# Quantum-Chemical Descriptors in QSAR/QSPR Studies

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## I. Introduction

Quantitative structure−activity and structure−property relationship (QSAR/QSPR) studies are unquestionably of great importance in modern chemistry and biochemistry. The concept of QSAR/QSPR is to transform searches for compounds with desired properties using chemical intuition and experience into a mathematically quantified and computerized form. Once a correlation between structure and activity/property is found, any number of compounds, including those not yet synthesized, can be readily screened on the computer in order to select structures with the properties desired. It is then possible to select the most promising compounds to synthesize and test in the laboratory. Thus, the QSAR/QSPR approach conserves resources and accelerates the process of development of new molecules for use as drugs, materials, additives, or for any other purpose.

While it is not easy to find successful structure−activity/property correlations, the recent exponential growth in the number of papers dealing with QSAR/QSPR studies clearly demonstrates the rapid progress in this area. To obtain a significant correlation, it is crucial that appropriate descriptors be employed, whether they are theoretical, empirical, or derived from readily available experimental characteristics of the structures. Many descriptors reflect simple molecular properties and thus can provide insight into the physicochemical nature of the activity/property under consideration.

Recent progress in computational hardware and the development of efficient algorithms has assisted the routine development of molecular quantum-mechanical calculations. New semiempirical methods supply realistic quantum-chemical molecular quantities in a relatively short computational time frame. Quantum chemical calculations are thus an attractive source of new molecular descriptors, which can, in principle, express all of the electronic and geometric properties of molecules and their interactions. Indeed, many recent QSAR/QSPR studies have employed quantum chemical descriptors alone or in combination with conventional descriptors.

Quantum chemistry provides a more accurate and detailed description of electronic effects than empirical methods.[1] Quantum chemical methods can be applied to quantitative structure−activity relationships by direct derivation of electronic descriptors from the molecular wave function. In many cases it has been established that errors due to the approximate nature of quantum-chemical methods and the neglect of the solvation effects are largely transferable within structurally related series; thus, relative values of calculated descriptors can be meaningful even though their absolute values are not directly applicable.[2] Moreover, electronic descriptors derived from the molecular wave function can be also partitioned on the basis of atoms or groups, allowing the description of various molecular regions separately.

Most work employing quantum chemical descriptors has been carried out in the field of QSAR rather than QSPR, i.e. the descriptors have been correlated with biological activities such as enzyme inhibition activity, hallucinogenic activity, etc.[3−6] In part this has been because, historically, the search for quantitative relationships with chemical structure started with the development of theoretical drug design methods. Quantum-chemical descriptors have also been reported to correlate the reactivity of organic compounds, octanol/water partition coefficients, chromatographic retention indices, and various physical properties of molecules.[7−11]

The present article reviews applications of quantum chemical descriptors in the development of QSAR/QSPR dealing with the chemical, physical, biochemical, and pharmacological properties of compounds.

## II. Quantum Chemical Methods

Methods based on classical molecular force fields and quantum-chemical methods are each capable of

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minimizing the potential energy of a molecular structure. Both approaches can be used for thermodynamic and dipole moment calculations but only quantum-chemical methods can estimate atomic $\sigma$ charges, molecular orbital energies, and the many other electronic descriptors of potential value to QSAR studies.[12]

In principle, quantum-chemical theory should be able to provide precise quantitative descriptions of molecular structures and their chemical properties. However, due to mathematical and computational complexities this seems unlikely to be realized in the foreseeable future. Thus, researchers need to rely on methods which, although approximate, have now become routine and have been demonstrated to provide results of real utility.

While the *ab initio* model Hamiltonian[8] provides a complete representation of all nonrelativistic interactions between the nuclei and electrons in a molecule, available solutions of the respective Schrödinger equations are necessarily approximate and the computational time is proportional to a high exponential ($N^4$, $N^5$) of the number of electrons in the molecule, $N$; thus, practical *ab initio* calculations are severely limited by the types of atoms and size of molecules.[13] However, even within these limitations molecules may be described by *ab initio* methods with some degree of reliability after an accurate search on the potential energy surface(s) has been carried out at a lower level of theory.[8] Most *ab initio* calculations have been based on the orbital approximation (Hartree−Fock method). In general, this method provides better results the larger the basis set (i.e. number of atomic orbitals) employed, although according to the variational principle this is strictly valid only for the total electron energy of the molecule.[14] Other electronic properties, particularly those describing electron distribution in the molecule (dipole and higher moment, partial charges on atoms), are less directly related to the size of the basis set,[15] and for such properties more attention has to be paid to the balance of the basis set used.[16]

A wide variety of *ab intio* methods beyond Hartree−Fock have been developed and coded to account for electron correlations in the molecule. These include configuration interaction (CI),[16−18] multiconfigurational self-consistent field (MC SCF),[19−21] correlated pair many-electron theory (CPMET)[22] and its various coupled-cluster approximations,[23−27] and perturbation theory (e.g. Møller−Plesset theory of various orders, MP2, MP3, MP4).[17,28,29] Most of these methods are extremely time consuming and require large CPU memories and are therefore impractical for the calculation of extended sets of relatively large molecules (i.e., more than 10 atoms).

As an alternative to *ab initio* methods, semiempirical quantum-chemical methods can be used for the calculation of molecular descriptors. These methods have been developed within the mathematical framework of the molecular orbital theory (SCF MO), but based on simplifications and approximations introduced into the computational procedure which dramatically reduce the computational time.[30,31] Experimental data on atoms and prototype molecular systems have often been used to estimate values of quantities used in the calculations as parameters. For this reason, these procedures are widely known as semiempirical methods.[30,31]

In principle, any semiempirical method can be used to calculate quantum chemical descriptors.[1] A number of semiempirical methods have been developed over the last several decades. To name but some of the most popular: extended Hückel theory (EHT), complete neglect of differential overlap (CNDO),[32,33] intermediate neglect of differential overlap (INDO),[34] modified INDO (MINDO),[35] modified neglect of diatomic overlap (MNDO),[36] Austin model 1 (AM1),[37] and parametric model 3 (PM3).[38] Descriptors calculated by different methods may have different significance in obtaining correlations[8] which strictly should be defined only within the framework of one particular method.[3]

The extended Hückel theory (EHT) is an extension of the Hückel $\pi$-electron approximation and treats all valence electrons in a molecule.[8] Overlap integrals are calculated over Slater-type atomic functions while electronic and nuclear repulsion are neglected; parameters for almost all types of atoms are available. This method is preferably used to describe qualitatively the electronic structure of molecular systems. Because of the neglect of important electronic interactions, the charge distributions deduced are often unrealistic.[8]

CNDO is the simplest (and most approximate) semiempirical method, involving the neglect of both diatomic and single-atom atomic orbital overlap.[32] The same principles apply to the improved version CNDO/2.[33] The CNDO approximation is incorrect in the sense that there is no justification to neglect single-atom differential overlap.[31] The INDO and MINDO procedures were developed as a compromise in which the one-center overlaps are retained in one-center integrals.[31,34,35]

