===================== **REVIEW** =====================

Some Modern Methods for Estimation of Reactivity of Organic Compounds

Yu. E. Zevatskii and D. V. Samoilov

St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: yuri@newchem.ru

Abstract—The review analyzes main tendencies in the development of some modern methods for estimation of reactivity of organic compounds and reaction regioselectivity. The up-to-date correlation analysis, reactivity descriptors, QSPR, and other methods are compared with respect to their advantages and disadvantages.

1. INTRODUCTION

Relations between the structure of organic compounds and their reactivity constitute a fundamental problem of modern chemistry. However, the term

Yurii Zevatskii was born in 1969 in Kiev. In 1993 he graduated from the Department of Chemical Technology of Organic Dyes and Phototropic Compounds, St. Petersburg State Institute of Technology. Candidate of chemical sciences since 2005. Yu. Zevatskii is now head of the Research Laboratory at *Novbytkhim* Ltd.

Field of scientific interest: physical organic chemistry.

Denis Samoilov was born in 1974 in Leningrad. In 1997 he graduated from the Department of Chemical Technology of Organic Dyes and Phototropic Compounds, St. Petersburg State Institute of Technology. Candidate of chemical sciences since 2001. D. Samoilov is now Senior research worker at the Physical Chemistry Department, St. Petersburg State Institute of Technology.

Fields of scientific interest: physical organic chemistry and chemistry of xanthene dyes.

reactivity is now ambiguous. On the one hand, reactivity implies dependence of reaction rate of compounds belonging to a definite group upon their structure and reaction conditions; on the other hand, reactivity is treated as a set of quantitative parameters of possible reaction centers in a molecule of an organic compound with respect to different reagents and reaction types. These quantitative parameters are usually called reactivity indices (RI). In some cases, calculated values of RIs correlate with the relative reaction rates at potential reaction centers. In the latter approach, a more appropriate and frequently used term is *regioselectivity* which is sometimes opposed to *reactivity*.

By *estimation of reactivity* we mean comparative analysis of some quantitative parameters of a substance related to kinetic or thermodynamic reaction parameters. Obviously, a qualitative approach utilized in some modern methods is a limiting case of quantitative methods when the accuracy of experimental data and calculation capabilities are impartially restricted.

The existing methods for estimation of reactivity are focused mainly on quantum-chemical calculations of the distribution of various RIs (characterizing the reactivity of particular molecular fragments or reaction centers toward a definite reaction) over the volume of a molecule. However, other methods based on correlations between experimental rate or equilibrium

constants and parameters reflecting the influence of different fragments on the reactivity (e.g., substituent constants) or reaction conditions are also used fairly frequently. These methods include correlation analysis and calculations and analysis of potential energy surfaces and predict the reactivity in the classical sense (i.e., for molecules as a whole). Empirical quantitative structure–property relationship (QSPR) methods occupy an intermediate place, for they employ both calculated and experimental data.

2. STATE-OF-THE-ART CORRELATION ANALYSIS

Correlation analysis was introduced in 1930s by Hammett [1], though attempts to reveal quantitative effects of various factors on reaction kinetics were made since the end of the XIXth century [2]. The golden age of correlation analysis was in 1970s due to Taft's and Pal'm's studies. At present, interest in correlation analysis considerably weakened. Correlation analysis is a semiempirical method based on the chemical similarity and linear free energy relationship principles and mathematical polylinearity formalism [3]. In the last decade, extensive databases have been created, which cover huge experimental data on substituent constants in various reaction series (successfully treated in terms of correlation analysis) and on effects of the medium [4].

Due to simplicity of mathematical processing and obviousness of physical principles underlying correlation analysis, it remains an effective tool for estimation of reactivity of compounds and their physical properties. This follows from the data reported during the past decade on quantitative estimation of inductive effects of substituents [5], quantitative description of radical reactions [6], and thermodynamic substantiation of the experimental nonlinearity of the Brønsted equation for CH acids [7] on the basis of the hard and soft acid and bases (HSAB) principle [8, 9]; also, the review [10] on correlation analysis and prediction of nucleophilic substitution reactions must be noted.

Cherkasov et al. [5] extended the concepts of correlation analysis to estimate the inductive effect. The authors reported new constants σ for different groups of compounds. The new constants were used to interpret substituent effects on NMR, IR, Raman, and photoelectron spectra, reduction potentials of organic compounds, and solvatochromism. The overall substituent effect on a reaction center is generally divided into inductive, resonance, steric, and sometimes polar-

ization constituents. Appropriate quantitative separation of substituent effects is one of the main obstacles that restrict development of quantitative organic chemistry and correlation analysis. The difficulty is that no reliable criteria for the separation of the overall effect into its constituents can be derived on the basis of commonly used empirical methods for quantitative estimation of substituent effects in standard reaction series. Therefore, the authors [5] proposed a universal scale of constants σ with account taken of substituent steric effects and an additivity scheme for calculating the contribution of inductive effect:

$$\sigma^* = \sum_{i=1}^{n} \frac{(\sigma_A)_i}{r_i^2}. \qquad (1)$$

Here, σ^* is the Taft inductive constant, σ_A is the empirical constant of an ith atom (determined by statistical processing while solving the inverse task on the large number of known group constants), and r_i^2 is the distance from that atom to the reaction center. Group constants for 427 substituents were determined, and the correlation coefficient was equal to 0.991. Although σ_A is defined as an empirical quantity, the following correlation ($r = 0.982$) was found for a large group of compounds: $\sigma_A = 7.840\Delta\chi R^2$, where $\Delta\chi$ is the difference in the electronegativities of a given atom and carbon, and R is its covalent radius. Application of the proposed approach to inductive effect of alkyl substituents showed the existence of a linear correlation and genetic relation between steric and inductive effects of such substituents.

The use of correlation analysis for building up a quantitative nucleophilic substitution model was reviewed in [6]. Similarities, differences, advantages, disadvantages, scope, and limitations of various methods and types of constants σ for several groups of compounds were discussed. Numerous modifications of the Hammett equation, both single- and multiparameter, were considered with a view to obtain best correlations within a series of compounds or to extend their number. It was emphasized that the main advantages of linear correlations are (as they were) physical clarity of their fundamental principles and a large number of good results in the description of nucleophilic reactions using such a simple mathematical model. Disadvantages of linear correlations are the following: (1) no account taken of the nature of leaving group and exclusion of the corresponding cross terms; (2) necessity of considering the isokinetic temperature (while passing the isokinetic temperature, the ρ parameter in

the Hammett equation changes its sign, the reaction mechanism remaining unchanged; this may lead to misinterpretation); (3) in some cases, good linear correlations cannot be substantiated from the physical viewpoint; and (4) relations between the energy barrier and heat effect of a reaction are really nonlinear over a broad range of $\Delta E°$. Therefore, nonlinear equations like Marcus equation (2) [11] were considered.

$$\Delta E^{\neq} = \Delta E_0^{\neq} + \frac{\Delta E°}{2} + \frac{(\Delta E°)^2}{16 \Delta E_0^{\neq}}. \qquad (2)$$

The Marcus equation was the starting point for other nonlinear models which generally better describe energy profiles of reactions. Drawbacks of these models are narrow range of applicability with respect to $\Delta E^{\neq}$ and the assumption that transition state is equally similar in energy and structure to both initial compounds and reaction products, which is not always valid. More O'Ferrall–Jencks and cubic diagrams have been recognized as the most appropriate method for the description of nucleophilic substitution reactions. The latter approach is the closest to the modern *no barrier theory* (NBT), which is considered in Section 5 of the present review. These methods were developed as early as 1980s and are based on the known Hammond postulate and Thornton rule [11].

Cherkasov et al. [6] also reviewed numerous attempts of using correlation analysis for quantitative description of radical reactions; unlike heterolytic processes, this problem remains so far difficult to solve. It was shown that none of the existing scales of radical constants σ can be regarded as general, for appropriate separation of proper radical stabilization and polar (inductive and resonance) contributions to the overall substituent effect was not performed. Nevertheless, some examples illustrating successful application of classical constants σ⁺ and modified Hammett equations for some radical cation-mediated processes were given. The use of constants σ⁻ and σ* in the analysis of reactions involving neutral radical species was much less effective.

