K/K^0) = \varrho_1^0 \sigma_1 \epsilon^n . \quad (2)$$

An experimental decision between the equations (1) and (2) is not possible on the basis of common open-chain acids because their uncertain conformation does not allow to evaluate the geometrical parameters r and θ . In addition, Eq. (2) is more flexible and not able to predict the actual value of the relative dissociation constant in a singular case. Eq. (1) is able to do so only provided the value of ϵ_{eff} can be calculated on the basis of a simplified model⁶. Hence attention was focused to special rigid molecules and to comparison between similar systems for which the prediction of the purely topological sigma-inductive approach may sharply differ from the description in geometrical terms used by the electrostatic theory. For example in the molecules *I* and *II* the number of bonds n is the same but the angles θ differ fundamentally¹⁰.* On the other hand in *III* and *IV* the geometrical factors are very close in spite of the different number of bonds¹¹. Many similar model systems involve multiple bonds and will be disregarded here since the substituent effects may be transmitted by an additional mechanism.



The experimental results obtained on the above models were mostly explained in favour of the electrostatic approach and a conclusion was reached that substituent effects are transmitted through space rather than through bonds¹⁰⁻¹⁷. We have already pointed out^{3,4} that this formulation is not correct. The transmission must take place in space and the question reads whether this inhomogeneous space is described better as a continuum with a uniform permittivity, or, in topological terms, as a system of channels (bonds) irrespective of their direction. There is a still more fundamental problem^{3,4} whether the bond energy of the O—H bond is actually independent of substitution; this is implicitly assumed by Eq. (1) but not by Eq. (2).

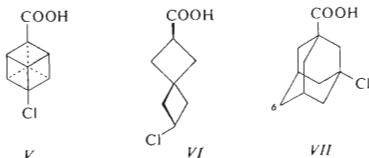
* The substituent X actually used¹⁰ was only OH. In this case the angle θ cannot be precisely defined due to the rotation around the C—O bond⁴.

Hence the antagonism between the two theories persists, regardless of the exact formulation.

The previous reasoning¹⁰⁻¹⁷ in favour of the electrostatic theory has the following serious defect. The latter theory has been developed in a rather sophisticated manner as far as the value of ϵ_{ef} is concerned⁶, in the last resort the latter may be even given several values within different regions of one molecule¹⁸. On the contrary, the alternative topological approach has been tested only in its original oversimplified form. Eq. (2) has been devised for straight aliphatic chains and may be viewed as well documented experimentally within this range¹⁹ (on carboxylic acids or still better on ammonium ions). Rigid molecules involve, however, one or several rings. Therefore, Eq. (2) was extended¹² in a simple way, summing up over all the chains through which the substituent effect can be transmitted:

$$\log(K/K^0) = \varrho_1^0 \sigma_1 \sum \epsilon^n. \quad (2a)$$

For instance in *III* the transmission is accounted for^{9,12} by the factor $3\epsilon^4$ in *IV* by (ref.¹¹) $\epsilon^3 + 2\epsilon^4$. The weakness of this reasoning is evident in the case of more complex molecules, where the number of paths cannot be unambiguously defined. Thus in the system of cubane (*V*) six paths¹⁵, in [3,3]spiroheptane (*VI*) four paths¹⁶ were assumed, so some bonds are used twice. In *I* and *II* the number of paths was four¹⁰, so the unsubstituted branch is used twice in opposite directions. Similarly in 1,3-adamantane derivatives *VII* the bridge in position 6 can be used in either direction or even neglected. In our opinion all conclusions drawn from comparing Eqs (1) and (2) are irrelevant if the latter is in its extended form (2a); such an equation is no more simplified but evidently wrong.



The objective of the present paper is to do justice to the sigma-inductive theory by suggesting a refined treatment of polycyclic molecules. We do not not claim that this theory is superior to the electrostatic approach. On the contrary we have ourselves contributed some pieces of evidence^{3,4} that a treatment of substituent effects in purely topological terms is insufficient and that the angle Θ is significant, although its effect is usually overestimated by Eq. (1). Topological descriptions of molecules

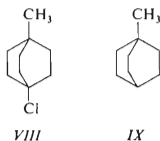
are necessarily restricted in scope but they are being used continuously as a useful approximation in empirical^{20,21} (system DARC) as well as in simple quantum chemical calculations (HMO). Hence our final aim is to locate the limits of this approach if applied to ionization equilibria.

We have used three methods which would be in principle able to predict the propagation of substituent effects through saturated systems: the charge distributions calculated according to Smith–Eyring^{22,23}, or according to Del Re²⁴, and a simple extension of Eq. (2), applicable to cyclic systems.