MNDO,[36] AM1,[37] and PM3[38] are the methods based on the correct inclusion of one-center overlap (i.e. neglecting diatomic differential overlap only). The MNDO and AM1 methods have the advantages of relatively short computational times (compared with *ab initio* calculations) and the availability of parametrization for a variety of atoms (all the elements of the second period, halogens, Al, Si, P, S, Sn, Hg, and Pb). In contrast to MNDO, the AM1 method provides good descriptions even for anions and hydrogen bonded systems.[8,37] The MNDO method tends to overestimate electronic repulsion; electronic properties calculated by the MNDO method may well be less reliable than those calculated by the AM1 method.[13] Comparison of *ab initio* (STO-3G) and AM1 derived descriptors in the QSAR study of toxicity[39] suggests that the use of AM1 values instead of STO-3G values is completely acceptable and even desirable, given that AM1 calculations are obtained more rapidly. Further arguments in favor of employing AM1 molecular descriptors include notably the general observation that minimal basis set *ab initio* results are frequently inferior both to the more sophisticated extended basis set calculations and to semiempirical calculations.[39] In effect, AM1 semiempirical charges, dipoles, and bond lengths are more reliable than those obtained from low-quality *ab initio* methods.[39] Moreover, some reports demonstrate that the AM1 method can be used to calculate electronic effects which are difficult to deal with by *ab initio* methods.[13]

It has already been mentioned that while the results produced by different semiempirical methods are not generally comparable, they do often reproduce similar trends. For example, the net electronic charges calculated by the AM1, MNDO, and INDO methods are quite different in their absolute values, but consistent in their trends. The variation in the molecular orbital indices is generally largest for AM1 and diminishes in the order AM1 > MNDO > INDO.[40]

For additional background information on *ab initio* and semiempirical quantum chemical methods, as well as for a comparison of their applicability, readers are referred to a comprehensive, although now somewhat outdated, review by Loew and Burt.[243]

## III. Quantum Chemical Descriptors

Quantum-chemical methods and molecular modeling techniques enable the definition of a large number of molecular and local quantities characterizing the reactivity, shape and binding properties of a complete molecule as well as of molecular fragments and substituents. Because of the large well-defined physical information content encoded in many theoretical descriptors, their use in the design of a training set in a QSAR study presents two main advantages: (a) the compounds and their various fragments and substituents can be directly characterized on the basis of their molecular structure only; and (b) the proposed mechanism of action can be directly accounted for in terms of the chemical reactivity of the compounds under study.[41] Consequently, the derived QSAR models will include information regarding the nature of the intermolecular forces involved in determining the biological or other activity of the compounds in question.

Quantum-chemically derived descriptors are fundamentally different from experimentally measured quantities, although there is some natural overlap. Unlike experimental measurements there is no statistical error in quantum-chemical calculations. There is inherent error however, associated with the assumptions required to facilitate the calculations. In most cases the direction but not the magnitude of the error is known.[12] In using quantum chemistry-based descriptors with a series of related compounds, the computational error is considered to be approximately constant throughout the series. A basic weakness of quantum-chemical descriptors is the failure to directly address bulk effects.[12]

A summary of the most frequently used quantum-chemical descriptors is given in Table 1. Several reviews have been published on the application of quantum-chemical descriptors in QSAR, for example see refs 3 and 12 and references cited therein. The descriptors given in the table can be subdivided as follows:

**Atomic Charges.** According to classical chemical theory, all chemical interactions are by nature either electrostatic (polar) or orbital (covalent). Electrical charges in the molecule are obviously the driving force of electrostatic interactions. Indeed, it has been proven that local electron densities or charges are important in many chemical reactions and physico-

**Table 1. Quantum-Chemical Descriptors**[a]

| definition | name | ref(s) |
|---|---|---|
| | **Charges** | |
| $Q_A$ | net atomic charge on atom A | 7, 8, 13, 39, 41−44, 46, 55, 65, 68, 79, 82, 87, 98, 192, 195, 197, 198, 225 |
| $Q_{min}$, $Q_{max}$ | net charges of the most negative and most positive atoms | 1, 42, 236 |
| $Q_{AB}$ | net group charge on atoms A, B | 7, 40, 79, 190 |
| $\sum q_A^2$ | sum of squared charge densities on atoms of type A | 45 |
| $q_{E,A}$, $q_{N,A}$ | electrophilic and nucleophilic electronic charges calculated from the occupied and unoccupied orbitals, respectively | 7 |
| $Q_T$, $Q_A$ | sum of absolute values of the charges of all the atoms in a given molecule or functional group | 1, 9, 10, 40, 41, 225, 226, 235 |
| $Q_T^2$, $Q_A^2$ | sum of squares of the charges of all the atoms in a given molecule or functional group | 9, 10 |
| $Q_m$ | mean absolute atomic charge (i.e. the average of the absolute values of the charges on all atoms) | 42, 46 |
| | **HOMO and LUMO Energies** | |
| $\epsilon_{HOMO}$, $\epsilon_{LUMO}$ | energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals | 1, 7−9, 13, 39, 42−44, 46, 48, 50, 53, 55, 56, 65, 68, 69, 79−81, 83, 99, 100, 185, 186, 189, 191, 194, 196, 197, 225, 227−232, 234−238, 241, 242, 244−246 |
| $\epsilon_{HOMO,A}$, $\epsilon_{LUMO,A}$ | fraction of HOMO/LUMO energies arising from the atomic orbitals of the atom A | 1 |
| $\epsilon_{LUMO} - \epsilon_{HOMO}$ | HOMO and LUMO orbital energy difference | 1, 9, 41, 43, 53, 225, 235, 236 |
| $\eta = (\epsilon_{LUMO} - \epsilon_{HOMO})/2$ | absolute hardness | 47, 65 |
| $\Delta\eta = \eta_R - \eta_T$ | activation hardness, R and T stand for reactant and transition state | 47 |
| | **Orbital Electron Densities** | |
| $q_{A,\sigma}$, $q_{A,\pi}$ | $\sigma$- and $\pi$-electron densities of the atom A | 43, 193 |
| $Q_{A,H}$, $Q_{A,L}$ | HOMO/LUMO electron densities on the atom A | 51, 53, 80, 100, 232, 234, 244, 245 |
| $f_r^E = \sum (C_{HOMO,n})^2$ | electrophilic atomic frontier electron densities, $C_{HOMO,n}$ are the coefficients of the atomic orbital $X_n$ in the HOMO | 51, 55, 65, 188 |
| $f_r^N = \sum (C_{LUMO,n})^2$ | nucleophilic atomic frontier electron densities, $C_{LUMO,n}$ are the coefficients of the atomic orbital $X_n$ in the LUMO | 51, 55, 65, 185, 187 |
| $F_r^E = f_r^E/\epsilon_{HOMO}$<br>$F_r^N = f_r^N/\epsilon_{LUMO}$ | indices of frontier electron density | 3, 56 |
| | **Superdelocalizabilities** | |
| $S_{E,A}, S_{N,A} = 2\sum_j \sum_{m=1}^{N_A} (C_{jm}^A)^2/\epsilon_j$ | electrophilic and nucleophilic superdel ocalizabilities (sum over the occupied (E) or unoccupied (N) MO ($j$) and over the number of valence AO in the atom A ($m = 1, ..., N_A$)) | |
| $\sum S_{E,A}$, $\sum S_{N,A}$ | sums of electrophilic and nucleophilic superdelocalizabilities | 41, 42, 225, 235, 236 |
| | **Atom−Atom Polarizabilities** | |
| $\pi_{AA}, \pi_{AB} = 4\sum_i \sum_a \sum_p \sum_r \frac{C_{pi}^A C_{pa}^A C_{ri}^B C_{ra}^B}{\epsilon_i - \epsilon_a}$ | self-atom polarizabilities and atom−atom polarizabilities (sum over MOs ($i$,$a$) and over valence AOs ($p$,$r$)) | 1, 7, 42, 225 |
| $\sum \pi_{AA}$ | sum of self-atom polarizabilities | 41, 42, 225 |
| | **Molecular Polarizabilities** | |
| $\alpha$ | molecular polarizability | 53, 65, 226, 227, 236 |
| $\alpha = {}^1/_3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$ | mean polarizability of the molecule | 1, 41, 225 |
| $\beta^2 = {}^1/_2[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2]$ | anisotropy of the polarizability | 1, 41, 225 |
| $P = \sum_{A=1}^{N} \lvert Q_A \rvert / N$ | polarization of the molecule, sum of net atomic charges over all atoms in a molecule | 43 |
| $\alpha$ | polarizability tensor | 50, 236 |