Three approaches to the determination of pure radical constants σ* were noted. The first approach is based on classical correlation analysis implying kinetic parameters of reactions, but it involves specific selection of reagents and reaction conditions in such a way that the substituent polar effect be equal to zero; as a result, the pure radical stabilization effect may be revealed. A number of criteria were formulated for the reaction series, the most important of which is pro-

nounced radical character of the transition state. Several two-parameter equations and sets of substituent constants σ were obtained; however, none of these met the above criteria. Therefore, the obtained constants also included resonance effect to greater or lesser extent.

The second approach implies experimental determination of spin density distribution and the degree of its delocalization in radical species by ESR spectroscopy; just the latter parameter is a measure of radical stabilization. Obviously, the main advantage of this approach is direct measurement of a parameter reflecting substituent effect; on the other hand, possible influence of non-radical (inductive and resonance) substituent effects on spin density delocalization cannot be ruled out. Therefore, it is necessary to separate the effects by statistical analysis, and in this case the procedure becomes non-advantageous against the kinetic method.

The third is thermodynamic approach operating with energy parameters. For example, it involved relative energy of homolytic dissociation $\Delta H_1°$ of an RR' compound:

$$\Delta H_1° = \Delta H°(\dot{R}) + \Delta H°(\dot{R'}) - \Delta H°(RR'), \qquad (3)$$

where $\Delta H°(\dot{R})$, $\Delta H°(\dot{R'})$, and $\Delta H°(RR')$ are the corresponding enthalpies of formation of radicals and their recombination products. The resonance stabilization energy $E_R(R)$ was defined as the enthalpy of isodesmic reaction (4)

$$R\cdot \ + \ CH_4 \ \longrightarrow \ RH \ + \ \dot{C}H_3 \qquad (4)$$
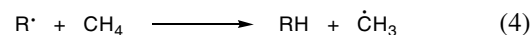
in which the number and character of bonds do not change:

$$E_R(R) = \Delta H_2° = E_D(CH_3–H) - E_D(R–H), \qquad (5)$$

or as covalent constituent of the XR–Z bond dissociation energy, where R is an invariable core, and X is a substituent:

$$E_{RS}(R) = 1/2\,E_a(XR–RX) - E_a(HR–RH). \qquad (6)$$

Also, redox potentials may be used. However, this approach was subjected to strong criticism in the same aspects as the spectral method.

Cherkasov et al. [6] proposed a new method for quantitative description of radical reactions, which was called *r^{-2} analysis*. It is based on the topological

approach described previously [5] and employs the two-parameter Taft equation which was modified using discrete atom contributions:

$$Y = \rho \sum_i \sigma^* + \delta \sum_i E_s; \qquad (7)$$

$$Y - Y^\circ = \sum_{i \neq rc}^{N-1} \frac{e_i}{r_{rci}^2}. \qquad (8)$$

Here, N is the number of atoms, rc is the atom selected as reaction center, r_{rci} is the distance between the ith atom and the reaction center, Y is some physical parameter, Y° is the value of that parameter for unsubstituted reaction center, and e_i is a parameter characterizing the ability of certain atom to exert intramolecular effects determining the Y values.

The proposed procedure allowed the authors to separate inductive and steric substituent effects and obtain good correlations with the energy of ionization and electron affinity of C-, N-, S-, and O-centered radicals, as well as with the energy of ionization of amines, although resonance effect cannot be taken into account in terms of the given approach. However, the physical sense of e_i remains not clearly understood, despite the existence of a formal relation between e_i and electronegativity.

$$e_i = a\chi_{i-rc}R_i^2 + bR_i^2. \qquad (9)$$

Here, a and b are parameters, R is the atomic radius, and χ_{i-rc} is the difference in the electronegativities of the ith atom and reaction center.

Tupitsyn and Zatsepina [7] formulated the problem of isolation of solvation factors while measuring thermodynamic and kinetic CH acidities. For this purpose, the authors developed a procedure for exclusion of the solvent-independent electrostatic component from pK_a values. With a view to develop a phenomenological approach in terms of the electrostatic solvation model, linear correlations between the experimental gas-phase acid dissociation energies ΔH_{gas}, Gibbs protonation energies $\Delta G_S = -RT$pK_a, and pK_a values of various CH acids in different media were analyzed. Using the HSAB principle, the authors obtained a modified pK_a scale for CH acids in DMSO, which was free from the electrostatic component. Deviations of reaction rates from those calculated by the Brønsted equation were rationalized [8, 9] using classical $\sigma\rho$ correlation analysis with modified con-

stants σ^- in combination with the HSAB principle. It was found that (1) electrostatic contribution to pK_a of CH acids in DMSO is minimal; (2) intramolecular electronic interactions in CH acids are similar, and differences in the behavior of CH acids result from different solvation effects which are responsible for deviations from the Brønsted equation; and (3) for benzene and methane derivatives giving rise to nonplanar anions, the inductive effect is determining in ΔG_{gas} and pK_a, while deprotonation rate constants are determined mainly by the resonance effect.

In the series of studies on the effects of substituents (including those containing heteroelements) on the ionization potentials of amines [12], sulfides [13], phosphines, and other organophosphorus compounds [14], the linear free energy relationship principle was applied assuming that the main contribution to the ionization energy is provided by the heat effect (enthalpy) of electron abstraction. The entropy contribution did not exceed 5% and therefore was not taken into account. On the other hand, it was noted that the Koopmans theorem approximation assuming that the energy of ionization is equal to the HOMO energy was not fulfilled for the examined compounds. As a result, polylinear correlations with $r > 0.85$ were obtained. An acceptable correlation was obtained only when the polarization contribution to substituent effect was taken into account in addition to traditional inductive and resonance contributions. All the revealed relations were rationalized in terms of clearly understandable concepts and fundamental principles of organic chemistry.

Quite interesting results were recently reported by Rao et al. [15] who observed the effect of substituents on the rate of dehydrogenation of isolated molecules of halobenzenethiols using a scanning tunneling microscope (STM) [15]. The dehydrogenation was induced by tunneling current of STM. The reaction rate was calculated from the time elapsed from the current switch-on till its abrupt fall down, which corresponded to the moment of proton abstraction. The observed reactivity relations were fully consistent with the Hammett equation, as followed from a good correlation between the obtained substituent constants and reference values.

The main disadvantage of classical correlation analysis is that a high accuracy in the prediction of rate constants can be obtained only within certain reaction series. If such series are not large, the prediction efficiency is poor. The main advantages of correlation

analysis are undoubtedly its obviousness and availability of huge experimental data on kinetic parameters of reactions, which underlie drawing-up and analysis of all quantitative relations.

3. QUANTUM-CHEMICAL REACTIVITY DESCRIPTORS

A *descriptor* or *reactivity index* is some scalar quantity characterizing the ability of a molecule as a whole (global descriptor) or its particular fragment (local descriptor) to undergo a chemical reaction in general or a certain kind of reactions. Historically, the first calculated reactivity indices (RI) were charges on atoms and free valence indices. Probable directions of electrophilic and nucleophilic reactions were qualitatively estimated on the basis of the calculated charge distribution over the corresponding atoms. Empirical free valence indices which were also related to particular atoms were used to estimate the ability of these atoms to act as reaction centers in radical reactions. The free valence indices were calculated from the calculated or experimental orders of bonds [16]. Among the formerly used indices, a special place was occupied by the Fukui function [17] which was introduced as a universal reactivity parameter. The Fukui function has become a numerical parameter demonstrating that the reactivity of a molecule is determined mainly by electron density distribution over its frontier molecular orbitals, LUMO (with respect to nucleophiles), $f^+(r) = c_{LUMO}^2$, and HOMO (toward electrophiles), $f^-(r) = c_{HOMO}^2$; here, $\rho_{N+1}(r)$ is the electron density in a molecule with one electron missing, and $\rho_{N-1}(r)$ is the electron density in a molecule with one electron added. These expressions acquired a new sense and significance in terms of the electron density functional theory (DFT).