1) The Smith–Eyring method was devised to predict dipole moments of non-conjugated molecules²². It assumes that each atomic charge induces a dipole in the adjoining bond, this dipole is represented by an additional charge which is added to that originally present. The resulting equation* expresses the charge q_A on the atom A as a function of charges q_B on all this neighbours B_i :

$$q_A = (\sum_i \alpha_{A-B_i} + \sum_i \beta_{B_i(A)} q_{B_i}) / (1 + \sum_i \beta_{A(B_i)}) \quad (3)$$

The calculation of q 's requires to solve a linear system of equations (3) in as many unknowns as is the number of nonequivalent atoms in the molecule. The constants α and β have some physical meaning but were determined partly empirically^{22,23}. In order to characterize the transmission ability of a given system, we chose a model compound with a terminal methyl group and a halogen atom (say Cl) as the standard substituent. For instance the transmission in bicyclo[2,2,2]octane from the position 1 to 4 is represented by the charge on the methyl carbon in VIII.



2) The Del Re method²⁴ is based on the MO-LCAO principle but is also largely empirical in character. The calculation of atomic charges is similar as above, but proceeds in two steps. In the first one the parameter δ_X , representing the coulomb integral of the atom X, is defined by an equation* formally analogous to (3):

$$\delta_A = \delta_A^0 + \sum_i \gamma_{A(B_i)} \delta_{B_i} \quad (4)$$

* We have modified slightly the symbols originally used²²⁻²⁴ in order to stress the similarity of the two theories and to avoid confusion if the same letter would be used with different meaning.

In the next step the atomic charges q are calculated from δ 's using a similar equation, *i.e.* the procedure taking into account all neighbouring atoms is repeated once more;

$$q_A = -\frac{1}{2}\delta_A \sum_i \varphi_{ABi} + \frac{1}{2} \sum_i \delta_{Bi} \varphi_{ABi} . \quad (5)$$

The constants γ , δ^0 and φ (the reciprocal value of the exchange integral) are again essentially empirical or only estimated. For our purposes the theory was exploited in a similar way as the preceding one, but an allowance was necessary for the charge distribution in the unsubstituted compound. It means that the transmission in bicyclo[2,2,2]-octane is represented by the difference of charges on methyl carbon atoms in *VIII* and *IX*, respectively. (In the Smith-Eyring method this allowance is not necessary since the latter value is zero with a proper choice of parameters.)

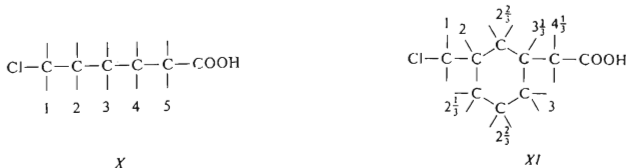
3) A simple and logical extension of Eq. (2) for cyclic systems is possible as follows: Let us assume that the substituent effect on the n -th atom of a straight-chain molecule is expressed by the value ϵ^n . Then the value of n for any non-terminal atom is connected with those of the neighbouring atoms by a trivial relation (the arithmetic mean).

$$n_i = \frac{1}{2}(n_{i-1} + n_{i+1}) . \quad (6)$$

This principle can be applied to an arbitrary atom in a branched and/or cyclic system, if the summation is extended over all neighbouring atoms:

$$n_A = \frac{1}{s} \sum_i^s n_i . \quad (7)$$

This equation resembles partly Eqs (3) and (4) but does not hold for terminal atoms to which the substituent and the functional group are attached. Hence there are two equations less than unknowns but an unambiguous solution may be achieved as follows: In a straight chain (*X*) the first two atoms are given values $n = 1$ and 2, respectively, according to Eq. (2). In a cyclic system the symbolic charges are obtained if a short side-chain is attached as in *XI* and the first two values of n are retained as



in a straight chain; the remaining ones are calculated from Eq. (7). The only empirical parameter in this approach is thus the transmission coefficient ε like in Eq. (2), provided that only relative values are required. Let us stress that the values of n in Eqs (6) and (7) do not mean any atomic charges. They serve only to express the transmission of the sigma-inductive effect from one position to another; the effect is given by the value ε^n on the terminal atom.

The three above theories were compared on selected straight-chain and cyclic molecules, mostly on those for which experimental dissociation constants are available^{4,11-16}. As only relative values can be compared, all results were related to the 1,4-derivatives of bicyclo[2,2,2]octane as a standard which had been experimentally investigated most thoroughly.

CALCULATIONS

The Smith-Eyring method, applied to chloro derivatives of alkanes or cycloalkanes, requires to solve a set of equations (3) for all atoms C, H, and Cl. Seven empirical parameters would be needed: $\beta_{C(C)}$, $\beta_{C(H)}$, $\beta_{H(C)}$, $\beta_{Cl(C)}$, $\beta_{C(Cl)}$, α_{H-C} , α_{Cl-C} , whereas α_{C-C} is zero by definition for a symmetrical bond. The problem may be simplified since the equations for Cl and H atoms contain only two unknowns, *e.g.* q_{Cl} and q_C of the C atom to which is Cl attached. Hence all the unknowns q_H and q_{Cl} can be eliminated and the set of equation is reduced to as many as is the number of different carbon atoms. Simultaneously the number of parameters is reduced to five; instead of $\beta_{C(C)}$, $\beta_{C(H)}$, and α_{Cl-C} only their functions $\vartheta_{Cl-C} = \beta_{C(Cl)}/(1 + \beta_{C(C)})$ and $\eta_{Cl-C} = \alpha_{Cl-C}/(1 + \beta_{C(H)})$ are needed, similarly for H. The equation for a particular carbon atom has the form:

$$q_C = (-m\eta_{Cl-C} - n\eta_{H-C} + \beta_{C(C)} \sum_i q_{C_i}) / [1 + m\vartheta_{Cl-C} + n\vartheta_{H-C} + (4 - m - n)\beta_{C(C)}],$$

where m and n are the numbers of Cl and H atoms on the respective C, and the summation involves all adjacent carbon atoms. We used the original values^{22,23}: $\vartheta_{H-C} = 0.13$, $\vartheta_{Cl-C} = 0.71$, $\eta_{H-C} = 0$, $\eta_{Cl-C} = -1.49$, and an empirically corrected²⁵ value $\beta_{C(C)} = 0.43$. In addition all calculations were repeated with an ad hoc value $\beta_{C(C)} = 1.12$ (see Discussion). Some calculations were also carried out with other halogens ($\vartheta_{Br-C} = 0.91$, $\eta_{Br-C} = -1.44$, $\vartheta_{I-C} = 1.29$, $\eta_{I-C} = -1.42$) and further with a charged CH_2^- group instead of the terminal methyl group. The procedure was programmed specially for the given simple case, *viz.* for the molecule with one halogen atom in the position 1. The only input is then the incidence matrix, *i.e.* its non-zero elements; in the output one obtains the atomic charges. In the case of symmetrical molecules the number of carbon atoms is reduced, *e.g.* in VIII to five. There is only a condition that adjoining atoms, even topologically equivalent, must not be labelled equally; for example the symmetry of chlorocyclopentane cannot be exploited and the C atoms must be labelled from 1 to 5.

The Del Re calculations for the same set of chloro derivatives require eleven parameters: $\delta_C^0 = 0.07$, $\delta_H^0 = 0$, $\delta_{Cl}^0 = 0.35$, $\gamma_{C(C)} = 0.1$, $\gamma_{C(H)} = 0.3$, $\gamma_{H(C)} = 0.4$, $\gamma_{C(Cl)} = 0.2$, $\gamma_{Cl(C)} = 0.4$, $\varphi_{CC} = 1$, $\varphi_{CH} = 1$, $\varphi_{CCl} = 1/0.6$. These were adopted from the original source²⁴, only φ_{CCl}

is corrected²⁶. Actually the number of independent parameters is only nine since the same simplification would be possible as in the Smith-Eyring method concerning the constants for hydrogen and chlorine. Additional calculations were made for substituents F ($\delta_F^0 = 0.57$, $\gamma_{C(F)} = 0.1$, $\gamma_{F(C)} = 0.1$, $\rho_{CF} = 1/0.85$) and $N(CH_3)_3$ ($\delta_N^0 = 0.24$, $\gamma_{C(N)} \approx 0.1$, $\gamma_{N(C)} = 0.1$, $\rho_{CN} = 1$). A universal computer program was devised usable for all molecules consisting of atoms for which the parameters are available. In the input the kind of atoms must be given in addition to the incidence matrix, in the output the atomic charges and the total energy are obtained. The same precaution is necessary concerning the symmetrical molecules as above.

The calculations according to Eq. (7) involve as many equations as is the number of different C atoms minus two. The set can be easily solved successively beginning on the side of the halogen atom as in the formula VIII, or, only one unknown is necessary as for XI. The values of n were converted to ε^n using the value of the transmission coefficient⁸, $\varepsilon = 0.36$.

In Table I are collected only the relative substituent effects which correspond to charge differences on the terminal carbon atom raised by substituents. The charges themselves as well as the charges on the remaining atoms are not tabulated.

RESULTS AND DISCUSSION

We have defined a model of the sigma-inductive effect referring to the charge produced by a standard substituent in a given position. In two of the procedures employed, those of Smith-Eyring and Del Re a particular substituent (chlorine) must be arbitrarily chosen. The first point in question arises: inasmuch the results can be affected by this choice. Within the framework of correlation analysis one would expect the proportionality between substituent effects for almost all molecules of Table I. This is expressed by the Taft equation⁸