**Table 1 (Continued)**

| definition | name | ref(s) |
|---|---|---|
| | **Dipole Moments and Polarity Indices** | |
| $\mu$ | molecular dipole moment | 1, 9, 10, 41−43, 46, 50, 53, 65, 68, 69, 186, 192, 197, 226, 234, 236 |
| $\mu_{char}$, $\mu_{hybr}$ | charge and hybridization components of the dipole moment | 65 |
| $\mu^2$ | square of the molecular dipole moment | 10, 41 |
| $D_X$, $D_Y$, $D_Z$ | components of dipole moment along inertia axes | 41, 42, 236 |
| $\Delta$ | submolecular polarity parameter (largest difference in electron charges between two atoms) | 48 |
| $T^E = \sum_{ij,i\neq j} \frac{\lvert q_i - q_j \rvert}{r_{ij}^2}$ | topological electronic index (sum of the absolute differences in electronic excess charges on all atomic pairs in a given molecule, divided by the squares of the respective interatomic distances) | 66 |
| $D = \sum_{A,B} \lvert Q_A - Q_B \rvert / N_{AB}$ | local dipole index, sum over all connected pairs of atoms | 42, 43 |
| $\boldsymbol{\tau}$ | quadrupole moment tensor | 50 |
| | **Energies** | |
| $E_T$ | total energy | 48, 66, 67, 236 |
| $E_b = \sum_i^N E_{A_i} - E_T$ | binding energy | 67 |
| $\Delta H_f^0$ | heat of formation | 9, 236 |
| $\Delta(\Delta H_f^0)$ | relative heat of formation | 8, 13, 237, 244, 245 |
| IP | ionization potential | 9, 41, 88, 240 |
| EA | electron affinity, difference in total energy between the neutral and anion radical species | 51, 81 |
| $\Delta E$ | energy of protonation, the difference between the total energy of the protonated and neutral forms | 68 |

[a] For other extensive lists of quantum-chemical descriptors see refs 41 and 225.

chemical properties of compounds. Thus, charge-based descriptors have been widely employed as chemical reactivity indices or as measures of weak intermolecular interactions. Many quantum-chemical descriptors are derived from the partial charge distribution in a molecule or from the electron densities on particular atoms.

Most modern semiempirical methods use Mulliken population analysis[14] for the calculation of the charge distribution in a molecule. In fact, this definition of atomic charge is arbitrary and other definitions are available, although none of them corresponds to any directly experimentally measurable quantity.[42] Moreover, semiempirical methods are mostly parametrized to reproduce heats of formation, ionization potentials, and/or geometric characteristics of the molecules. Therefore the calculated atomic charges may be less reliable. For these reasons the values of atomic charges calculated by different semiempirical methods are in sometimes poor agreement with each other. However, these numerical quantities are easy to obtain and they give at least a qualitative picture of the charge distribution in a molecule.[8]

Atomic partial charges have been used as static chemical reactivity indices.[3] The calculated $\sigma$- and $\pi$-electron densities on a particular atom also characterize the possible orientation of the chemical interactions and, thus, are often considered to be directional reactivity indices. In contrast, overall electron densities and net charges on atoms are considered as nondirectional reactivity indices.[43] The latter are obtained by subtracting the number of valence electrons belonging to the atom according to the classical valence concepts from the total electron density on the atom.[3] Such calculated net atomic charges are suitable for characterizing interactions according to classical point-charge electrostatic model.[44] Various sums of absolute or squared values of partial charges have been also used to describe intermolecular interactions, e.g. solute-solvent interactions.[9,10,45] Other common charge-based descriptors are the most positive and the most negative net atomic charges,[1,42] and the average absolute atomic charge.[42,46] Atomic charges are also used for the description of the molecular polarity of molecules.

**Molecular Orbital Energies.** Energies of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are very popular quantum chemical descriptors (see Table 1). It has been shown[47] that these orbitals play a major role in governing many chemical reactions and determining electronic band gaps in solids; they are also responsible for the formation of many charge-transfer complexes.[3,48] According to the frontier molecular orbital theory (FMO) of chemical reactivity, the formation of a transition state is due to an interaction between the frontier orbitals (HOMO and LUMO) of reacting species.[3,49] Thus, the treatment of the frontier molecular orbitals separately from the other orbitals is based on the general principles governing the nature of chemical reactions.[49]

The energy of the HOMO is directly related to the ionization potential and chracterizes the susceptibility of the molecule toward attack by electrophiles. The energy of the LUMO is directly related to the electron affinity and characterizes the susceptibility of the molecule toward attack by nucleophiles. Both the HOMO and the LUMO energies are important in radical reactions.[50,51] The concept of hard and soft nucleophiles and electrophiles has been also directly related to the relative energy of the HOMO/LUMO orbitals. Hard nucleophiles have a low-energy HOMO; soft nucleophiles have a high-energy HOMO; hard electrophiles have a high-energy LUMO; and soft electrophiles have a low-energy LUMO.[52]

