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Reactivity indices: Remarks on present state and prospects

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Summary. After arguing that reactivity indices are still a very important tool of molecular design, the general perturbation treatment of reactivity indices, originally due to Coulson and to Fukui, is revisited on the basis of its most general (but little familiar) form, when all electrons are taken into account, and the AO basis is nonorthogonal. The difficulties in the physical interpretation of the generalized "perturbabilities" are discussed. An example of how a new reactivity index can be derived starting with a supermolecule model in the reduced coupling approximation is proposed not so much with the intent to add one more individual to the bestiary of those indices as to give a concrete illustration of the path to be followed to get an index of actual significance and sufficiently general scope. A number of comments on the situation and prospects of work in the field are proposed.

Key words: Reactivity indices – Molecular design – Perturbabilities

1 Molecular design and reactivity indices

Reactivity indices are a typical product of "chemical thinking", as incorporated in Ingold's "theoretical chemistry". The notion that molecular structure is responsible for all the properties of a molecule, including characteristic conformations and ease of reaction by a given mechanism (nucleophilic, electrophilic, radicalic) is essential to organic chemistry [1] and is one of the basic axioms in the "axiomatic construction of chemistry", as pointed out by L. Paoloni [2].

The indices in question should be quantities which express quantitatively the way in which the various features of the structure determine the reactive tendency or "reactivity" of a molecule. Since, as is well known, the sensitivity to a given reagent or class of reagents may be different for the various atoms or bonds of a molecule, the reactivity indices are expected to be molecule-, bond- and site-specific. In certain cases it may be interesting to distinguish between different directions of approach of a reagent, and this might require that the proper reactivity index be a directional quantity (vector).

Some theoreticians seem to consider reactivity indices as subsidiary concepts bound to become obsolete as soon as computer programmes are available that will make it possible to predict the outcome of any given reaction. An extreme point of view is the rejection of reactivity indices, as being concepts belonging to the "plague of non-observables" [3]. This view neglects the requirements of chemists engaged in molecular design and synthesis. They often have to design molecules that have specific properties, e.g. a region which has a given structure, to be preserved while another region undergoes a substitution reaction leading to some important intermediate. There are empirical rules and recipes for procedures of this kind, such as protecting a hydroxyl group by etherification: but in the case of highly sophisticated compounds the modifications induced in the rest of the molecule by those minor structural changes may be such that the various requirements become difficult to reconcile unless general rules serve as guidelines. To meet this need, theoretical chemistry should provide simple quantities to be used as thinking aids in designing large molecules (cf. e.g. [4, 5]). Therefore, work devoted to improving and formalizing reactivity indices is still actual and necessary.

The difficulties yet to be overcome in this connection already emerge when one tries to generalize to all MO methods the fundamental work of Coulson and Longuet-Higgins (CLH), which goes back to the years immediately after the second world war [6, 7]. As is well known, those authors worked within the frame of the Hückel method, reaching such conclusions as the identification of net atomic charges with the derivatives of the total binding energy of a molecule with respect to the pertinent atomic parameters, which we shall call "atomic perturbabilities". Their conclusions are now tacitly assumed in all population analyses; yet, a detailed critical discussion, as far as we have been able to ascertain, has not been carried out, especially as regards σ systems.

We propose here a contribution to that critical discussion by (a) recasting the CLH's argument concerning atomic charges into a more general form and (b) providing (as a hint for the future) a new type of atomic reactivity index based on a supermolecule model for the incipient stage of reactions. This work is in line with work by Fukui [8] and with the analysis by Koutecky et al., based on the Green matrix formalism ([9]; cf. also [10]), although those fundamental papers cover a variety of reactivity indices rather than just atomic "perturbabilities". It probably overlaps to some extent with results published especially in the course of discussions of computational results. Unfortunately, it is almost impossible to detect and analyze all such results, and we confine ourselves to a few recent references [11–14], without any pretence to completeness.