$$\log(K/K^0) = \rho_1 \sigma_1, \quad (8)$$

which — in contradistinction to Eq. (2) — does not describe the propagation along the chain and treats ρ_1 as mere constant characteristic for a given system. The validity of Eq. (8) was verified²⁷ for most of the rigid molecules of Table I, mainly on the basis of dissociation constants; it holds, however, only approximately (standard deviation about 0.04 pK units). Hence, our question reads whether the Smith-Eyring and Del Re procedures are compatible with Eq. (8) within the usual accuracy of similar empirical correlations. We compared the Smith-Eyring calculations with substituents Cl, Br, and I and obtained virtually the same relative figures. It is true that a monoatomic substituent is characterized by two constants ρ_{X-C} and η_{X-C} , the charge on the terminal atom is thus function of two independent variables and cannot be proportional for all substituents. The respective functions are very similar for some systems but not for all. For example the charge on $C_{(2)}$ of 1-halogenoethane is equal to $-0.2363\eta_{X-C} (1.5884 + \rho_{X-C})$, on $C_{(3)}$ of 1-halogenopropane to $-0.0503\eta_{X-C} (1.5984 + \rho_{X-C})$ which is virtually proportional; on $C_{(9)}$ of VIII the charge is, however, $-0.00558\eta_{X-C} (2.0158 + \rho_{X-C})$ and the proportionality is only roughly ful-

TABLE I
Transmission of the Inductive Effect of Substituents through Saturated Systems











System	Calculated relative values ^a				Experi- mental ^{a,b} ρ_1 \pm s.d.
	S.-E. (0.43) ^c S.-E. (1.12) ^c	Del Re	Eq. (7) ($\epsilon = 0.36$)	Eq. (2a) ($\epsilon = 0.36$)	
1 	1 1	1	1 ϵ^2	1 $3\epsilon^4$	1
2 	0.793 0.928	0.859	0.600 $\epsilon^{2.5}$	0.667 $2\epsilon^4$	0.76 ^d ± 0.08
3 	1.672 1.406	1.543	1.190 $\epsilon^{1.83}$	2.000 $6\epsilon^4$	0.92 ± 0.06
4 	2.239 1.592	3.171	1.154 $\epsilon^{1.86}$	1.592 $\epsilon^3 + 2\epsilon^4$	1.17 ± 0.04
5 	1.859 1.305	2.950	0.893 $\epsilon^{2.11}$	1.166 $\epsilon^3 + 2\epsilon^5$	0.89 ^e ± 0.04
6 	1.705 1.135	2.600	1.000 ϵ^2	1.166 $\epsilon^3 + 2\epsilon^5 + 2\epsilon^7$	0.94 ± 0.10
7 	1.951 1.452	3.284	0.711 $\epsilon^{2.33}$	1.046 $\epsilon^3 + \epsilon^5$	^f
8 	2.266 1.751	3.666	0.815 $\epsilon^{2.2}$	1.259 $\epsilon^3 + \epsilon^4$	—
9 	3.738 2.583	6.401	1.000 ϵ^2	1.852 $2\epsilon^3$	—
10 	0.275 0.472	0.184	0.360 ϵ^3	0.480 (0.240) $4\epsilon^5 (2\epsilon^5)$	0.47 ± 0.05

TABLE I
(Continued)




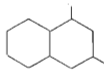


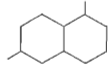
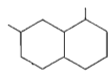
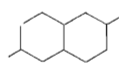
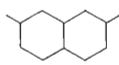
System	Calculated relative values ^a				Experimental ^{a,b} ρ_1 \pm s.d.
	S.-E. (0.43) ^c S.-E. (1.12) ^c	Del Re	Eq (7) ($\epsilon = 0.36$)	Eq. (2a) ($c = 0.36$)	
11 	0.731 0.788	0.671	0.775 $\epsilon^{2.25}$	0.764 $2\epsilon^4 + 2\epsilon^6 + 2\epsilon^8$	0.51 ^g
12 	8.17 3.082	21.21	1.291 $\epsilon^{1.75}$	2.670 $\epsilon^2 + 2\epsilon^6 + 2\epsilon^8$	1.10 ^h ± 0.10
13 	8.18 3.108	21.25	1.255 $\epsilon^{1.78}$	2.658 $\epsilon^2 + 2\epsilon^6$	1.26 ^j (± 0.06)
14 	1.931 1.369	3.249	0.725 $\epsilon^{2.31}$	1.048 $\epsilon^3 + \epsilon^5 + \epsilon^9$	—
15 	0.718 0.767	0.780	0.627 $\epsilon^{2.46}$	0.672 $2\epsilon^4 + \epsilon^8$	—
16 	0.354 0.415	0.334	0.417 $\epsilon^{2.86}$	0.420 $\epsilon^4 + 2\epsilon^6 + \epsilon^{10}$	—
17 	0.148 0.270	0.108	0.320 $\epsilon^{3.11}$	0.258 $2\epsilon^5 + \epsilon^7 + \epsilon^9$	—
18 	0.374 0.429	0.356	0.350 $\epsilon^{3.03}$	0.388 $\epsilon^4 + \epsilon^6 + 2\epsilon^8$	—
19 	0.046 0.144	0.050	0.232 $\epsilon^{3.43}$	0.135 $3\epsilon^6 + \epsilon^8$	—
20 	0.085 0.183	0.085	0.239 $\epsilon^{3.4}$	0.167 $\epsilon^5 + 3\epsilon^7$	—