The HOMO−LUMO gap, i.e. the difference in energy between the HOMO and LUMO, is an important stability index.[53] A large HOMO−LUMO gap implies high stability for the molecule in the sense of its lower reactivity in chemical reactions.[47] The HOMO−LUMO gap has also been used as an approximation to the lowest excitation energy of the molecule.[43] This concept, however, neglects the electronic reorganization in the excited state and therefore may often lead to conceptually incorrect results. The concept of "activation hardness" has been also defined on the basis of the HOMO−LUMO energy gap (see Table 1).[47,54] The activation hardness distinguishes between the reaction rates at different sites in the molecule and thus is relevant for predicting orientation effects.[47] The qualitative definition of hardness is closely related to the polarizability, since a decrease of the energy gap usually leads to easier polarization of the molecule.[54]

**Frontier Orbital Densities.** Frontier orbital electron densities on atoms provide a useful means for the detailed characterization of donor−acceptor interactions.[51,55] According to the frontier electron reactivity theory, the majority of chemical reactions take place at the position and in the orientation where overlap of the HOMO and LUMO of the respective reactants can reach a maximum.[49] In the case of a donor molecule, the HOMO density is critical to the charge transfer (electrophilic electron density $f_r^E$) and in the case of an acceptor molecule the LUMO density is important (nucleophilic electron density $f_r^N$).[3] These indices have been employed in QSAR studies to describe drug−receptor interaction sites.

However, frontier electron densities can strictly be used only to describe the reactivity of different atoms in the same molecule.[3,49] To compare the reactivities of different molecules, frontier electron densities have to be normalized by the energy of the corresponding frontier molecular orbitals: $F_r^E = f_r^E/\epsilon_{HOMO}$, $F_r^N = f_r^N/\epsilon_{LUMO}$. For example, the electron density of the HOMO at an atom is a measure of the relative reactivity of the HOMO at that atom within a single molecule, while the energy level of the HOMO reflects the relative reactivity of different molecules, thus molecules with smaller ionization potentials ($-\epsilon_{HOMO}$) are expected to be more reactive as nucleophiles.[56]

**Superdelocalizabilities.** A similar idea has been utilized in the definition of superdelocalizability,[49,57] which is an index of the reactivity of occupied and unoccupied orbitals (see Table 1). The superdelocalizability ($S_r$) on an atom r is, to some extent, related to the contribution made by atom r to the stabilization energy in the formation of a charge-transfer complex with a second molecule,[3] or to the ability of a reactant to form bonds through charge transfer.[58] This parameter is frequently employed to characterize molecular interactions[7,43,55] and can be used to compare corresponding atoms in different molecules.[43] Soft interactions are influenced by the ability to accept or donate electron density (superdelocalizability) through orbital rather than electrostatic charge transfer.[59]

A distinction is made between electrophilic and nucleophilic superdelocalizability (or acceptor and donor superdelocalizability respectively), the former describing the interactions with the electrophilic center and the latter describing the interactions with the nucleophilic center in the second reactant.[3,7,44] If the electrons of the frontier orbital predominate in those interactions, the one-orbital analog of superdelocalizability, i.e. the superdelocalizability calculated based only on the frontier orbital, can be used.[3,49]

Superdelocalizabilities are so-called dynamic reactivity indices.[3] While the static indices (e.g. charges) describe isolated molecules in their ground state, the dynamic indices refer to the transition states of the reactions.

**Atom−Atom Polarizabilities.** Self-atom and atom−atom polarizabilities ($\pi_{AA}$, $\pi_{AB}$) have also been employed to describe chemical reactivity.[1,7] These quantities are defined on the basis of perturbation theory and merely represent the effect of a perturbation at one atom on the electronic charge at the same ($\pi_{AA}$) or a different atom ($\pi_{AB}$).[7]

**Molecular Polarizability.** The polarization of a molecule by an external electric field is given in terms of the *n*th order susceptibility tensors of the molecular bulk.[60] The first-order term is referred to as the polarizability; the second-order term is called the first hyperpolarizability, etc. Thus, the most significant property of the molecular polarizability is the relation to the molecular bulk or molar volume.[53] Polarizability values have been shown to be related to hydrophobicity and thus to other biological activities.[61−63] Furthermore, the electronic polarizability of molecules shares common features with the electrophilic superdelocalizability.[64]

The first-order polarizability tensor contains information about possible inductive interactions in the molecule.[1,50,53,65,226] The total anisotropy of the polarizability (second-order term) characterizes the properties of a molecule as an electron acceptor.[1]

**Dipole Moment and Polarity Indices.** The polarity of a molecule is well known to be important for various physicochemical properties and many descriptors have been proposed to quantify the polarity effects. For example, molecular polarity accounts for chromatographic retention on a polar stationary phase.[10,226] The most obvious and most often used quantity to describe the polarity is the dipole moment of the molecule.[1,9,10,43,50] The total dipole moment, however, reflects only the global polarity of a molecule.

Local polarities can be represented by local dipole moments, but these are conceptually difficult to define. First approximations of these quantities can be obtained by considering the atomic charges in the localized regions of the molecule. The following charge based polarity indices have been proposed (see Table 1): the local dipole index,[43] the differences between net charges on atoms,[43,48] and the topological electronic index.[66] The quadrupole moment tensor can be also used as an index to describe possible electrostatic interactions. However, such tensors depend on the choice of the coordinate system and therefore the orientation of the molecular root fragment must be the same for all molecules in the series.[50]

**Energy.** The total energy calculated by semiempirical methods has been shown to be a good descriptor in a number of different cases.[8,9,48,67] For example, the total energy has been used as a measure of nonspecific interactions between a solute and stationary phase in gas-chromatography.[66] The reaction enthalpy can be accounted for by the difference in heats of formation between reactants and products or between conjugated species.[8,244,245]

The energy of protonation, defined as the difference between the total energies of the protonated and neutral forms of the molecule, can be considered as a good measure of the strength of hydrogen bonds (the higher the energy, the stronger the bond) and can be used to determine the correct localization of the most favorable hydrogen bond acceptor site.[68]

**Others.** The descriptors discussed above constitute the majority of quantum chemical descriptors published and successfully used in QSAR/QSPR studies. The following descriptors have also been proposed but do not fall into the above-mentioned categories: atomic orbital electron populations,[69] overlap populations,[50] vectors of lone pair densities,[50] partitioning of energy data into one-center and two-center terms,[50] and free valence of atoms.[55]

To our knowledge, the only previous systematic comparison of quantum-chemical (AM1) descriptors with both empirical and experimental descriptors was made by De Benedetti and co-workers.[41] Fifty theoretical (quantum-chemical and others) descriptors calculated for 50 monosubstituted benzenes were analyzed by the principal component analysis (PCA) and partial least-squares method (PLS).[41]

According to the PCA,[70] the substituent descriptors considered clustered into three main groups: (a) descriptors recording the substituent effects on the aromatic ring (net atomic charges, resonance and field substituent constants,[73,74] and substituent-induced chemical shifts[75]); (b) descriptors describing the bulk properties of the substituents (Verloop's steric parameters[76,77] and the molecular refractivity[73]) clustered together with theoretical descriptors defining the polarizability properties of substituents, the anisotropy of the molecular polarizability, dispersion interaction terms, and the electrophilic superdelocalizability of the substituents (the hydrophobicity parameter[73] is also close to this cluster); and (c) theoretical and experimental molecular and substituent dipole moments and their square terms.[41] The authors also noted that the descriptors are well spread in the principal component space.