2 General expression of perturbabilities in the MO–LCAO scheme

The Hückel method has the great quality of translating into a simple mathematical formalism the essence of chemistry – molecular structure – at least as far as π bonds are concerned. Atoms are represented by the appropriate atomic parameters α, bonds by the bond parameters β. Molecular energy is but the sum of the energies of the occupied molecular orbitals multiplied by their occupation numbers. The arguments of Coulson and Longuet-Higgins for deriving reactivity indices follow from these premises in a very straightforward way. We now recast those arguments into a more modern matrix formalism including overlap. The first systematic attempt to include overlap in the definition of reactivity indices had recourse to the covariant and contravariant components of LCAO molecular orbitals, and can be found in the sixth paper of the CLH series [15].

As is known, e.g. from the Hellman–Feynman theorem, the derivative of an orbital energy E_j with respect to a parameter q is given by:

$$\frac{\partial}{\partial q} E_j = C_j^{+} \left(\frac{\partial}{\partial q} H - E_j \frac{\partial}{\partial q} S \right) C_j, \tag{1}$$

whence, since the total energy in this approximation is:

$$E_{\text{tot}} = \text{Tr}(nE) \tag{2}$$

(with E the diagonal matrix of the E_j's and n the MO population matrix):

$$\frac{\partial}{\partial q} E_{\text{tot}} = \sum_j C_j^{+} \left(\frac{\partial}{\partial q} H - E_j \frac{\partial}{\partial q} S \right) C_j \cdot n_j. \tag{3}$$

If we now define two matrices:

$$R = CnC^{+}, \qquad P_E = CnEC^{+}/E_{\text{tot}}, \tag{4}$$

we can write:

$$\frac{\partial}{\partial q} E_{\text{tot}} = \text{Trace} \left(\frac{\partial}{\partial q} HR - E_{\text{tot}} \frac{\partial}{\partial q} SP_E \right). \tag{5}$$

Coulson and Longuet-Higgins's theorem is found if q is identified with one of the elements of H (all elements being considered independent variables) and the basis is orthonormal ($S = I$). Then:

$$\partial E_{\text{tot}}/\partial H_{mn} = R_{mn}. \tag{6}$$

Since, under the special assumptions of the Hückel method, the R matrix also coincides with Mulliken's population bond-order matrix, the physical content of Eq. (6) can be stated as follows: the derivative of the total energy with respect to an atomic or bond parameter is the corresponding element of the population bond-order matrix.

Equation (5) yields a generalization of Eq. (6) which may be very important if, as is the case with ordinary atomic orbitals, the basis is not orthonormal and the parameter q is an orbital exponent or an interatomic distance. An interesting case is provided by the "extended Hückel" method [16], whose Hamiltonian matrix can be represented as:

$$H = (1 - 2k)\alpha + k(\alpha S + S\alpha) \tag{7}$$

where α is the diagonal matrix of atomic parameters.

Although a rigorous proof has not been given, work going back to the first *ab-initio* computations [17] has shown that Eq. (7) reproduces the trends of Hartree–Fock molecular Hamiltonians. This means that, if a diagonal element of H is taken as q, then $\partial H/\partial q$ will not reduce to a single unit element, but to a block containing all those overlap elements which belong either to the row or to the column specified by q. If S is independent of q, the result (obtained from Eq. (5) with account of Eq. (7)) will be:

$$\partial E_{\text{tot}}/\partial \alpha_p = R_{pp} + k \sum_q S_{pq} R_{pq}, \tag{8}$$

which is now a k-dependent form of the gross population of the given orbital, in conceptual accordance with the interpretation of Eq. (6) for the standard Hückel method. This is anyway an "orbital perturbability" distinct from a population inasmuch as the quantities in Eq. (8) do not add up to the total number of electrons. On the other hand, it is possible to obtain from it a general "atomic perturbability" by summing over all p's corresponding to the same atom.

The above discussion can be extended to cover other cases. For example, it could be shown that, since overlap depends on the atomic orbital basis, and the latter depends on the condition of the atom under consideration, the assumption made in Eq. (8) that overlap does not depend on α_p is not strictly correct. Then Eq. (1) suggests that a sum of terms weighted by the appropriate orbital energies should be added to Eq. (8), and this might serve to connect the results of CLH with Fukui's frontier electron theory [8]. We shall not pause on these other aspects because the above equations suffice to show that a generalization of the argument of CLH is possible as far as the mathematical formulation is concerned.