TABLE I
(Continued)

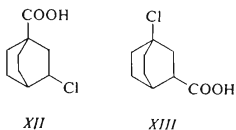
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	S.-E. (0.43) ^c	Del Re	Eq. (7)	Eq. (2a)	
	S.-E. (1.12) ^c		($\epsilon = 0.36$)	($\epsilon = 0.36$)	
21 $-\text{CH}_2-$	50.22 14.60	236.5	2.778 ϵ	7.145 ϵ	2.90 ^k , 4.62 ^l ± 0.10
22 $-(\text{CH}_2)_2-$	10.65 5.284	31.72	1.000 ϵ^2	2.572 ϵ^2	1.79 ^l ± 0.16
23 $-(\text{CH}_2)_3-$	2.259 1.912	4.249	0.360 ϵ^3	0.926 ϵ^3	0.51 ^{l,m} (± 0.05)
24 $-(\text{CH}_2)_4-$	0.479 0.692	0.547	0.130 ϵ^4	0.333 ϵ^4	0.30 ^{l,m} (± 0.05)
25 $-(\text{CH}_2)_5-$	0.102 0.250	0.063	0.047 ϵ^5	0.120 ϵ^5	—

^a All the relative values are related to the 1,4-bicyclo[2,2,2]octane system as reference; ^b ρ_1 constants determined in mixed aqueous solvents or in water, ref.²⁷; ^c the Smith-Eyring calculations with the common value²³ of $\beta_{\text{C(C)}} = 0.43$ or with the modified value of 1.12, respectively; ^d *trans* configuration; ^e ref.⁴; ^f the value in ref.²⁷ is quite untrustworthy as it is based only on little polar substituents; ^g based on substituents Cl_2 and Br_2 (ref.²⁸), for mono substitution *cis*-Cl and *cis*-Br a value of 0.33 is obtained; ^h ref.²⁹; ^j based on a single substituent⁴, CN; ^k in 50% ethanol²⁷; ^l in water²⁷; ^m these values are based only on a single substituent, Br, pK' s in water ref.³⁰.

filled. Within the framework of Del Re method we compared the substituents F, Cl, and $\text{N}^+(\text{CH}_3)_3$ on all systems of Table I and obtained exact proportionality; for a broader sets of substituents and more sensitive systems the proportionality was no more exact but still very good³¹. We conclude that Taft equation conforms with the Smith-Eyring and Del Re calculations within a reasonable accuracy, similarly as Hammett equation conforms with the HMO treatment³²; quite generally the linear free energy relationships are much better compatible³³ with the topological approach than with the electrostatic theory. Note also that Taft equation has been little tested experimentally on different alicyclic systems, merely on different reactions within the aliphatic series. Further discussion will be based on calculated effects of the substituent Cl and it will be assumed to have a more general validity. In calculations according to Eq. (7) this general validity is inherent.

Another fundamental property of all the mathematical models used is their symmetry with respect to the substituent and the reaction centre. It means that equal substituent effects are predicted *e.g.* for the molecules *XII* and *XIII*. For this reason

we included similar unsymmetrical systems only once into Table I (lines 5, 11–14 17, 18). In the case of Eq. (7) this symmetry is inherent, in the case of Smith–Eyring and Del Re calculations it has been proven empirically on several examples. As far as we know the equal intensity of the inductive effect in either direction was always assumed as self-evident and never intentionally examined by experiment; some data are available on naphthalene derivatives³⁴ where the inductive and mesomeric effects are combined.



The next point in which the theoretical results are to be compared with experiment concerns the propagation of the inductive effect along an aliphatic chain. According to the definition of our model, we are not interested in the charge distribution within one aliphatic molecule (compare ref.³⁵) but in comparison of the end-standing methyl groups of several molecules with an increasing chain. Fig. 1 reveals an essential analogy of all calculated results, at least as regards the relative values. The charges according to Smith–Eyring decrease regularly, the ratio of two subsequent values being almost constant in agreement with the classic theory, Eq. (2), or with Eq. (7). This is why the parametrisation with the value²³ $\eta_{H-C} = 0$ was chosen. While $\eta_{H-C} = 0.418$ might be more realistic with respect to the actual dipole of the C—H bond, it results in a less regular charge distribution not related so simply to substituent effects. With $\eta_{H-C} = 0$ the agreement with Eq. (2) is qualitative in character, but the calculated transmission factor, $\epsilon = 0.21$, is too low. Since the experimental value, approximately $\epsilon = 0.36$, seems to be well documented⁸, we tried to improve the calculations by readjusting the parameter $\beta_{C(C)}$. This parameter is even so purely empirical in character since the original value²² of 0.718 was later replaced²⁵ by 0.43 in order to match the experimental dipole moments. When we use an *ad hoc* value of 1.12, the agreement with Eq. (2) is almost perfect (Fig. 1). The atomic charges according to Del Re yield a similar picture: they accord qualitatively with Eq. (2) but the transmission factor is calculated still lower, about 0.13. In this case, we have not tried to improve the fit empirically since there are more independent parameters involved in the calculations. Hence the results of this approach will have merely a qualitative significance, mainly for comparison of systems of the same length. The third approach, our Eq. (7), is of course identical with the experimentally supported Eq. (2) as far as straight-chain compounds are concerned. Summarizing, the three methods describe the attenuation of the inductive effect along a saturated

chain in rather similar terms; for the Smith-Eyring method and our Eq. (7) a quantitative agreement can be reached by readjusting a single parameter.