PLS[71,72] analysis was performed to establish whether the theoretical molecular descriptors bear the same information content as the so-called physicochemical parameters. The conclusions from this analysis[41] were as follows:

(a) Substituent induced chemical shifts,[75] Hammett substituent constants,[76,77] and Taft and Swain−Lupton resonance constants[73,74] are modeled by the first component. The main contributions to the first component are from the net atomic charges on the carbon atoms, the electrophilic superdelocalizability of the benzene ring, and the energy of the frontier molecular orbitals.

(b) The molecular refractivity[73] and Verloop steric parameters[76,77] together with the molecular weight and substituent van der Waals volumes are modeled by the second component to which contributions are made mainly by the polarizabilities, dispersion forces, and substituent reactivity indices (superdelocalizabilities).

(c) The third component models the liphophilic[73] and lipophobic parameters.[78] The descriptors which contribute to this component are the solvent accessible surfaces of the substituents, the dipole moments, and their squared terms, and the HOMO/LUMO energy difference.

In a recent study Cocchi et al. compared the performance of quantum-chemical descriptors to model binding affinities of congeneric and noncongeneric $\alpha_1$-adrenoceptor antagonists.[225] According to their conclusions, MO-derived indices describing atom or local fragment properties, such as net atomic charges or frontier orbital electron densities, are often preferrable for congeneric series, while descriptors characterizing the molecule as a whole, such as molecular polarizability and size-shape descriptors, have wider applicability.[225] Significantly, the observed PCA clustering of 66 descriptors derived from the AM1 calculations was similar to that previously reported for the monosubstituted benzene series.[41]

## *IV. QSAR/QSPR Results*

### A. Biological Activities

Quantum-chemical descriptors have been long used in quantitative structure−activity relationship studies in biochemistry. In particular, net atomic charges, HOMO−LUMO energies, frontier orbital electron densities, and superdelocalizabilities have been shown to correlate with various biological activities. There are several extensive reviews on QSAR studies, see, for example, refs 3−6, and 12.

Linear regression analysis has provided good correlations between the CNDO/2 calculated total net ($\sigma + \pi$) atomic and group charges and anhydrase inhibition by heterocyclic sulfonamides.[79]

$$\log \Pi_{50} = 37.84 q_{SO_2NH_2} + 8.78$$

$$n = 28, \quad r = 0.909, \quad s = 0.336, \quad F = 123.2$$

$$\log \Pi_{50} = 119.74 q_O + 64.74$$

$$n = 28, \quad r = 0.899, \quad s = 0.364, \quad F = 109.3$$

where $q_{SO_2NH_2}$ is the charge of the -$SO_2NH_2$ group

and $q_O$ is the charge on the oxygen atom of the $SO_2$ group.

In a QSAR study on the mutagenicity of quinolines, the best correlation was found using AM1 calculated net atomic charges on carbon atoms ($q_2$) and the hydrophobic parameter (log *P*), although the HOMO and LUMO energies and electron densities were also considered:[82]

$$\log \text{TA100} = 1.14 \log P - 45.76q_2 - 5.39$$

$$n = 21, \quad r = 0.852, \quad s = 0.565, \quad F = 11.9$$

The involvement of the net atomic charge on carbon atom number 2 ($q_2$) suggests that the 2-position on the quinoline ring is the site of activation.

Significant correlations were found[51,80,81] between Ames TA100 mutagenicity and both the electron affinities (EA) or LUMO energies (i.e. the stability of the corresponding anion radical) of the molecules

$$\ln(\text{TA100}) = 12.53\text{EA} - 21.40$$

$$n = 5, \quad r = 0.9556$$

$$\ln(\text{TA100}) = -14.23\epsilon_{\text{LUMO}} - 13.39$$

$$n = 19, \quad r = 0.958, \quad s = 1.309$$

The correlations involving other AM1 electronic parameters of chlorofuranones were inferior, e.g. the correlation with the frontier electron densities of the LUMO at the α-carbon had $r = 0.8882$ only.

The correlations observed suggest a reaction mechanism in which chlorofuranones act as electron acceptors in the interaction with DNA. In general, the participation of frontier orbitals in mutagenic or carcinogenic activity seems to be essential, but most often it is almost entirely masked by the hydrophobicity.[81,245,246]

A good linear correlation was found between the calculated LUMO energy of the nitrogen atom of the nitro group and the logarithm of the mutagenicities of nitroarenes,[83] aromatic and heteroaromatic nitro compounds,[228,229] and polycyclic aromatic nitro compounds.[230,244] Analogous relationships were observed for aromatic and heteroaromatic amines, in which Ames TA98 and TA100 mutagenecities correlate linearly with the HOMO and LUMO energies of the amine.[231] Mutagenic activities of aryltriazenes and heterocyclic triazenes were found to be equally well correlated ($r = 0.919$ and $r = 0.931$) by a two parameter equation involving *logP* and either the HOMO energy or the electron density on the $sp^3$-hybridized N in the HOMO.[244,245] In another study, the carcinogenic and mutagenic potencies of benzanthracenes were shown to correlate with LUMO energies.[232]

Quantitative analysis of the antirhinoviral activity of 9-benzylpurines produced correlation equations involving Hückel MO generated electronic parameters and physicochemical properties of substituents.[55] For example, the following equation employs the LUMO energy and the total π-electron energy ($E^T_\pi$):

$$-\log \text{IC}_{50}(1\text{B}) = 6.044 + 2.056R_{\text{R2}} + 0.873F_{\text{R4}} - 0.289\pi_{\text{R4}} - 0.094E^{\text{T}}_{\pi} - 2.323\epsilon_{\text{LUMO}}$$

$$n = 50, \quad r = 0.827, \quad s = 0.503, \quad F = 19.00$$

where *R*, *F*, and π are physicochemical parameters of the corresponding substituents. However, it was determined that various serotypes of rhinovirus behave differently in terms of the electronic parameters that inhibit their action.

CNDO/2 calculated charges, in the form of the charge at the most highly charged atom in the molecule, and sizes, in the form of the smallest dimension of the molecule, have both been shown to be important descriptors in quantitative structure−activity relationships of some arylalkylamine and arylalkylamino acid activators of carbonic anhydrase:[42]

$$\log A = 0.4840Q_{\text{max}} - 0.0418L_{\text{y}} + 2.208$$

$$n = 19, \quad r^2 = 0.714, \quad s = 0.043, \quad F = 20.01$$

where $L_y$ is the length of an ellipsoid of uniform density (1.66 g/mL), with the same principal moments of inertia as the molecule.