The remaining question is whether its *physical content* will survive the generalization. That is to say: is it possible to generalize the interpretation of Eq. (6) as a structure-dependent reactivity index, based on the intuitive correspondence established in the Hückel method between molecular structure and elements of H? If not, what parameters represent molecular structure in the quantum-mechanical description of chemical reactions, and what quantities are legitimate representatives of the *tendency* of a given molecule to undergo reactions of a certain class at a given site?

We shall not attempt to answer these questions completely, but will point to what seems to us the most promising line of attack for attaining a non-intuitive solution of this problem. It will appear from our discussion that once again the orbital picture, in spite of its quantitative limitations, is the scheme to which reference must be made, pending further work on the physical model underlying the general configuration interaction scheme, a model which should combine the VB and MO approaches.

3 What parameters represent structure?

How exactly does one justify the Hückel and extended Hückel scheme for relating structure to reactivity? How can that procedure be generalized?

The original justification was that an approaching ionic reactant would affect one site or one bond of the substrate by modifying the corresponding element of the Hückel matrix, and the reaction would take place the more easily the greater the derivative of the net molecular energy E_{mol} with respect to that parameter. Now,

$$E_{\text{mol}} = E_{\text{tot}} - \mathrm{Tr}(n_{\text{at}}\alpha) \tag{9}$$

where n_{at} is the atomic orbital occupation matrix before formation of the molecule. Therefore, in the simpler case of site reactivity, the derivative of interest is not that of Eq. (6) but:

$$\partial E_{\text{mol}}/\partial\alpha_p = \partial E_{\text{tot}}/\partial\alpha_p - n_p = -Q_p, \tag{10}$$

where Q_p is the net charge of site p. Now suppose that approach of an ion produces a sort of inductive effect by changing the atomic parameter of any given site by a small $\Delta\alpha_p$. If $\Delta\alpha_p$ is positive, the corresponding energy change ΔE_{mol} can only be negative if the corresponding net charge is positive. Since α_p is a negative energy proportional to the electronegativity of site p, it will increase if, because of the approach of a positive charge, electrons are pulled from the rest of the substrate molecule towards p. Thus sites with negative net atomic charges are most susceptible of reacting upon approach of an electrophilic reagent. If on the contrary $\Delta\alpha_p$ is negative, then E_{mol} will decrease when the net charge is negative, and $\Delta\alpha_p$ is negative if electrons are pushed away from site p. Of course, the changes of E_{mol} must be added to some standard activation energy, roughly corresponding to the radicalic mechanism of the same reaction.

The extension of this approach to an all-valence scheme over non-orthogonal orbitals requires computation of Eq. (5), and, in the case of the Extended Hückel scheme, of the modified gross populations of Eq. (8). We shall devote a separate paper to a numerical study of these extensions, but they present no difficulty for those who wish to try to apply them.

Things stand otherwise as regards the "trick" by which indices exclusively dependent on the substrate structure have been obtained. That "trick" consists in assuming that the only effect of the approaching reagent is to modify the atomic parameter at the site involved. This satisfies the requirement that the results should be independent of the type and precise direction of the approach, but clearly remains at a very intuitive stage, so that it can only work in comparisons between closely related molecules. In other words, in the physical model underlying the mathematical work of CLH, Fukui, Koutecky and others, not only is a standard activation energy assumed – to be identified with localization energy in conjugated hydrocarbons, the major object of interest of those authors, but the structural pattern of atoms and bonds is arbitrarily assigned a specific role; it would be interesting to bring to surface the underlying line of reasoning. One way to do so is to refer directly to the supermolecule consisting of the given molecule M and the approaching ion X in the limit when the new bond is extremely weak and the electronegativity of X is either very high or very low.