In the recent time, the reactivity of organic compounds and regioselectivity of organic reactions are estimated using reactivity indices based on local parameters, i.e., those characterizing a particular molecular fragment. In the past decade, such parameters as *hardness, softness, electronegativity, electrophilicity, nucleophilicity, amphiphilicity* (general philicity), and *polarizability* are used most frequently. These local parameters are determined by quantum-chemical calculations of electron density [18–59] and electrostatic potential distribution [60] in a molecule. Except for electrostatic potential, polarizability, and electron density [19], all the above quantities cannot be measured experimentally. The calculations are performed

using formal DFT equations, and extensive development of computer engineering makes it possible to perform as complex calculations as necessary [34]. The mathematical details and basic principles of the electron density functional theory [18] are unlikely to be interesting for specialists working in organic chemistry; therefore, they are not considered in the present review. It should be noted only that the fundamental equation from which formal expressions for all the above listed reactivity indices are derived is the definition of the chemical potential [Eq. (10)].

$$\mu = -\chi = \left[\frac{\partial E}{\partial N}\right]_{\upsilon(r)}. \tag{10}$$

Here, E is the electronic energy of a molecule, N is the number of electrons, $\upsilon(r)$ is the external potential (which is determined exclusively by nuclei [16]), μ is the chemical potential, and χ is the electronegativity. The other local parameters are determined on the basis of the chemical potential. This definition implies that the chemical potential is related to the magnitude and direction of charge transfer in a chemical reaction. It is important that the external potential is assumed to be constant, which is not always the case. Expressions for the other reactivity indices are derived from the definition of the chemical potential. For example, the global chemical softness in terms of DFT is given by Eq. (11) [20]:

$$S = \left[\frac{\partial N}{\partial \mu}\right]_{\upsilon(r)}. \tag{11}$$

The global hardness is determined by Eq. (12) [21]:

$$\eta = \frac{1}{2}\left[\frac{\partial u}{\partial N}\right]_{\upsilon(r)} = \frac{1}{2}\left[\frac{\partial^2 E}{\partial N^2}\right]_{\upsilon(r)}. \tag{12}$$

The polarizability is defined by Eq. (13) [33, 46]:

$$\alpha = -\left[\frac{\partial^2 E}{\partial F_a \partial F_b}\right]; a, b = x, y, z, \tag{13}$$

where $F_{a,b}$ is the field strength along the given coordinates.

Complex reactivity indices, such as electrophilicity ω [22] and amphiphilicity ω^+ and ω^- [23, 24], have been introduced relatively recently and are defined by the expression $\omega = \mu^2/\eta$ [23]; the definition of the nucleophilicity [25] is not obvious, and this reactivity index will be considered below.

New local and global reactivity indices are defined in terms of DFT through the electronegativity $\chi = -(I + A)/2$, chemical hardness $\eta = (I - A)/2$, and chemical softness $S = 1/2\eta = 1/(I - A)$, which were proposed in the early 1960s by Pearson [26] and are related to experimentally measurable electron affinity A and ionization energy I. Insofar as these relations are retained in the corresponding local indices, they are frequently used to substantiate physical sense of newly introduced descriptors. The transition from global to local reactivity indices is performed using the Fukui function. The local Fukui function, being a universal reactivity parameter characterizing the ability of a given molecular fragment to enter a reaction with any mode of electron density redistribution between the substrate and reagent, is expressed by Eq. (14).

$$f(r) = \left[\frac{\partial \rho(r)}{\partial N}\right]_V = \left[\frac{\partial \mu}{\partial \upsilon(r)}\right]_N. \qquad (14)$$

Its nucleophilic, electrophilic, and radical constituents are represented by Eqs. (15a)–(15c):

$$f^+(r) \approx \rho_{N+1}(r) - \rho_N(r); \qquad (15a)$$

$$f^-(r) \approx \rho_N(r) - \rho_{N-1}(r); \qquad (15b)$$

$$f^0(r) \approx 1/2[\rho_{N+1}(r) - \rho_{N-1}(r)]. \qquad (15c)$$

Here, $\rho_N(r)$ is the electron density of a molecule, $\rho_{N+1}(r)$ is the electron density of a molecule minus one electron, and $\rho_{N-1}(r)$ is the electron density of a molecule plus one electron [27–32]. At present, a shortened notation of the local Fukui function in the general form is used: $f^\alpha(r)$, where α is the index corresponding to the reaction type, i.e., electrophilic (+), nucleophilic (–), or radical (0).

The local reactivity indices formed the basis for the application of DFT to analysis of regioselectivity via calculation of local descriptors: local hardness, local softness, their derivatives, the corresponding global parameters, and local Fukui functions. Thus it is necessary to calculate only the corresponding local Fukui function in order to obtain a distribution diagram of some reactivity index over the molecular entity (RI profile) with respect to a given reaction type. The RI profile described by local RIs is obtained from the experimental values of global descriptors according to the following equations:

$$\eta^-(r) = \eta f^-(r); \eta^+(r) = \eta f^+(r); \eta = I - A; \qquad (16a)$$

$$s^-(r) = S f^-(r); s^+(r) = S f^+(r); S = 1/(I - A); \qquad (16b)$$

$$\omega^-(r) = \omega f^-(r); \omega^+(r) = \omega f^+(r); \omega = \mu^2/\eta. \qquad (16c)$$

It is seen that the local descriptors are defined in such a way as to retrace the Fukui function profile. However, calculation of the local Fukui functions is a complex computational task related to selection of appropriate method and basis set [28–31]. Improper choice often leads to inadequate results [32].

Most studies aimed at development of DFT extensions as applied to reactivity and regioselectivity follow a general scheme. New reactivity indices are proposed on the basis of fundamental equations of the density functional theory [16] and by analogy with the above listed RIs, and new descriptors are often combinations of the old ones. They are introduced with a view to find an optimal and universal reactivity index that could describe regioselectivity with respect to any reagent equally well. Their physical consistency is justified on the basis of traditional views on the relations between the electronic structure of a molecule and its reactivity and empirical principles, such as the hard and soft acids and bases principle, the maximum hardness principle (MHP) [26], and the minimum polarizability principle (MPP) proposed recently [33]. The proposed descriptors are tested for adequate qualitative description of well known reactions of simple model compounds which act as both reagents and substrates in different types of reactions. The tests are performed by analyzing three-dimensional diagrams demonstrating distribution of new RIs over a molecule (RI profile). Considered below are those studies which, in our opinion, demonstrate most clearly general trends in the development of the DFT method.

As shown in [34–36], physical foundations of the HSABP, MHP, and MPP, as well as of the electronegativity equalization principle [11, 16, 37], acquire a formal mathematical expression in terms of DFT. Therefore, these principles can be used to analyze regioselectivity since the parent quantities, chemical hardness and softness, can be calculated for particular fragments of molecules. In a addition, they are clearly interrelated through global and local RIs.

Pérez et al. [35] used DFT reactivity indices to interpret the reactivity of dienes and dienophiles in the Diels–Alder cycloadditions, protonation of amines in the gas phase, and empirical Markovnikov rule. However, the use of the Fukui function for the HOMO of transition state was not always appropriate; therefore, electron density distribution over the next occupied molecular orbital having a lower energy was employed.

The use of the global hardness as reactivity index is based on the maximum hardness principle [27, 38], according to which the most stable among possible products of a given reaction is that characterized by the maximum hardness. As noted in [39, 40, 43], the local hardness can be used to estimate the regioselectivity with respect to hard reagents, while the local softness, with respect to soft reagents [41, 42]. In keeping with the more recent minimum polarizability principle [33], the preferential reaction path is that involving transition state with the minimal polarizability. This principle is an extension of the HSAB principle and of the relation between the chemical softness and polarizability [43]; it has developed when the term *local softness* has been introduced.