The pharmacological activities of the 2-, 3-, and 4-mono derivatives of 1,4-dihydropyridine and para-substituted toluenes have been correlated with classical and various quantum-chemical (AM1) parameters such as net atomic charges, dipole moment, frontier orbital densities, and frontier orbital energies.[65,234] In the case of dihydropyridine derivatives, the 2- and 3-positions of the phenyl ring are affected by electronic parameters, and the correlation analysis resulted in the following equation:

$$\log(1/\text{IC}_{50}) = 0.56\pi - 3.4\epsilon_{\text{HOMO}} - 0.49L_{\text{m}} - 3.40B_{1,\text{p}} - 17.4$$

$$n = 35, \quad r = 0.91, \quad s = 0.61, \quad F = 35.85$$

where π is the Hansch hydrophobic constant, and $B_1$ and *L* are the Verloop sterimol parameters.[84] For substituted toluenes, it was found that the rate constant of hydroxylation can be described by a two-parameter expression involving the dipole moment, whereas binding free energies are well described by the combination of molecular volume with various frontier orbital parameters, such as the HOMO energy and greatest populations in the HOMO and LUMO for methyl group hydrogen atoms.[234]

Another QSAR study of a series of 8-substituted xanthines provided correlation equations between classical and MNDO calculated parameters and the affinity toward $A_1$ and $A_2$ adenosine receptors:[44]

$$\text{p}K_i(\text{A}_1) = 0.57\pi_8 - 2.06I_7 + 1.54I_{13} - 59.21q_1 - 17.02$$

$$n = 37, \quad r = 0.91, \quad s^2 = 0.32, \quad F = 37.66$$

$$\text{p}K_i(\text{A}_2) = 0.66\pi_8 - 0.47I_7 + 0.41\pi_1 + 61.57S_{\text{N},8} + 45.39q_3 + 5.90$$

$$n = 38, \quad r = 0.83, \quad s^2 = 0.35, \quad F = 14.17$$

where $\pi$ is the substituent hydrophobicity parameter, $I$ is the substituent indicator variable, $S_N$ is the donor superdelocalizability, and $q$ is the net atomic charge. According to the polyelectronic perturbation theory of Klopman and Hudson,[85] drug−receptor interactions are under either charge or orbital control. Thus, the net atomic charges characterize electrostatic interactions, while the donor superdelocalizability characterizes the covalent component of the interaction.[44]

The CNDO/2 calculated molecular polarizability ($\alpha$) and the HOMO/LUMO energy difference ($\Delta E$) have been successfully correlated with a number of biological activities (ethanol inhibition, rate of oxidative metabolism, and acute toxicity) in the series of 20 nitriles:[53]

$$-\log K_i = -1.25\alpha/\Delta E + 0.95$$

$$n = 13, \quad r = 0.76, \quad s = 0.282, \quad F = 15.3$$

$$\log \text{EtOH/glucose} = -0.006\alpha + 0.227$$

$$n = 20, \quad r = 0.79, \quad s = 0.046, \quad F = 30.5$$

$$-\log \text{LD}_{50} = -0.03\alpha + 0.43$$

$$n = 13, \quad r = 0.87, \quad s = 0.199, \quad F = 42.1$$

$$-\log \text{LD}_{50} = -1.69\alpha/\Delta E + 0.47$$

$$n = 13, \quad r = 0.87, \quad s = 0.199, \quad F = 42.4$$

The $\alpha/\Delta E$ parameter is an orbital energy weighted polarizability term and thus implies that the acute toxicity of nitriles is a function of molecular size/polarity and electronic activation energy.[53] However, the dipole moment does not correlate with the activity for this series, which suggests that the enzyme−substrate interaction may be of the second order.

An index of frontier orbital electron density derived from semiempirical molecular orbital calculations (MNDO-PM3) was found to correlate with fungicidal activity of $\Delta^3$-1,2,4-thiadiazolines.[56]

$$\text{pEC}_{50} = 0.42R(1) + 2.04$$

$$n = 7, \quad r = 0.94, \quad s = 0.17, \quad F = 39.46$$

$$\text{pEC}_{50} = 2.14R(1) - 0.18R(1)^2 - 1.91$$

$$n = 17, \quad r = 0.88, \quad s = 0.21, \quad F = 24.76$$

An index $R(1) = f_r(1)/(-\epsilon_{\text{HOMO}} \times 10^2)$ was derived from the HOMO electron density at the sulfur atom ($f_r(1)$) and the HOMO energy of the molecule ($\epsilon_{\text{HOMO}}$) in electronvolts measured from the zero level, which is equivalent to the ionization potential in MNDO-PM3 calculations.[56]

The acute toxicity of soft electrophiles such as substituted benzenes, phenols, and anilines has been correlated with MNDO calculated descriptors of soft electrophilicity for aromatics: average superdelocalizability and LUMO energy.[58]

$$\log(1/\text{LC}_{50}) = -1.49 + 0.56 \log P + 13.7S_{\text{av}}^{\text{N}}$$

$$n = 114, \quad r^2 = 0.81, \quad s^2 = 0.19, \quad F = 238.7$$

The average acceptor superdelocalizability $S_{\text{av}}^{\text{N}}$ was obtained by averaging the sum of $S_i^{\text{N}}$ over the atoms involved in the $\pi$ bonds. The hydrophobicity (log $P$) and soft electrophilicity descriptors were shown to be orthogonal for the 114 compounds studied.[58]

A significant correlation was obtained between the inhibition potency of indanone−benzylpiperidine inhibitors of acetylcholinesterase and the MNDO HOMO energy:[69]

$$-\log(\text{IC}_{50}) = 2.21C_4 - 6.65\mu + 1.18\mu^2 - 162.9\epsilon_{\text{HOMO}} - 8.58\epsilon_{\text{HOMO}}{}^2 - 757.52$$

$$n = 16, \quad r = 0.939, \quad s = 0.25, \quad F = 14.8$$

where $C_4$ is the HOMO out-of-plane $\pi$-orbital coefficient of the ring carbon atom, $\mu$ is the total dipole moment. The inhibition potency of charged sulfonamide inhibitors of carbonic anhydrase has also been correlated with the HOMO energy, positive charge on the pyridinium ring, and anisotropic polarizability.[235]

The dissociation constants of $\beta$-adrenergic active compounds were found to be governed mainly by the CNDO/2 calculated total anisotropy of polarizability which characterizes the properties of the molecule as an electron acceptor.[1]

Overall, the importance of quantum-chemical descriptors in QSAR studies is well recognized, e.g. see refs 3−6, 12, and 243. However, quantum-chemical parameters can easily be misused, e.g. led to chance correlations,[247,248] or misinterpreted. In some cases, a quantum-chemical descriptor has appeared to be important due to a high correlation with a conventional descriptor, such as hydrophobicity or a Hammett constant, whereas the latter would be more appropriately used on other considerations.[249]