4 The supermolecule scheme and a new reactivity index

Consider the MO-LCAO one-electron Hamiltonian matrix H^0 of an isolated molecule M with n electrons for a basis of m AO's, for simplicity in the nearest-neighbour approximation, and an approaching centre forming with M a sort of incipient supermolecule. The overall one-electron Hamiltonian H will be formed by bordering H^0 with a column vector $G_{\cdot 0}$ and its Hermitean conjugate $G_{0\cdot}$ (the dot specifies the position of the running subscript), where the $(r, 0)$ elements are small quantities $g_r\,\Delta q$, and q is a "reaction coordinate" specifying the points of the reaction path defined by the approach (to which a small overlap vector $S_{\cdot 0}$ with elements $s_r\,\Delta q$ also corresponds). The $(0, 0)$ element of H is an energy X either much lower or much higher than the lowest (resp. highest) eigenvalue of H^0. In the former case the total electron population is $n + 2$, in the latter the population is taken as n. These situations represent the incipient formation of a bond between an orbital of the r-th site and a strongly electronegative orbital already carrying two electrons or a very weakly electronegative orbital not contributing any electron to the system, respectively.

Let us now apply the so-called "reduced coupling scheme" [18] to the new matrix. Consider the matrices:

$$H = \left|\begin{array}{c|c} X & G_{\cdot 0} \\ \hline G_{0\cdot} & H^0 \end{array}\right|, \qquad S = \left|\begin{array}{c|c} 1 & S_{\cdot 0} \\ \hline S_{0\cdot} & I \end{array}\right|$$

Let us introduce the transformation T which on acting on H diagonalizes H^0 with overlap S^0:

$$T = \left|\begin{array}{c|cccc} 1 & 0 & 0 & 0 & 0 \\ \hline 0 & & & & \\ 0 & & C^0 & & \\ 0 & & & & \\ 0 & & & & \end{array}\right|, \tag{12}$$

where

$$C^{0+}H^0C^0 = E^0, \qquad C^{0+}S^0C^0 = I.$$

We have:

$$H' = \left|\frac{X}{V_{0\cdot}}\middle|\frac{V_{\cdot 0}}{E^0}\right|, \qquad S' = \left|\frac{1}{S'_{0\cdot}}\middle|\frac{S'_{\cdot 0}}{I}\right|, \tag{13}$$

where E^0 is the matrix of the orbital energies of the unperturbed matrix, and:

$$V_{j0} = \sum_r C^0_{rj} g_r \, \Delta q; \qquad S'_{j0} = \sum_r C^0_{rj} s_r \, \Delta q. \tag{14}$$

The secular equation leading to the new orbital energies E_j is:

$$\det(H' - E_j S') = 0. \tag{15}$$

This expression can be written in ordinary algebraic form by considering that, because of the special form of the matrices of Eq. (11), the determinant in question can be easily expanded. Indeed, as has already been mentioned, it corresponds to the standard "reduced coupling scheme" to which many authors have applied a Green function analysis [19, 20]. Confining ourselves to the case of non-degenerate unperturbed eigenvalues, we can write $m+1$ forms of the same final equation, each particularly suitable for the analysis of a specific E_j:

$$E_0 - X = \sum_k \frac{|V_{k0} - E_0 S'_{k0}|}{E_0 - E^0_k} \tag{16a}$$

$$E_j - E^0_j = \frac{|V_{j0} - E_{j0} S'_{j0}|^2}{(E_j - X) - \sum_k |V_{k0} - E_j S'_{k0}|^2/(E_j - E^0_k)}. \tag{16b}$$

If E_j is close to E^0_j, $E_j - E^0_k$ is always $\neq 0$. Then, for very small values of Δq Eq. (16b) can be written:

$$E_j - E^0_j \cong \frac{|V_{j0} - E^0_j S'_{j0}|^2}{E^0_j - X}. \tag{17}$$

Under the same approximation, the change in binding energy of the *substrate molecule* is:

$$\Delta E_b = \sum_j n_j (E_j - E^0_j) \cong \frac{\sum_j |V_{j0} - E^0_j S'_{j0}|^2}{E^0_{\text{occ}} - X}, \tag{18}$$

where the denominators coming from Eq. (17) have been simplified according to the assumption that X is very far from all eigenvalues of H_0, and therefore the individual orbital energies can be replaced by their mean value E^0_{occ}.