Most important is now the test on cyclic and polycyclic compounds since — as stated already at the beginning — the original simplified theory⁷⁻⁹, Eq. (2a), is particularly unsatisfactory for such compounds. From this point of view it is very instructive to compare several systems with the same length, of the transmitting chains but with their unequal number, see Fig. 2, corresponding to the lines 1, 2, 3, and 24 of Table I. Even in this case all the theories yield a similar picture, mostly they overestimate the significance of the number of paths, see in particular the cubane derivatives. This overestimating is, however, by far the worst in the case of the original "primitive" approach⁷⁻⁹, Eq. (2a). Note that the example of Fig. 2 is particularly

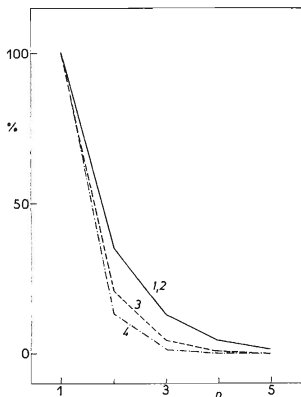


FIG. 1

Propagation of the Inductive Effect Along an Aliphatic Chain According to Various Theories

The values for the chains $-(CH_2)_n-$ are related to CH_2 (100%); 1 a constant transmission factor $\epsilon = 0.36$, Eq. (2) or Eq. (7), 2 Smith-Eyring charge distribution with $\beta_{C(C)} = 1.12$ (indiscernible from 1); 3 the same with $\beta_{C(C)} = 0.43$, 4 Del Re charge distribution.

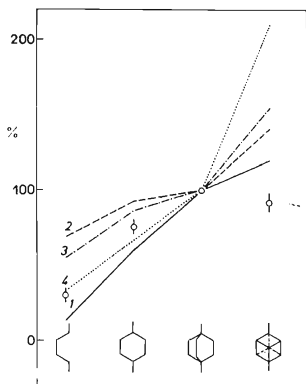


FIG. 2

Propagation of the Inductive Effect in Cyclic Systems with Different Number of Paths

Relative values with respect to the bicyclo[2,2,2]octane system are plotted according to the theories: 1 Eq. (7) with $\epsilon = 0.36$, 2 Smith-Eyring with $\beta_{C(C)} = 1.12$, 3 Del Re, 4 primitive counting of the number of paths, Eq. (2a), \circ experiment.

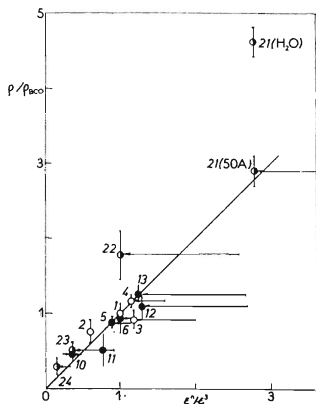
suitable since the substituent is equally oriented in three of the compounds and its position is not fixed in the fourth. Hence there is no controversy with the electrostatic theory, see angle Θ in Eq. (1). This reasoning does not apply to the second example, given by the lines 4, 5, and 6 of Table I; here the angle Θ is appreciable in two compounds and part of the observed disagreement may be attributed to its neglecting. Even so it is evident that mechanical counting of the number of paths leads to overestimating the substituent effect in line 4.

We conclude that all three models under examination are superior to the simple treatment, Eq. (2a), when different cyclic systems are to be compared. However, it is only the last model, Eq. (7), which is able to describe reasonably well both the attenuation along a saturated chain (Fig. 1) and the behaviour of cyclic systems (Fig. 2). Hence it can be confronted with experiment in the whole extent. Fig. 3 reveals a good agreement, in particular the improvement against the previous theory, Eq. (2a), is striking. (This improvement is shown by arrows in Fig. 3.) Remarkably enough, the compounds 5, 6, 10–13 with angularly oriented substituents do not deviate in a significantly manner, giving thus no support to the electrostatic theory, *i.e.* to the importance of the angle Θ in Eq. (1). Note further appreciable experimental errors of some ρ_1 constants, which were determined in different solvents²⁷. Of course, they relate always to the reference system of 1,4-substituted bicyclo[2,2,2]octane in the same solvent, but sometimes they are average values. The solvent effects which cannot be accounted for in topological terms seem also to be responsible for the most conspicuous deviations in Fig. 3: the four aliphatic acids (21–24)