An illustrative example of the joined application of the MPP and MHP for analysis of reactivity was given by Gomez et al. [44]. The authors compared the calculated energy profiles for the Beckmann rearrangement and condensation of amino acids to polypeptides with the variation of the calculated global hardness and polarizability in the course of these processes. In the first case, the most energetically favorable transition states were characterized by minimal polarizabilities, though their hardness was not always maximal. In the second case, the real two-step mechanism was consistent with both MPP and MHP, whereas alternative synchronous mechanism involving a transition state with higher energy can be described only in terms of the MPP. It was presumed that these reactions are not orbital-controlled (i.e., the energy of the transition state is determined not only by the energies and populations of frontier molecular orbitals); therefore, they cannot be interpreted in terms of the maximum hardness principle.

Analogous considerations as applied to the Fukui function were given in [45]. It was shown that the local Fukui function is not an adequate descriptor for reactions involving two hard reagents. The reason is that such reactions are governed mainly by charge interactions between atoms weakly shielded by electrons, for hard reagents usually possess a localized electric charge. Electrostatic potential was proposed as optimal reactivity index for such reactions. Soft–soft interactions are governed mainly by frontier molecular orbitals, for which the Fukui function is the best reactivity index by definition.

Theoretical study on some compounds like SF_4, SF_4O, PCl_xF_{5-x} [46] showed that for each molecule the isomer in which the more electronegative atom occupies the axial position has maximum hardness; this is consistent with the MHP. However, only a combination of the MHP and MPP calculations could predict correctly the most stable isomer, but the stability series of the isomers cannot be predicted correctly.

Pérez et al. [36] theoretically substantiated the use of the simplest semiempirical Hückel molecular orbital method in the framework of the density functional theory and successfully applied the obtained model to interpret the regioselectivity in Diels–Alder reactions on the basis of the classical expressions of the Fukui function.

$$f^+(r) = c^2_{LUMO}; f^-(r) = c^2_{HOMO}. \qquad (17)$$

Here, $c_{LUMO,i}$ and $c_{HOMO,i}$ are the orbital coefficients of a carbon atom under study in the LUMO and HOMO energies, respectively. These expressions were obtained by transformation of the principal equation for chemical potential in terms of the Hückel molecular orbital method.

$$\mu = \alpha_r - \frac{X_{HOMO} - X_{LUMO}}{2} \beta_{rs} = \sum_r f_r \alpha_r + \sum_{r,s} f_{rs} \beta_{rs}. \quad (18)$$

Here, X_{HOMO} and X_{LUMO} are the roots of the equation $\det(H_{\mu\nu} - E_i) = 0$.

In the recent time, so-called condensed Fukui functions f^+_A, f^-_A, and f^0_A are used in addition to local Fukui functions to estimate regioselectivity of reactions. They are obtained by integration of local Fukui functions over an atom [31, 49–52] and are thus atomic parameters. The corresponding expressions are analogous to those for the local functions with the difference that charges on atoms (q_A) are used instead of electron density:

$$f^+_A = q_A(N + 1) - q_A(N);$$
$$f^-_A = q_A(N) - q_A(N - 1); \qquad (19)$$
$$f^0_A = 1/2[q_A(N + 1) - q_A(N + 1)].$$

The charges are calculated by analysis of the Mulliken orbital populations or by other methods [28–31]. These ideas were reflected in [30], where the local hardness was proposed to be considered in the framework of the Bader "atom in a molecule" (AIM) approach [50]. It was shown that the local hardnesses of atoms calculated through the atomic Fukui functions (electrophilic, nucleophilic, or radical) fit a simple additivity scheme for the calculation of global hardness.

On the other hand, the local hardness retains its function as a local descriptor related to an atom. The atomic Fukui functions for six three-atom molecules were also calculated from the AIM charges on atoms. All the calculated reactivity indices ensured qualitatively consistent description of the reactivity of the examined three-atom molecules.

Olah et al. [31] estimated the regioselectivity in the addition to carbonyl compounds (at the carbon or oxygen atom) of anionic di- or triatomic nucleophiles, i.e., compounds with clearly competing nucleophilic and electrophilic centers (various anilines), using the atomic Fukui functions and related atomic softnesses:

$$s_A^\alpha = s f_A^\alpha, \qquad (20)$$

where the subscript α is "+," "–," or "0," in keeping with the reaction type as in Eq. (15). A qualitative correlation with the known reactivity data was obtained. It was emphasized that the results of calculation of the atomic Fukui functions strongly depend on the method selected for the calculation of charge distribution.

These concepts were further developed by Kolandaivel et al. [49], who introduced indices like

$$s f_A^\alpha = S (f_A^\alpha)^2, \qquad (21)$$

which were tested for description of regioselectivity in electrophilic, nucleophilic, and radical reactions of glycine, alanine, *m*-anisidine, and aniline. The regioselectivity profile obtained on the basis of the proposed reactivity indices was analogous to that provided by the atomic Fukui functions, but the authors succeeded in avoiding difficulties related to the calculation method.

Meneses et al. [39] proposed Eq. (22) instead of the system of two equations determining the local hardness with respect to electrophiles and nucleophiles.

$$\eta(r) = I f^-(r) - A f^+(r). \qquad (22)$$

This equation defines the local chemical hardness in a different way than it follows from the fundamental DFT equations (see above). The concept was based on the following considerations. A hard electrophile (reagent) should have a high ionization energy. This means that its HOMO has a low energy and that it should react with a hard nucleophile (substrate) having a high ionization energy and low electronegativity at the reaction center where variation of the electron density upon removal of charge therefrom is the maximal. Insofar as both reacting molecules are characterized by high ionization energies, the HOMO energy of the nucleophile should be similar to the LUMO energy of the electrophile, and the reaction should be orbital-controlled. By analogy, the new local chemical softness is defined as

$$s(r) = 1/2 [s^+(r) - s^-(r)] \text{ or } 1/2 S[f^+(r) - f^-(r)]. \qquad (23)$$

With the goal of involving the experimental HOMO (ε_{HOMO}) and LUMO energies (ε_{LUMO}) in the analysis of regioselectivity, the expression for the local chemical hardness with account taken of the Koopmans theorem ($\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO}$) was transformed [39] into the following equation:

$$\eta(r) = \varepsilon_{LUMO} f_A^+ - \varepsilon_{HOMO} f_A^-. \qquad (24)$$

In keeping with the local version of the HSAB principle [34], the preferred sites of electrophilic replacement are those characterized by the maximal local hardness. The main argument in support of such definition of the local hardness is a good agreement between the calculated values and experimental data obtained in 1950s on the isomeric composition of the nitration, benzylation, chlorination, and sulfonation products of 21 benzene derivatives. This is the main advantage of the model proposed in [39] over analogous purely theoretical studies.

A similar positive tendency is characteristic of the model proposed by Clark et al. [51], which was tested on electrophilic alkylation of benzene derivatives and reactions of toluene with various electrophiles. A good correlation between the calculated values and experimental product ratios was obtained. Here, the key reactivity index is the Fukui overlap integral (FOI) which relates the reactivity information to the energetic quantities in terms of the transition state theory (Eq 25a). The corresponding expression involving the atomic constituents is given by Eq. (25b):

$$I_{tr} = \int [f_A^+(r) f_B^-(r)] \partial r; \qquad (25a)$$

$$I_{tr} = \sum_{j=1}^{N_A} \sum_{k=1}^{N_B} \int [f_{A,j}^+(r) f_{B,k}^-(r)] \partial r. \qquad (25b)$$

Here, the indices A and B refer to molecules, and *j* and *k*, to atoms. The Fukui overlap integral "measures the coincidence of electron donating regions on a nucleophile with electron accepting regions on the cor-

responding electrophilic reactant. Configurations with high values of this overlap integral tend to have lower density-functional theory energies." The procedure consists of searching for possible transition state configurations corresponding to possible reaction centers and choosing those for which the FOI value is the maximal. It implies less computational work than in the total transition state calculations: it is necessary to preliminarily calculate only the Fukui functions of the reagents, while the calculation of FOI is a simple computational task. The proposed method combines electronic structure calculations with force field calculations within a transition state theory framework and partially replaces the former by the latter. It is important that the method provides the possibility for taking into account steric effects due to fairly simple calculated criterion for exclusion of sterically unfavorable structures.