Considering for simplicity only real quantities, in virtue of Eq. (14) we write for Eq. (18):

$$\Delta E_b \cong \sum_{\mu} \sum_{j} \sum_{\nu} \phi_{\mu\nu}(E_j^0, \vec{r}) C^0_{j\mu} C^0_{j\nu} n_j (\Delta q)^2, \tag{19}$$

where

$$\phi_{\mu\nu}(E_j^0, \vec{r}) = \frac{g_\mu g_\nu - E_j^0 (g_\mu s_\nu + s_\mu g_\nu) + E_j^{02} s_\mu s_\nu}{E^0_{\mathrm{occ}} - X} \tag{20}$$

and $\vec{r}$ denotes the position at which the approaching ion is located, which is contained in the g's and s's; the subscript 0 has been dropped.

Now, if $\phi_{\mu\nu}(E_j^0, \vec{r})(\Delta q)^2$ coincided with $S_{\mu\nu}$, the summation in Eq. (19) would be the sum over μ of the gross atomic populations:

$$P_\mu = \sum_{\nu} S_{\mu\nu} R^{(j)}_{\nu\mu} \quad (\text{with } R^{(j)}_{\nu\mu} = C^0_{\nu j} n_j C_{\mu j}) \tag{21}$$

(cf. Eq. (4)) associated to the j-th MO of the unperturbed molecule. By analogy, we can proceed towards new AO reactivity indices (AORI) by introducing quantities defined as:

$$N^{(j)}_\mu = \sum \phi_{\mu\nu}(E_j^0, \vec{r}) R^{(j)}_{\mu\nu}, \tag{22a}$$

$$N_\mu = \sum_j N^{(j)}_\mu, \tag{22b}$$

respectively.

Let us now write the change in binding energy in the form:

$$\Delta E_b = \frac{\partial E_b}{\partial q} \Delta q + \frac{1}{2} \frac{\partial^2 E_b}{\partial q^2} (\Delta q)^2; \tag{23}$$

then Eqs. (19) and (20) tell us that:

$$\frac{\partial E_b}{\partial q} = 0, \qquad \frac{\partial^2 E_b}{\partial q^2} \simeq 2 \sum_{\nu} N_\nu. \tag{24}$$

This master equation, which could have been derived by simple perturbation theory, is formally analogous to the CLH result, but differs from it in several respects:

1. It corresponds to a sort of polarizability, because the second and not the first derivative appears in Eq. (24);

2. it contains energy-dependent atomic populations;

3. it corresponds to the change in the molecular energy, rather than the change in binding energy, which is the same only if the atomic orbital energies are taken to remain constant.

If only one atom μ is assumed to be involved in incipient bond formation with the approaching ion, then all g's and s's are zero except for the subscript

μ, and the summation over ν in Eq. (24) reduces to a single term having the form:

$$\frac{\partial^2 E_b}{\partial q^2} \simeq 2N_\mu \quad \text{or} \quad \Delta E_b \approx (\Delta q)^2 N_\mu . \tag{25}$$

It may appear surprising that the model here used always leads to an energy extremum – possibly except in the case not discussed of degenerate eigenvalues; a short discussion of this and other points is given in the next section. Possible doubts regarding the validity of the approximations in realistic cases seem unjustified in view of a few numerical tests, whose essentials are illustrated in Tables 1 and 2. For a Δq of .001 (which, with reference to the units of the Hückel method is of the order of .05 kcal/mol) the change in total energy (computed, of course, as the sum of the orbital energy of the six electrons under consideration and in units $\beta \simeq -2$ eV) is:

$$\begin{aligned} E_{1b} - E_{0b} &= -4.2326E-4 \quad \text{exact,} \\ &= -3.7718E-4 \quad \text{est.d.,} \end{aligned}$$

the latter value having been obtained from Eq. (23) with the values of Table 1.

Considering that $X = 4$ is not very large as compared with the mean energy of an occupied orbital in the isolated molecule (1.2095 in the same units), and Δq is not really vanishingly small, the agreement seems excellent.