FIG. 3

Topological Estimation of the Inductive Effect According to Eq. (7)

Relative experimental reaction constants ρ_1 are plotted against the relative calculated ones ($\epsilon = 0.36$); \circ rigid molecules with an axially symmetrical position of the substituent, \bullet flexible molecules, \bullet rigid molecules with an unsymmetrical position of the substituent; the numbers refer to Table I; error limits $\pm 2\sigma$; the arrows show the improvement against the primitive treatment, Eq. (2a).



investigated in water deviate on the same side while 21 in 50% ethanol lies on the line. The striking disagreement between the two points for the substituted acetic acids (21) is not due to their different ρ_1 constants but essentially to different ρ_1 constants of the reference system. The fundamentally dissimilar sensitivity to solvent effects in the case of substituted acetic and bicyclo[2,2,2]-octanecarboxylic acids was already noted⁹. It is understandable within the framework of the electrostatic theory if the effective dielectric constant in Eq. (1) is calculated using a cavity model⁶ with a constant depth of the acidic proton under the cavity surface³⁶. Then a smaller molecule is relatively better isolated from the surrounding solvent. Final decision of this problem must be probably postponed until the gas phase acidities are available. A similar plot as Fig. 3, based on the Smith-Eyring theory, is less satisfactory. The difference between cyclic and straight-chain is still more expressed and even the former group itself would be correlated poorly; it is just the reference system which deviates appreciably (Fig. 4). A plot based on the Del Re calculations would be still worse in this respect since in addition a too strong attenuation of the inductive effect is predicted. As mentioned, Eq. (7) is clearly the best possibility when widely different molecules are to be correlated.

With the results obtained we are now able to reexamine some claims of the literature in which a disagreement with Eq. (2a) was believed to disprove the sigma-inductive effect and to arbitrate in favour of the field effect. A comparison of lines 4 and 1 of Table I yields the experimental ratio of 1.17 ± 0.04 , the values in the original literature¹¹ are 1.175, 1.183 and 1.195 in three solvents. Electrostatic calculations¹¹ according to the Eq. (1) and with a special adjustment of ϵ_{ef} resulted in the ratio

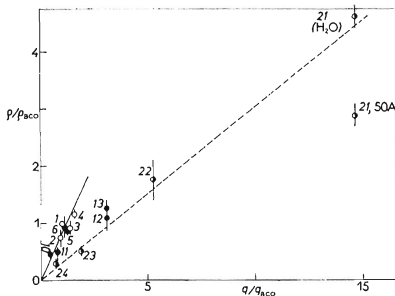


Fig. 4

Topological Estimation of the Inductive Effect According to the Smith-Eyring Charge Distribution
The same symbols are used as in Fig. 3; $\beta_{C(C)} = 1.12$.

of 1.20, while Eq. (2a) gives 1.59. The latter value is, however, improved to 1.154 by using Eq. (7) and no decision between the two theories is thus possible. The experimental ratio of the lines 10 and 1, 0.47 ± 0.05 , was in agreement with the predictions of Eq. (1) and (2a) as well¹⁶ (0.52 and 0.48, respectively). However, the latter value originates in the unacceptable assumption that there are four paths of transmission in VI, with Eq. (7) it is changed to 0.36 and the data are still unable to decide between the two theories. The comparison³⁷ of lines 6 and 21 is particularly unfit since the two systems are too different. The experimental ratio of 0.32 disagrees with the value of 0.16 calculated from Eq. (2a). (Ref.³⁷ gives erroneously 0.058 since the substituent in acetic acids included the CH_2 group.) Eq. (7) improves the fit in a deciding manner (0.36). The relation of the lines 3 and 1 was discussed only in qualitative terms¹⁵ in favour of the electrostatic theory: the similar size of the two molecules is compatible with the experimental ratio near to unity (0.92 ± 0.06). However, the calculation¹⁵ of the number of paths in V is rather naive taking each bond twice; Eq. (7) again represents a great improvement (1.19). In a previous paper³ we offered the opinion that the difference in $\text{pK}'\text{s}$ of isomeric indanone-4(6)-carboxylic acids reflects the significance of the angle Θ , although it is not so big as anticipated by Eq. (1). By applying Eq. (7), even this reasoning might be weakened since the calculated ratio of the inductive effect (1.23 : 1) agrees approximately with the experiment. However, the whole model system is not quite conclusive due to the presence of an aromatic ring.