Electrophilic substitution reactions are well described using the electrophilic Fukui function and the new local hardness index [39], whereas none of the descriptors proposed till 2004 ensured appropriate regioselectivity pattern for nucleophilic attack. Therefore, Morell et al. [42] introduced a new descriptor which is generally used to estimate regioselectivity toward nucleophiles but is also suitable for electrophiles:

$$\Delta f(r) = f^+(r) - f^-(r) \approx \rho_{LUMO}(r) - \rho_{HOMO}(r). \qquad (26)$$

Its positive values characterize fragments preferred by nucleophilic attack, while negative values are typical of those at which nucleophilic attack is unfavorable. The descriptor takes values from −1 to +1. Its physical sense is change of the hardness upon variation of the external potential, as follows from Eq. (27):

$$\Delta f(r) = f^+(r) - f^-(r) \approx \left[\frac{\Delta(I-A)}{\Delta\upsilon(r)} \right]_N \approx \left[\frac{\Delta\eta}{\Delta\upsilon(r)} \right]_N. \qquad (27)$$

The proposed descriptor can be successfully used for analysis of regioselectivity in terms of the maximum hardness principle, for it is related to the global hardness through Eq. (28):

$$\Delta\eta = \int \Delta f(r)\Delta\upsilon(r)\partial r. \qquad (28)$$

Equation (28) makes it possible to estimate on a qualitative level variation of hardness in a certain molecular fragment with known $\Delta f(r)$ value, depending on the external electrostatic potential which is determined in turn by the charge on the reagent:

$$\delta\upsilon(r) = \frac{Z-N}{r^2}\partial r. \qquad (29)$$

Here, Z is the atomic charge, N is the number of electrons, and r is the distance from the reagent to the molecular fragment.

The efficiency of the proposed descriptor was confirmed by calculated diagrams of its spatial profile in benzonitrile, phenol, aniline, and benzaldehyde molecules, which showed qualitative consistence between the predicted directions of electrophilic attack and experimental data. The descriptor

$$\Delta s_k(r) = S(f_k^+ - f_k^-) = s_k^+ - s_k^- \qquad (30)$$

defined in a similar way was tested on a series of carbonyl compounds in comparison to the previously proposed s_k^+, s_k^-, and $s_k^r = s_k^+/s_k^-$ [41]; it conformed better to the relative reactivity of the carbonyl carbon and oxygen atoms, as well as of the α- and β-carbon atoms, toward electrophiles and nucleophiles.

An interesting approach was proposed in [25]; the global nucleophilicity was defined as

$$\omega^- = \omega_0^- + \delta\Delta E_{solv} = -I + \delta\Delta E_{solv}, \qquad (31)$$

where ω_0 is the first approximation of nucleophilicity, I is the ionization energy of nucleophile in the gas phase, and

$$\delta\Delta E_{solv} = \delta\Delta E_{solv}(N) - \delta\Delta E_{solv}(N-1) \qquad (32)$$

is variation of the energy of solvation of nucleophile upon abstraction of one electron; $\Delta E_{solv}(N-1)$ and $\Delta E_{solv}(N)$ are the energies of solvation of nucleophile itself and of the same nucleophile without one electron. Obviously, the effects of solvation on the proposed reactivity index are opposite for negatively charged and neutral nucleophiles, but the largest contribution to it is provided by ΔE_{solv} of a charged molecule. Good correlations between the experimental nucleophilicities N^+ [61] and ω^- values calculated by the above scheme were obtained for weak and medium-strength nucleophiles [H_2O, $NH_2CONHNH_2$, $CF_3CH_2NH_2$, NH_3, CH_3ONH_2, NH_2OH ($r = 0.94$)], as well as for strong nucleophiles [CH_3O^-, $C_2H_5S^-$, $C_3H_8S^-$, $HOCH_2CH_2S^-$, $C_6H_5S^-$, piperidine, morpholine ($r = 0.97$)]. Cyanide ion (CN^-) clearly fell out from both these series. The first approximation ω_0^- poorly reproduced the experimental data. The local

nucleophilicity was defined according to the usual scheme as $\omega_s^-(k) = -f_k^- I$, where I is the ionization energy; it ensured adequate relative nucleophilicity distribution over atoms of 18 nucleophiles, including the above groups.

While searching for a universal descriptor for any reaction type, Parthasarathi et al. [52], by analogy with the group softness (s_g^α) [53], proposed the concept of group philicity (ω_g)

$$\omega_g^\alpha = \sum_{k=1}^{n} \omega_k^\alpha, \qquad (33)$$

based on the generalized philicity [23, 24] (ω_k^α):

$$\omega_k^\alpha = \omega f_k^\alpha. \qquad (34)$$

Here, the superscript α takes the value "+," "–," or "0," depending on the reaction type [see Eq. (15)], $\omega = \mu^2/2\eta$, ω_k^α is the atomic philicity, and f_k^α is the atomic Fukui function. The new reactivity descriptor was tested on 11 carbonyl compounds and compared to the local nucleophilic softness, nucleophilic Fukui function and philicity, and relative softness [41]. The group nucleophilicity of a carbonyl carbon atom included its intrinsic atomic nucleophilicity and nucleophilicities of three neighboring atoms. The relative reactivity series obtained with the use of that reactivity descriptor were qualitatively consistent with the traditional views on the reactivity and substituent effects, while the other examined RIs gave rise to inappropriate pattern.

Ponti [54] made an attempt to create DFT-based regioselectivity criteria for cycloaddition reactions and introduced the term *atomic grand potential*. In keeping with the AIM theory, this reactivity index is the main thermodynamic quantity characterizing a molecule whose atoms are considered to be open systems [50].

$$\Omega = E - N\mu. \qquad (35)$$

Here, E is the energy, N is the number of electrons, and μ is the chemical potential. The atomic grand potential is related to the global and local softnesses through the following equations:

$$S = \left[\frac{\partial N}{\partial \mu}\right]_{\upsilon(r)} = \left[\frac{\partial^2 \Omega}{\partial \mu^2}\right]_{\upsilon(r)}; \qquad (36a)$$

$$s(r) = \left[\frac{\partial}{\partial \mu}\left[\frac{\partial \Omega}{\partial \upsilon(r)}\right]_\mu\right]_{\upsilon(r)}. \qquad (36b)$$

On the basis of these equations and the HSAB principle, the author formulated the principle of separate minimization of grand potential (SMGP) as some generalization of the HSAB principle. It implies that a reaction between molecules A and B is preferred if the following condition is met:

$$(\Delta\Omega_A)_{min} = (\Delta\Omega_B)_{min}; \; S_A = S_B, \qquad (37)$$

where S_A and S_B are the global hardnesses, and $\Delta\Omega_A$ and $\Delta\Omega_B$ are the variations of the grand potentials of molecules A and B in the reaction. In terms of local parameters, the SMGP principle is represented as follows:

$$(\Delta\Omega_{A,i})_{min} = (\Delta\Omega_{B,k})_{min}; \; s_{A,i} = s_{B,k}, \qquad (38)$$

where i and k are the numbers of the interacting atoms in molecules A and B, respectively. Obviously, it is impossible to predict exactly which atoms interact in a real case, and the local softness is not equalized between these atoms. Assuming that the contribution of charge redistribution after reaction is insignificant as compared to the charge transfer accompanying bond-forming process, the most favorable is bond formation between those atoms i and k in molecules A and B which give rise to minimal variation of the resulting grand potential:

$$\Delta\Omega_i^k = -1/2(\mu_A + \mu_B)^2 \frac{s_{A,i}s_{B,k}}{s_{A,i} + s_{B,k}}. \qquad (39)$$