The quantity N_μ is not yet a true reactivity index, because $\phi_{\mu\nu}$ has not been standardized with respect to the type of reaction and direction of approach. As

Table 1. Results for the quantities $N^{(j)}$ of Eq. (22a) and N of Eq. (22b) in a pyridine-like system described by a Hückel Hamiltonian with overlap (cf. Table 2) when a nucleophile ($X = 4$) approaches one of the α carbon atoms. Atom 6 is the nitrogen atom. The vectors s and g (defined in the text) correspond to overlaps $s\,\Delta q$ and interactions $g\,\Delta q$ of the approaching reagent with the various atoms of the conjugated cycle

at	s	g	$N(3)$	$N(2)$	$N(1)$	N_{tot}
1	2.0	10.0	31.4582	0.1659	−27.8345	3.7896
2	2.0	10.0	31.4582	−20.1783	−9.2586	2.0213
3	2.0	10.0	−0.0000	−28.6194	5.1912	−33.8107
4	2.5	10.0	−29.9874	−18.8825	−7.9351	−56.8050
5	6.0	40.0	−131.7161	0.7062	−127.2535	−258.2634
6	1.5	8.0	0.0000	12.1758	−46.2879	−34.1121

Table 2. Matrix of the parameters used for the test of Eqs. (22) on a pyridine-like system. The lower triangular part (*italics*) gives the relevant overlap integrals; the upper part and the main diagonal give the Hückel parameters adopted

0	1.0000	0	0	0	1.2000
0.2694	0	1.0000	0	0	0
0	*0.2694*	0	1.0000	0	0
0	0	*0.2694*	0	1.0000	0
0	0	0	*0.2694*	0	1.2000
0.2079	0	0	0	*0.2079*	1.0000

to the former, it is sufficient to give $E_{\rm occ}$—X a sufficiently large positive value A (in the units just specified) for nucleophilic reactions, and the value $-A$ for electrophilic reactions; from the example given, $A = 5$ should be sufficient. The way to standardize the g and s values is less immediate, but could consist in assigning a fixed orbital exponent to the "probe" centre orbital, using the Wolfsberg–Helmholtz rule to evaluate the g's from the overlap values, and fixing Δq to a small value such as .001. Of course, the values obtained will depend on the point P at which the probe is located, but that is expected.

The indices thus defined may or may not be useful, and an assessment of that side of the story is outside the scope of this paper. We just hope to have shown convincingly enough that further work on indices may open up interesting possibilities, which allow extension of general correlations to large molecules with σ as well as π bonds, in agreement with the strategy developed in [11]. A number of additional remarks are given in the following section.

5 Conclusion

This report has been divided into four parts. After an introduction trying to show that reactivity indices are not an obsolete notion, we have shown that the classical work of Coulson, Fukui, Koutecky and others can be formally extended to cover non-orthogonal orbitals as well as all-valence-electrons MO treatments for hydrogens and other molecules alike. This extension has a cost: the identification of atomic net charges with the first derivatives of the molecular binding energies is no longer possible. Indeed, the very argument by which net charges had been shown to be legitimate reactivity indices loses its force, for, if there is no equivalence between perturbabilities and charges, then the description of the incipient stage of a reaction as just an "inductive effect" at a site loses most of its appeal (see Sect. 3).

In this connection, referring to the CLH work [6, 15], Fukui et al. write: "The method of presenting the reactivity through [the net charge] q_r, [the self-polarizability] π_{rr} and [the free-valence indices] F_r is based on the magnitude of change in total π electron energy caused by the perturbation of the reagent (...), and in this sense these quantities have been said to tell us the relative height of the energy curve at an early stage of the reaction path, and the method in which they are used has been called the 'static method' or the 'isolated molecule approximation' " (Ref. [8], p. 836).

But can a sort of "isolated molecule" [7] scheme on which to base reactivity indices be extended beyond alternant hydrocarbons and related cases, even if the price is a heavier computational effort? Few attempts seem to have been made, one of them being the 1991 paper of Ref. [11], which could be compared with our analysis of the application of the perturbability approach to the Extended Hückel Method. More work would seem to be in order, e.g. along the lines illustrated in the preceding section, but a number of objections have to be met.

First of all, is the sum of the orbital energies multiplied by their occupation numbers a reasonable estimate of the molecular energy? Here, at least if the computational schemes adopted mimic *ab-initio* SCF results, the answer appears to be positive up to a multiplication factor 3/2 [21–23].