## B. Chemical Reactivities

The gas-phase acidity of substituted benzoic acids was related linearly with the AM1 calculated net charges on the oxygen atoms, with the energies of the highest occupied molecular orbital (HOMO) of the corresponding benzoate anions, and with the differences in heats of formation between the acids and their anions.[13]

$$\Delta(\Delta G^0) = -316.431\sum q_0 - 359.217$$

$$n = 14, \quad r = 0.981, \quad F = 302.8, \quad s = 0.853$$

$$\Delta(\Delta G^0) = 17.328\epsilon_{\text{HOMO}} + 81.891$$

$$n = 14, \quad r = 0.978, \quad F = 261.8, \quad s = 0.915$$

$$\Delta(\Delta G^0) = 0.887\Delta(\Delta H_f^0) - 0.396$$

$$n = 14, \quad r = 0.985, \quad F = 387.2, \quad s = 0.758$$

Analogous relationships were found in a related study: the AM1 calculated energy differences between the acids and their conjugate bases and the anion HOMO energies correlate satisfactorily with the experimental (condensed phase) acidity of phenols and of aromatic and aliphatic carboxylic acids.[8]

The best correlation employed four descriptors and included calculated atomic charge densities.

$$pK_a = 33.74d_{11} - 13.01d_1 + 0.16H_f + 0.12\epsilon_{HOMO}$$

$$n = 183, \quad r^2 = 0.88, \quad s = 1.01$$

where $d_1$ and $d_{11}$ are the atomic charges on acidic oxygen atoms in the acid and anion, respectively. The natural logarithm of the rate of glutathione S-transferase-catalyzed conjugation of the series of fluoronitrobenzenes also correlates with the LUMO energy and with the relative heat of formation of the Meisenheimer complex.[237]

Superdelocalizabilities, calculated by the CNDO/2 method, give good predictive correlations of the Hammett constants of aromatic compounds.[7]

$$\sigma = 8.599 - 1.417S_{N,C}$$

$$n = 13 \text{ (simple aromatics)}, \quad r = 0.864$$

$$\sigma = 3.090 + 1.565S_{E,C}$$

$$n = 25 \text{ (substituted benzenes)}, \quad r = 0.868$$

$$\sigma = 2.812 + 2.500S_{E,O_1}$$

$$n = 19 \text{ (benzoic acids)}, \quad r = 0.900$$

$$\sigma = 1.051 + 7.591S_{E,N}$$

$$n = 19 \text{ (phenyl amines)}, \quad r = 0.863$$

It was proposed that superdelocalizability apparently includes both electrostatic and perturbational effects, i.e. the density of electrons at an atom and a measure of their instability.

The activation hardness, calculated from Hückel MO theory (see Table 1), is an excellent index for predicting orientation effects.[47] Activation hardness, defined as the difference between the absolute hardness of the reactant and transition state, was used to predict successfully orientations in electrophilic aromatic substitutions. In general, the reaction coordinate is such that changes in the HOMO−LUMO gap, or hardness, are minimized.

## C. Partition Coefficients

The octanol/water partition coefficient (log $P$) is the standard quantity to characterize the hydrophobicity/hydrophilicity of a molecule, a property of major importance in biomedical applications. Over the years a number of procedures have been proposed for calculating partition coefficents from the molecular structure, see, for example ref 86.

Atomic charge densities has been proposed as the basis for calculating octanol/water partition coefficients.[45] The method is based on the linear correlation equation obtained for the set of 61 compounds including hydrocarbons, alcohols, ethers, ketones, acids, esters, amines, nitriles, and amides. The equation employs sums of squared atomic charge densities calculated by the MINDO/3 procedure:

$$\log P = 0.344 + 0.2078N_H + 0.093N_C - 2.119N_N - 1.937N_O - 1.389\sum q_C^2 - 17.28\sum q_N^2 + 0.7316\sum q_O^2 + 2.844N_A + 0.910N_T + 1.709N_M$$

$$n = 61, \quad r^2 = 0.985, \quad s = 0.15$$

where $N_H$, $N_C$, $N_N$, and $N_O$ are the number of hydrogen, carbon, nitrogen, and oxygen atoms, $q_C$, $q_N$, and $q_O$ are the corresponding atomic charges, and $N_A$, $N_T$, and $N_M$ are the numbers of carboxy, cyano, and amido groups. The method yields better results than the fragment approach and requires fewer parameters.

In another study, the above-mentioned approach has been extended by involving more molecular descriptors including the calculated dipole moment, the sums of absolute values of atomic charges and the charge dispersions.[9,87] All quantum chemical parameters were calculated using the AM1 procedure and regression equations were extended to a larger set of partition coefficient data.

$$\log P = -1.167 \times 10^{-4}S^2 - 6.106 \times 10^{-2}S + 14.87O^2 - 43.67O + 0.9986I_{alkane} + 9.57 \times 10^{-3}M_w - 0.13D - 4.929Q_{ON} - 12.17Q_N^4 + 26.81Q_N^2 - 7.416Q_N - 4.551Q_O^4 + 17.92Q_O^2 - 4.03Q_O + 27.273$$

$$n = 118, \quad r = 0.9388, \quad F = 115.1$$

where $S$ is the molecular surface, $O$ is the ovality of the molecule,[9] $I_{alkane}$ is the indicator variable for alkanes, $M_w$ is the molecular weight, $D$ is the calculated dipole moment, $Q_{ON}$ is the sum of absolute values of atomic charges on nitrogen an oxygen atoms, $Q_N$ is the square root of the sum of the squared charges on nitrogen atoms, and $Q_O$ is the square root of the sum of the squared charges on oxygen atoms. The predictive power of the model has been demonstrated by the accurate estimation of log $P$ for complex molecules.

A model has been derived to estimate log $P$ of substituted phenols, which includes molecular mass, melting point, charge on the oxygen atom, energies of HOMO and LUMO, molecular volume, total surface area, refractivity, and polarizability.[241]

## D. Chromatographic Retention Indexes and Response Factors

It is generally accepted that chromatographic retention of a compound on a polar stationary phase depends on the polarity of the compound, which has been expressed in terms of dipole moment, polarizability, net atomic charges, and energy parameters.[48,66,226,227]

The gas chromatographic retention indexes of 43 mono- and bifunctional molecules on four stationary phases of different polarity were best described by a combination of topological and quantum chemical (QA, QA2, and QT2) parameters.[10] These quantum

chemical parameters represent different sums of CNDO/2 calculated atomic charges (see Table 1) and account for both the local (QA, QA2) and global polarities (QT2) of the molecules. By means of factor analysis, it was shown that these parameters are more closely related to the retention indexes on polar stationary phases than simple or squared dipole moments.

The total energy ($E_T$) or binding energy ($E_b$) for a homologous series of esters were both shown to give straight line correlations with the gas chromatographic retention indexes for both nonpolar and polar stationary phases.[67] The energies $E_T$ and $E_b$ had been calculated by CNDO/2 method. As the polarity of the stationary phase increases, a greater differentiation between the homologous series appears.