The following regioselectivity criterion was formulated for a model interaction between molecules A and B [$A_1–A_2 + B_1–B_2$ or $A_1–A_2 + B_2–B_1$; here, A_1, A_2, B_1, and B_2 are arbitrarily different atoms (with respect to surrounding atoms) of molecules A and B, respectively, that participate in the cycloaddition]:

$$\Delta\Omega_{12}^{12} - \Delta\Omega_{12}^{21} = CPQ, \qquad (40)$$

where

$$C = 1/2(\mu_A + \mu_B)^2; \; Q = (s_{A,1} - s_{A,2})(s_{B,2} - s_{B,1});$$

$$P = \frac{s_{A,2}s_{B,1}s_{B,2} + s_{A,1}s_{B,1}s_{B,2} + s_{A,1}s_{A,2}s_{B,2} + s_{A,1}s_{A,2}s_{B,1}}{(s_{A,1} + s_{B,1})(s_{A,1} + s_{B,2})(s_{A,2} + s_{B,1})(s_{A,2} + s_{B,2})}.$$
$$\qquad (41)$$

Positive values of CPQ indicate preference of the first path, and the sign of CPQ is determined by the sign of Q provided that the local softness is positive. The proposed procedure is advantageous over the minimum local softness (MLS) principle for the anal-

ysis of more complex reactions than reactions involving diatomic molecules; it defines n in the expression for the regioselectivity criterion based on the MLS principle:

$$\Delta s_{ij}^{kl} = \left[\left| s_{A,i} - s_{B,k} \right|^n \left| s_{A,i} - s_{B,j} \right|^n \right]^{1/n}, \qquad (42)$$

where $n = \pm 1, \pm 2, \ldots$, depending on the reaction type.

A pseudothermodynamic approach was used in [55, 56] to describe chemical bonds and stability of molecules through the parameters *local electronic temperature* and *local entropy* $S_e(r)$, the latter being regarded as a pseudothermodynamic reactivity index:

$$S_e(r) = 3/2 \, k_B \rho(r) \left[\lambda + \ln \left| \frac{t[\rho(r)]}{t_{TF}[\rho(r)]} \right| \right]. \qquad (43)$$

Here, $t_{TF}[\rho(r)] = c_k \rho(r)^{5/3}$ is the kinetic energy of a homogeneous electronic gas, $t[\rho(r)] = 3/2 \rho(r) k_B \theta(r)$ is the local kinetic energy, $\rho(r)$ is the electron density, $\theta(r)$ is the local electronic temperature, and k_B is the Boltzmann constant. The mathematical formalism and pseudothermodynamic stability conditions were formulated in [55]. These theoretical statements were tested in [56] on a water molecule as an example by comparing the thermodynamic RI profiles with the electron density profile and the corresponding Laplacian and Fukui functions.

Some recent studies [57–59] were concerned with solvent effects on DFT-based RIs in combination with other methods; however, their detailed consideration falls beyond the scope of the present review.

Several attempts were recently made to build up universal electrophilicity [60–64] and nucleophilicity scales [60, 63]. The proposed models were usually tested on reactions involving diphenylmethyl cations [62, 64]. In this respect, the most illustrative is the approach described by Mayr et al. [60] who succeeded in obtaining a general experimental scale for cationic electrophiles and neutral nucleophiles using only three parameters: electrophilicity E, nucleophilicity N, and the slope parameter s which depends on the nucleophile nature:

$$\log k = s(N + E). \qquad (44)$$

The relation predicts with a good accuracy the kinetics of reactions of diphenylmethyl cations, diazonium salts, thiocarbenium and iminium ions, and prop-2-ynyl, Fe-tropyl, and Ps-allyl cations with σ-, π-, and n-nucleophiles (e.g., amino boranes), metal π-complexes, heteroarenes, and silyl enol ethers. The general parameters E were calculated by averaging the pair parameters E_{ij} from the kinetic data for a series of reactions, which depend (though to a small extent) on the selected electrophile–nucleophile couple.

$$E_i = \frac{1}{n} \sum_{j=1}^{n} E_{ij} = \frac{1}{n} \sum_{j=1}^{n} \left(\frac{\log k_{ij}}{s_j} - N_j \right). \qquad (45)$$

Here, n is the number of pair parameters involved in the description of electrophile. Seven large reaction series showed linear correlations between the calculated parameters E and Hammett substituent constants σ^+ ($r = 0.9986$). The Ritchie constant selectivity relationships

$$\log k = N_+ + \log k_0, \qquad (46)$$

where $\log k_0$ is the parameter depending on the electrophile, and N_+ is the parameter depending on the nucleophile, were subjected to criticism by Minegishi and Mayr [63]. As shown by the authors, these relationships contradict primarily the well established reverse relationship between the reaction rate and the selectivity. Comparison of Ritchie's equation (46) with Eq. (44) [63] revealed that this contradiction results from considerable variation of the additional nucleophile parameter s which is present in Eq. (46) in the implicit form. Treatment of the kinetic data for more than 150 reactions in terms of Eq. (44) (cf. [60]) gave good correlations and the corresponding parameters for 65 σ-, π-, and n-nucleophiles.

An important point is the existence of a correlation between the experimental parameters E from Eq. (44) for diphenylmethyl cations and the relative global ($\Delta \omega$, $r = 0.989$) and atomic ($\Delta \omega_k$, $r = 0.973$) electrophilicities (ω) referenced to bis(4-methoxyphenyl)-methyl cation (ω^0):

$$\Delta \omega_k = \omega_k - \omega_k^0; \quad \Delta \omega = \omega - \omega^0. \qquad (47)$$

Here, additivity of the atomic softness and electrophilicity was assumed, and the relations between the electrophilicity ω, local and global softnesses s_k^+ and S, local Fukui functions f_k^+, and chemical potential μ were employed:

$$\omega = \frac{\mu^2}{2\eta} = \frac{\mu^2}{2} S = \frac{\mu^2}{2} s_k^+ \sum_k \omega_k; \qquad (48)$$

$$\omega_k = \frac{\mu^2}{2\eta} s_k^+ = \frac{\mu^2 S}{2} f_k^+ = \omega_k f_k^+. \qquad (49)$$

Likewise, a correlation was obtained between the theoretical electrophilicity scale based on the local hardness ($\omega_k = \omega_k f_k^+$) and experimental values for diatomic halogen-containing molecules [64].

Relationships between the calculated reactivity indices and directly measurable parameters were represented in [65–69] as expressions formally resembling Hammett equations. On the basis of the DFT-defined chemical potential and local HSAB principle, Pérez et al. [65] succeeded in establishing a linear relation between local reactivity indices and experimental energy parameters of molecules using the following general equation:

$$\ln\left[\frac{\mu(N + \Delta N)}{\mu^\circ(N)}\right] = \rho\sigma = \gamma\sum_A \Delta f_A. \qquad (50)$$

Here, $\mu^\circ(N)$ is the chemical potential of the initial molecule, $\mu(N + \Delta N)$ is the chemical potential of the substituted molecule, N is the number of electrons in the initial molecule, ΔN is the change of the number of electrons upon substitution, Δf_A is the change of the Fukui function upon substitution, and γ is a parameter depending on the intrinsic substrate electronegativity and group charge capacity of the substituent.

In particular, the applications to the basicity of amines and acidity of alcohols and thiols in the gas phase are illustrated by good correlations between the experimental protonation energies (proton affinities, PA) of alkoxide (thiolate) ions or amines and local reactivity indices:

$$\ln\left[\frac{PA(RX^-)}{PA(CH_3X^-)}\right] = \rho\sigma = \rho s_X^-; \ X = S, O. \qquad (51)$$

$$\ln\left[\frac{PA(B)}{PA(B^0)}\right] = \rho\sigma = \rho\Delta f_N^-. \qquad (52)$$

Here, s_X^+ is the local hardness of the oxygen or sulfur atom in the corresponding alkoxide or thiolate ion, and Δf_N^- is the difference in the electrophilic Fukui functions of the nitrogen atoms in ammonia and substituted amine.