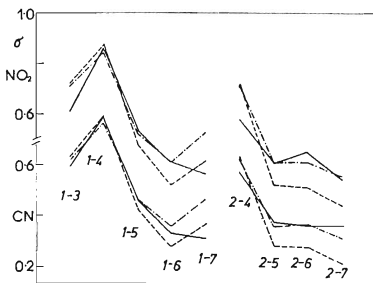
None of the foregoing cases thus yields an actual argument against the sigma-inductive theory. Our last example concerns the well known $F-M$ approach of Dewar and Grisdale³⁸ which describes the substituent effect in an aromatic system as consisting of the field and mesomeric components:

$$\log(K/K^0) = \rho(F/r + Mq). \quad (9)$$

FIG. 5

The $F-M$ Theory Applied to Nitro and Cyano Substituted Naphthalenecarboxylic Acids

Full lines experimental; dash-and-dot lines calculated according to the $F-M$ theory, Eq. (9); broken lines calculated according to a modification based on the sigma-inductive effect, Eq. (10).



If the substituent constants F and M are once determinated on the basis of benzene *meta* and *para* derivatives, Eq. (9) is able to predict the effect *e.g.* for the individual positions on the naphthalene nucleus. This needs only the distance r and the easily determinable constant q (Table II), characterizing the mesomeric interaction between the two respective positions³⁸. Fig. 5 reveals that the agreement with the experimental dissociation constants^{34,38} is not bad for nitro and cyano substituted naphthalene-carboxylic acids. (The F and M values of the CN group were recalculated from more recent σ values — Table II.) This is, however, no proof of the field-effect mechanism since a similar fit is obtained when replacing $1/r$ in Eq. (9) by a sigma-inductive parameter i (Table II) obtained from Eq. (7):

$$\log(K/K^0) = \varrho(F_1 i + M_1 q). \quad (10)$$

For this purpose we calculated first the modified constants F_1 and M_1 from benzene *meta* and *para* derivatives in the same way as in the original theory³⁸ replacing $1/r$ by the i values. Then we applied these constants to naphthalene derivatives according to Eq. (10) using i and q for the respective positions (Table II). According to Fig. 5 the fit is but slightly worse than in the original theory. Hence the Dewar-

TABLE II
Parameters of the Dewar-Grisdale Theory for Naphthalene Derivatives

Position	r^a	q^b	i^c	Experimental ^d $\log(K/K^0)/\varrho$	
				NO ₂	CN
1—3	$\sqrt{3}$	0	0.725	0.611	0.591
1—4	2	1/5	0.627	0.861	0.788
1—5	$\sqrt{7}$	1/20	0.417	0.539	0.460
1—6	3	0	0.320	0.407	0.329
1—7	$\sqrt{7}$	1/20	0.350	0.361	0.309
2—4	$\sqrt{3}$	0	0.725	0.585	0.572
2—5	3	0	0.320	0.407	0.375
2—6	$\sqrt{13}$	1/17	0.232	0.453	0.361
2—7	$\sqrt{12}$	0	0.239	0.342	0.361
Benzene 1—3	$\sqrt{3}$	0	0.711	0.710	0.620
Benzene 1—4	2	1/7	0.600	0.780	0.700

^a Defined³⁸ as the distance of the respective C atoms of the naphthalene nucleus, in C—C bond units; ^b the formal charge³⁸ at one of the indicated positions, produced by a CH₂⁺ group attached at the second position; ^c inductive parameter based on Eq. (7) and replacing $1/r$; ^d from dissociation constants^{34,38} of carboxylic acids in 50% (vol) ethanol.

-Gridale treatment is a purely empirical procedure without any clear physical meaning; its main shortcoming is in violating electrostatic laws when the distance is defined (Table II) and the function $1/r$ used instead of $1/r^2$. The first term of Eq. (9) does not mean actually the field effect and is not transferable to aliphatic or aryl-aliphatic compounds; its important part probably originates in the pi-inductive effect which might be related to the length of the aromatic system, *i.e.* r in Eq. (9). Similarly the second term does not match the mesomeric effect since it is zero for the *meta* position of benzene.

We conclude that a slight modification of the classic sigma-inductive theory, Eq. (7), is able to describe the experimental substituent effects in purely topological terms and with a better accuracy than anticipated. In particular, this improvement is able to invalidate the reasoning in which failure of the original oversimplified approach, Eq. (2a), was quoted in favour of the electrostatic theory. Nevertheless, it is not our intention to claim the contrary, *i.e.* to apologize the sigma-inductive theory as a fully satisfactory description. Any topological approach is limited in scope and must be necessarily insufficient when applied to stereoisomers or to rigid molecules with unusual orientation of substituents. Several such molecules were described which prove that the effect of the substituent depends on its orientation in space: the acids¹⁰ *I* and *II*, and esters of analogous epoxy acids³⁹, isomeric *para*-cyclophanecarboxylic acids¹⁷, and stereoisomeric dichlorodibenzobicyclo[2,2,2]octadiene carboxylic acids⁴⁰. Another limitation is connected with solvent effects which can be included into Eq. (2) only through the constant q_i^0 , hence they must be considered constant within a given reaction. In our opinion, the classic dilemma between the through-space and through-bonds transmission cannot be solved in these terms, a more important task would be to estimate the relative substituent effects on the O—H bond energy on the one hand, and on the energy of proton transfer, on the other.

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