The CLH point, that the effect of an incipient reaction is well represented by changes in the diagonal and off-diagonal elements of the Hamiltonian matrix of the isolated molecule, is less evident. In a slow-approach picture, it seems to imply that a reagent approaching the molecule from afar can select its target atom in spite of effects like temperature, solvation, steric hindrance, and the very electrostatic field of the substrate molecule [24, 25]. This picture would rather suggest, in our opinion, that net charges play a role as such because of their long-range electrostatic effect [26]. If, on the other hand, a reaction is modelled as a "sudden" event, whereby the solvation shell breaks down and close approach of the reagent is *followed* by molecular relaxation, then the notion that the inductive effect at the site of attack is the primary step of that relaxation does make sense, and the slope of the binding energy change should allow some evaluation of the probability that the newcomer will stick to the molecule at that site. If it is admitted that in a realistic inductive effect not the elements of the effective one-electron Hamiltonian matrix, but the very orbital exponents of the atom under consideration are modified, then the perturbation scheme involving one site will at least affect the energy parameters and overlaps of the bonds in which that site is engaged on two accounts – the Wolfsberg–Helmholtz relation and the exponent dependence of the overlap integrals (cf. Eq. (7) and subsequent discussion), so that the whole molecular region surrounding that site is actually involved. Moreover, the individual molecular orbitals would give contributions dependent on their energies (Sect. 2), in conceptual agreement with Fukui's fundamental contribution.

As an alternative to the isolated-molecule approach one can consider the supermolecule approach. This possibility, already taken up in Ref. [11], has been discussed above in a perturbational context, which seems particularly consistent with the very notion of reactivity index. We have tried to show in Sect. 4 that indeed CLH's and Fukui's path can be followed in that direction, but ours has avowedly been only a preliminary step along a rather difficult line of work.

To sum up, reactivity indices of the kind originally proposed by CLH, in particular net charges and other "atomic" indices, are indispensable for organic chemists, but their definition requires a broader mathematical analysis and a careful specification of the model mechanism from which they stem, if they must be extended to cover all kinds of molecules and schemes of treatment. We hope that the equations and remarks proposed in this paper will contribute to progress in that direction.

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References

1. Williams A (1984) Acc Chem Res 17:425
2. Paoloni L, in: Atti del 1o convegno di storia della chimica. Turin University Press, p 172
3. Platt JR (1961) in: Handbuch der Physik 37/2:1973
4. Berthod H, Pullman A (1965) J Chimie Phys 62:942
5. Berthod H, Giessner-Prettre C, Pullman A (1967) Theoret Chim Acta 8:212
6. Coulson CA, Longuet-Higgins HC (1947) Proc Roy Soc (London) A191:39 (1947) A192:16
7. Brown RD (1952) Quart Rev Chem Soc 6:63
8. Fukui K, Yonezawa T, Nagata C (1956) J Chem Phys 831
9. Koutecky J, Zahradnik R, Cizek J (1961) Trans Far Soc 57:169
10. Del Re G, Ladik J (1980) Chem Phys 49:321

11. Jug K (1984) Croat Chem Acta 57:941
12. Basilevsky MV, Weinberg NN, Zhubin VM (1984) Croat Chem Acta 57:1423
13. Weber J, Fluekiger P, Stussi D, Morgantini PY (1991) J Mol Str (Theochem) 227:175
14. Mestechkin M, Siv'akova L (1991) J Mol Str (Theochem) 228:117
15. Chirgwin BH, Coulson CA (1950) Proc Roy Soc (London) A201:196
16. Hoffmann R (1963) J Chem Phys 39:1397
17. Berthier G, Del Re G, Veillard A (1966) Nuovo Cimento 44:315
18. Messiah A (1960) Mécanique quantique. Dunod, Paris
19. Newns DM (1969) Phys Rev 178:1123
20. Grimley TB (1976) Crit Revs 6:239
21. Ruedenberg K (1977) J Chem Phys 66:375
22. March N (1980) J Chem Phys 72:1994 and refs. therein
23. Fliszar S (1983) Charge distributions and chemical effects. Springer, New York, p 77
24. Bonaccorsi R, Scrocco E, Tomasi J (1970) J Chim Phys 52:5270
25. Pullman A (1974) Jer Sym Q Chem and Bioch VI, Israel Ac. of Sci. and Hum., Jerusalem, p. 1
26. Del Re G, Otto P, Ladik J (1980) Isr J Chem 19:265