Equations (51) and (52) are analogous to the Hammett equations, but they relate the calculated numerical reactivity indices (which characterize electron density variation on the reaction center, depending on the substrate structure) to the experimentally measurable energy parameter, energy of protonation.

The inductive (electrostatic) and electronic (polarization) effects of substituents were related [66] to global changes in electronic chemical potential and variation of local softness on the reaction center upon substitution. The inductive effect was determined using Eqs. (53) and (54):

$$\Delta\rho_k = s_k\Delta\mu; \qquad (53)$$

$$\Delta\rho_k = f_k\Delta N, \qquad (54)$$

where s_k is the local softness, $\Delta\rho_k$ is the local change in electron density, $\Delta\mu$ is the change of the chemical potential, ΔN is the change of the number of electrons upon substitution, and f_k is the local Fukui function. The resonance effect is determined by Eq. (55)

$$\Delta s_k = t_k S\Delta\mu + f_k\Delta S = S\Delta f_k + f_k\Delta S, \qquad (55)$$

where Δs_k and ΔS are the changes in the local and global softnesses, respectively, in the substitution process.

$$t_k = \left[\frac{\partial f(\mathrm{r})}{\partial\mu}\right]_{\upsilon(r)} ; \ f_k = t_k\Delta\mu.$$

Analysis of the above relations in terms of the local HSAB principle led the authors to conclude that the sign of the corresponding effect is determined by the sign of the RI change. Taking into account the physical sense of the RIs involved, this conclusion is fully consistent with the classical views on electron density variations due to inductive and resonance substituent effects. The proposed model was tested on the same alcohol and thiol series as in [65]. The same approach was applied to multicenter amidine bases [67]. Analysis of the local Fukui function profiles and charges on atoms for 13 compounds unambiguously showed that the preferential protonation center in all the examined compounds is the imino nitrogen atom. The relations between the protonation energy and reactivity indices were described using Eq. (52) and analogous Eq. (56):

$$\ln\left[\frac{PA(B)}{PA(B^0)}\right] = \rho\Delta s_N^-, \qquad (56)$$

where $\Delta s_N^- = s_N^-(NH_3) - s_N^-(B)$ is the difference in the local softnesses of the imino nitrogen atom in a given base and the most basic imino nitrogen atom in the examined series of bases.

The correlation coefficients for Eqs. (51) and (56) were $r = 0.870$ and 0.894, respectively, after exclusion of two most complex structures. For five selected compounds, correlation coefficients r of 0.998 and 0.975,

respectively, were found. The authors presumed that protonation of the excluded members is accompanied by very strong reorganization of their molecular structure, leading to violation of the constant electrostatic potential condition which underlies the method.

Likewise, comparison of the local softnesses and local Fukui functions on the two potential protonation centers, amino (N^1) and imino (N^2), in the series of N^2-substituted N^1,N^1-dimethylformamidines showed [68] that the imino nitrogen atom is the preferred protonation center in all 16 compounds. This result is consistent with the relative energies corresponding to proton addition at two possible centers. The calculated protonation energies for real structures correlated with the experimental values with a coefficient r of 0.990; therefore, the authors used the calculated protonation energies for the analysis of hypothetical structures protonated at the amino nitrogen atom.

Galabov et al. [69] studied substituent effects on the reactivity of *para*-substituted *N*-phenylacetamides in alkaline hydrolysis. The rate-determining stage in this reaction is the addition of hydroxide ion. Therefore, search for optimal quantitative parameter of the substituent effect in the series consisting of 15 compounds was performed by analyzing correlations between the energy of activation of the rate-determining stage and various calculated and experimental parameters of the substrates. As the latter, the Hammett constants ($r = 0.946$), C=O stretching vibration frequencies ($r = 0.977$), electrophilicities according to Parr ($\omega = \mu^2/\eta$, $r = 0.974$), charges on the carbonyl carbon atom ($r = 0.967$), and electrostatic potentials on that atom ($r = 0.993$) were tested. Obviously, the latter parameter is the optimal descriptor for the substituent effect in the given series, which supports Politzer's concepts [70].

The existence of the above relations is a strong argument in support of appropriateness of both classical (including linear) correlation analysis models and quantum-chemical approaches based on reactivity indices, and it gives hopes that deeper and more general relations between their quantitative parameters will be found and that further development of these methods will be continued.

Eshermann et al. [71] introduced local descriptors based on Mulliken's electrostatic molecular surface potential within Politzer's concept [70] rather than on the principal DFT equations. The authors reasonably believe that the proposed approach is advantageous, for it operates with the electrostatic molecular surface potential which is an experimentally measurable quan-

tity [19], in contrast to the Fukui function and local reactivity indices considered above. On the other hand, they recognize that their model takes into account only electrostatic interactions and does not donor–acceptor interactions. The descriptors proposed in [71] are the local ionization energy

$$I_L = \sum_{i=1}^{HOMO} \frac{-\rho_i \varepsilon_i}{\rho_i}, \qquad (57)$$

local electron affinity

$$EA_L = \sum_{i=LUMO}^{N_{MO}} \frac{-\rho_i \varepsilon_i}{\rho_i}, \qquad (58)$$

local polarizability

$$\alpha_L = \sum_{j=1}^{N_{MO}} \rho_j^1 q_j \alpha_j^- \Big/ \sum_{j=1}^{N_{MO}} \rho_j^1 q_j, \qquad (59)$$

local electronegativity

$$\chi_L = \frac{IP_L + EA_L}{2}, \qquad (60)$$

and local hardness

$$\eta_L = \frac{IP_L - EA_L}{2}. \qquad (61)$$

In Eqs. (57)–(61), ρ_i is the electron density on the ith orbital in a given point, q_i is the orbital population, α_j is the isotropic orbital polarizability, N_{MO} is the number of molecular orbitals, and ε_i is the energy of the ith orbital. The authors involved the Koopmans theorem implying that the first ionization potential is equal to the HOMO energy; however, as shown in [12], this theorem is not always valid.

The proposed descriptors were tested by analysis of the corresponding three-dimensional profiles. It was shown that the relative reactivity of halomethanes in nucleophilic substitution is well described by the local electron affinity and that the use of local hardness is less appropriate. The reactivity of simplest di- and triatomic nucleophiles is reproduced best by joint consideration of the local ionization energy and hardness. The local ionization energy is also the best descriptor for the regioselectivity in electrophilic substitution in benzene derivatives. The local polarizability was recommended as reactivity index characterizing weak intermolecular interactions.

The main disadvantages of models based on reactivity indices are (1) the use of the isolated molecule

approximation which cannot rationalize, e.g., effects of the medium; (2) not clear physical sense of local parameters; (3) strong dependence of the calculation accuracy on the selected basis set [28–31]; and computational burden which restricts the application of these models to only simple molecules, while estimation of the reactivity and regioselectivity of just large and complex molecules is the most interesting from the practical viewpoint.

The main advantage of RI-based models for estimation of regioselectivity and reactivity of compounds is their pretension to universality, i.e., applicability to all groups of reagents and reaction series. However, the models considered above involve some inconsistency between the claimed goal (search for universal RIs) and methods for their testing. It seems that objects for testing are selected in such a way as to reflect apparent superiority of a new reactivity index over others for describing the reactivity. Complex structures whose reactivity is really difficult to predict on the basis of empirical rules and chemical intuition are considered only in a few cases. This tendency seems to be negative as compared to the approach employing first reactivity indices as early as 1980s. Studies performed at that period were based upon huge experimental data accumulated during several decades on the reactivity of structurally diverse compounds, and appropriate reactivity indices were selected among the existing ones and were then applied to estimate the reactivity of structurally related compounds. We believe that such application of RIs was more practical, though it had no such broad prospects as do modern approaches.

4. QUANTITATIVE STRUCTURE–PROPERTY RELATIONSHIPS (QSPR)

This methodology implies establishment of linear one- or multiparameter correlations between a target quantitative parameter of compounds (e.g., physical properties, biological activity, rate or equilibrium constant, etc.) with other calculated or experimental parameters of atoms, groups, or bonds in their molecules. The target parameter is always a quantity that can be determined experimentally, and the other parameter (descriptor) is usually calculated by quantum-chemical methods or defined as a complex function of some experimental properties and/or structural parameters of a molecule or its fragments. Here, quantum-chemical calculations are generally performed using the simplest semiempirical approximation, for the

QSPR approach is generally applied to describe complex molecules.

Despite low accuracy of the calculation and often unclear physical sense of descriptors, this empirical and simple approach [72–77] has become very popular in the recent time mainly for the prediction of physico-chemical properties and biological activity of compounds [72–74, 77]. Specificity of empirical methods is that most correlations used in practice lack physical sense, for many descriptors themselves make no physical sense, while empirical relations with other descriptors cannot be substantiated theoretically. Nevertheless, this method is extensively used for design of structures with required properties with the goal of synthesizing them subsequently.

In the framework of the present review it is important that the QSPR approach was successfully used to calculate the rate constants for electrophilic substitution in benzene derivatives [73], which showed a good correlation with the Hammett constants. The calculated superdelocalizability and activation hardness defined as the difference between the hardnesses of the initial molecule and transition state were used as descriptors. The method was also applied to the calculation of gas-phase acidity of benzoic acids on the basis of charges on atoms in the carboxy group, HOMO energies of the corresponding anions, and difference in the enthalpies of formation of the anions and acids. It was also used to predict rate constants for copolymerization of 30 various vinyl, acryl, and styrene monomers in all possible pair combinations [75]. The properties of the monomers were described by two complex functions involving resonance and polar effects and molecular graphs. The latter were optimized for a set including 40 monomers.

Katritzky et al. [77] calculated in terms of the QSPR approach rate constants and the Arrhenius equation parameters for $R^1R^2R^3C–CH_3$ bond dissociation in 58 compounds in the gas phase using five descriptors: LUMO energy, relative number of chlorine atoms in the $R^1R^2R^3C^{\cdot}$ radical, average valence of the central carbon atom therein, minimal bond order in $R^1R^2R^3C^{\cdot}$, minimal population of the atomic orbital, and maximal atom vibration frequency in the above radical.

The main advantage of the QSPR approach is that it makes it possible to predict the reactivity of complex molecules, regardless of their nature. Disadvantages of this method include its empirical character (like correlation analysis) and limited accuracy of prediction

for compounds falling out of the series for which appropriate descriptors were found. However, in such cases new descriptors ensuring a good correlation may be found for extended series with no need of performing additional experiments.

5. OTHER METHODS

Among other methods for prediction of reactivity, the most interesting is that based on the *no barrier theory* (NBT) [78]. This method may be regarded as generalization of the More O'Ferrall–Jencks diagrams [10] and the Marcus transition state theory [11] which are used to analyze potential energy surfaces of reactions. In terms of the NBT, *reactants* (or *reaction complex*) are assumed to be a combination of all species involved in the process (in keeping with the presumed mechanism), which occupies an intermediate place on the reaction coordinate between the initial compounds and reaction products. The principal postulates are the following:

(1) If a complex reaction includes only one elementary transformation, the energy barrier to the latter is equal to zero. Here, elementary transformations may be (a) bond rupture or bond formation not accompanied by change in the geometric structure of the reaction complex, (b) variation of bond angles therein, and (c) proton transfer between two atoms. Obviously, most reactions follow a complex mechanism including at least two elementary processes like those listed above. The coordinates of elementary reactions are transformed in such a way that they range from 0 to 1, namely via the equations $(r - r_0)/((r_1 - r_0)$ for bond length and $(\theta - \theta_0)/(\theta_1 - \theta_0)$ for bond angle, where the subscripts "0" and "1" denote the initial and final states, respectively, and the term with no index corresponds to the current state;

(2) Reactants are in equilibrium with starting material or product at each point along the reaction coordinate;

(3) For any process where only one elementary reaction coordinate changes, the energy will be a quadratic function of the corresponding reaction coordinate with the minimum at the lower energy end of the coordinate:

$$E = D_e\{1 - \exp[-\beta(r - r_0)]\}^2; \quad r_n = r_1 - \alpha \log(n), \quad (62)$$

where n is bond order, and r_n is the bond length.

For an overall chemical reaction involving two or more simple reaction dimensions, a two, three, four,...

dimensional diagram can be constructed, each edge of that diagram corresponding to a single elementary reaction whose coordinate changes from 0 to 1. Thus the main problem of searching for saddle point on the energy profile of the overall process (corresponding to the minimum activation energy) may be divided into the following subtasks: (1) calculation of the coordinates of the corners, i.e., of the energies of all possible intermediate states, and (2) search for the most favorable path on the potential energy surface with reference to the corners. The first subtask may be solved using the existing models, while the second is purely computational task. The proposed approach turned out to be appropriate for the description of hydroxide ion addition to carbonyl compounds, cyanohydrin formation, hydroxide ion abstraction from tertiary alcohols to give carbocations, and hydrolysis of phosphoric acid esters and alkyl halides. The error in the calculation of rate constants was less that 10%. Change of the reaction mechanism was predicted for the decarboxylation of β-keto acids in going from acetoacetate ion to acetoacetic acid.

An advantage of the no barrier theory is that it allows calculation of reaction rates for various compounds to be performed without invoking total quantum-chemical calculations. On the other hand, its application is possible when all possible elementary reaction mechanisms are known. In this case, rate constant ratios of alternative reactions can be estimated. The basic postulates are clearly substantiated from the physical viewpoint and rest upon well proved theories.

In the recent years, the molecular mechanics (MM) method, which is known since the middle of the XXth century, attracts attention due to the necessity of calculating very large biomolecules, conformational interactions of proteins and other related biochemical tasks [79, 80], and solvation effects [81], as well as of solving problems relevant to surface chemistry [82]. The MM method was popular at the early stage of development of computational methods, and it remains popular due to very low computational burden. In terms of MM, a molecule is considered to consist of elastic rods (bonds), force field centers (atoms), and electrical bond dipoles. The main procedure is optimization of the geometric structure by searching for potential energy minima and calculation of the external force field of the optimized fragment. The calculation employs parameters of atoms (polarizability, atomic radii, electrostatic potential profiles, etc.) and bonds (dipole moment, polarizability), which are determined preliminarily by high-precision nonempirical quantum-chem-

ical methods. Most of the listed parameters depend on the bond nature and hybridization of atoms.

Obviously, the MM method in its pure form is hardly suitable for simulation of bond formation or bond cleavage processes, i.e., those responsible for reactivity per se. Therefore, the main current trend in the application of MM is its combination with more precise quantum-chemical methods [81–83]. Nonempirical or semiempirical methods are used to calculate a molecular fragment (active center) in which formation of rupture of bonds occurs, while the effect of the rest of the molecule on that center is calculated by the MM method; in this case, an acceptable compromise between the accuracy of calculation and its cost is achieved. Thus the main problem intrinsic to modern approaches is proper separation of the scopes of the two methods and ensuring of continuous calculation potential in passing through their boundary [83–86]. For this purpose, procedures involving "frozen" orbitals, effective fragment potential, and virtual hydrogen atoms (acting as "plugs" for bonds at which the two methods are delimited) are used [83, 84].

Disadvantages of the MM method are the necessity of expensive preliminary computation of a large set of atom and bond parameters and their parameterization for different tasks. This is a specific compensation for strong simplification of the atom interaction model and calculation rate. Therefore, the role of MM as auxiliary method in the calculation of macromolecules is quite reasonable.

6. CONCLUSION

We can conclude that numerous methods for estimation of reactivity on the basis of quantum-chemical calculations of isolated molecules, their solvation, and energy profiles of reactions have been proposed so far. However, many of these methods are purely theoretical and involve complex mathematical operations; therefore, they may be interesting to specialists working in the field of quantum chemistry rather than to experimental organic chemists. Such methods were not included in the present review, and relevant data are covered by the recent comprehensive review [83].

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