In another study, a two-parameter regression equation was derived which satisfactorily describes the retention of structurally different polar solutes on a relatively non-polar stationary phases.[48] The equation involves the CNDO/2 calculated total energy ($E_T$) and the originally proposed submolecular polarity parameter ($\Delta$, see Table 1).

$$I_{OV\text{-}101} = 301.88 - 11.66E_T - 1016.80\Delta$$

$$n = 22, \quad r = 0.93, \quad s = 67.45$$

According to these authors, the total energy represents a bulk measure of the solute's ability to participate in nonspecific interactions with the stationary phase, while the submolecular polarity parameter is a measure of the solute's ability to take part in polar solute-stationary phase interactions.

To characterize differences in polar properties of molecules, a topological electronic index $T^E$ has been proposed (cf. Table 1).[66] This index is calculated as the sum of the absolute differences in excess electronic charges on all atomic pairs in a given molecule, divided by the squares of the respective interatomic distances. The topological electronic index, in combination with the total energy, provides a better regression equation for the retention data of a diverse group of aliphatic and heterocyclic amines.[66]

$$I_{OV\text{-}101} = 160.6 - 13.39E_T - 149.6T^E$$

$$n = 22, \quad r = 0.981, \quad s = 35.29$$

The ionization potential, calculated by MOPAC (AM1), was found to be the most suitable property to adjust the capacity ratios (liquid chromatography retention) of polychlorobenzenes, polymethylphenols, and polychlorophenols.[88]

Good six-parameter correlations have been obtained with nonpolar stationary phase retention times and response factors for a set of 152 diverse organic compounds ($R^2 = 0.959$ and $R^2 = 0.829$, respectively) using a combination of conventional and AM1 calculated quantum-chemical descriptors.[89]

$$t_R = 26.5 - 6.9N_{CH} - 0.87S^T/N + 0.046\alpha + 0.019M_w - 21.55V_{H,min} + 0.93AOP_{max}$$

$$n = 152, \quad R^2 = 0.959, \quad s = 0.515$$

$$RF = -2.33 + 10.96RW_{C_{eff}} - 0.0003E_{EE}^T - 1.16RN_{C_{eff}} - 0.21b_{C,min} + 3.32V_{H,min} - 0.03\mu_{hybr}$$

$$n = 152, \quad R^2 = 0.892, \quad s = 0.054$$

where $N_{CH}$ is the relative number of C−H bonds, $S^T/N$ is the total entropy of the molecule at 300 K divided by the number of atoms, $\alpha$ is the polarizability, $M_w$ is the molecular weight, $V_{H,min}$ is the minimum valency of a H atom, $AOP_{max}$ is the maximum atomic orbital electronic population, $RW_{C_{eff}}$ is the relative weight of "effective" C atoms, $E_{EE}^T$ is the total molecular one-center electron-electron repulsion energy, $RN_{C_{eff}}$ is the relative number of "effective" C atoms, $\mu_{hybr}$ is the total hybridization component of the molecular dipole; and $b_{C,min}$ is the minimal total bond order of a C atom. The most significant quantum-chemical descriptors correlated with the retention times are the molecular polarizability (characterizing molecular bulk and dispersion interaction with the media) and the minimum valency of a hydrogen atom (related to hydrogen bonding interactions).[89] The response factors are correlated by the minimum total bond order of a carbon atom and the total molecular one-center electron−electron repulsion, which reflect the inclination of the thermally cracked products to undergo "chemiionization" in the flame ionization detector of the chromatograph.

## E. Other Physicochemical Properties

Although numerous attempts have been made to correlate physical properties of organic compounds (particularly boiling point) with structural parameters,[90−96] there are very few papers employing quantum chemical descriptors for this purpose.

An approach for the estimation of several physical properties of organic compounds (critical temperature, molar critical volume, boiling point) based on the computation of the molecular surface interactions (MSI) has been proposed.[97] This approach employs MSI descriptors calculated from atomic surface areas and EHT net atomic charges. For instance, the following correlation equation has been proposed for the boiling point:

$$BP = 127.7 + 0.718A - 1.015A_- + 0.230A_+ + 8.800A_{HB}$$

$$n = 137, \quad r = 0.979, \quad F = 745.1, \quad s = 14.1$$

where $A$ is the total molecular surface area; $A_-$ is the sum of the surface areas of negatively charged atoms multiplied by their corresponding scaled net atomic charge; $A_+$ is the sum of the surface areas of positively charged atoms multiplied by their corresponding scaled net atomic charge; $A_{HB}$ is the sum of the surface areas of hydrogen-bonding hydrogen atoms multiplied by their corresponding scaled net atomic charge. This equation was derived from the theoretical principle that many bulk properties of liquids are driven by the intermolecular interactions which can be expressed through the molecular surface energy.[97] The latter can be presented as a sum of dispersion

interactions (proportional to the molecular surface area $A$), polar interactions (related to the first-order term of the electrostatic interactions $A_-$ and $A_+$), and hydrogen bonding interactions ($A_{HB}$).

Remarkably, results similar to mentioned above were obtained in independent correlations of boiling points, melting points, and flash points of substituted pyridines.[11] Hydrogen-bonded related surface areas of the molecules were found to correlate with all three properties, while polar interactions were represented by dipole moment components in these correlations. For example, the following six parameter correlation equation was derived for boiling points:

$$\mathrm{BP} = -247.4 + 0.278G_i + 19.25\mu_{char} + 1713.2S_{FHA} + 136.1b_{N,min} - 26.62S_{RN} + 2503.4\bar{f}^{N}_{r,N}$$

$$n = 85, \quad R^2 = 0.943, \quad F = 214.5, \quad s = 14.5$$

where $G_i$ is the gravitation index; $\mu_{char}$ is the total point-charge component of the molecular dipole; $S_{FHA}$ is the fractional hydrogen acceptors surface area; $b_{N,min}$ is the minimal total bond order of a nitrogen atom; $S_{RN}$ is the relative negatively charged surface area; and $\bar{f}^{N}_{r,N}$ is the average nucleophilic reactivity index for a nitrogen atom. All the descriptors involved, except the gravitation index, were calculated by the AM1 method. Charged surface areas were calculated from net atomic charges derived by AM1.

## F. Substituent Constants

The theoretical analysis of various empirical substituent constants related to intramolecular inductive, resonance, or steric effects, in terms of the quantum-chemical characteristics of the molecules has been of substantial theoretical and pragmatic interest. Already Jaffe[101−103] found that the values of Hammett $\sigma$-constant were linearly related with the $\pi$-electron densities on the respective substituents. Another linear relationship was reported early on between the $\sigma$-constants and $\pi$-electron localization energies.[104] The development of the concept of the electronic substituent effects has been extensively reviewed,[105−110] and we therefore consider here only those studies of direct correlations of empirical substituent constants ($\sigma$, $\sigma_I$, etc.) with quantum-chemical characteristics of the corresponding substituents or molecules. The operational value of such correlations lies in the possible extension of known correlations involving conventional electronic substituent constants to compounds for which such constants are unknown or difficult to define.

The Hammett $\sigma$ [111] and Taft $\sigma^o$ [112,113] constants were examined using the MNDO[114] quantum-chemical characteristics of a series of benzoic acids and benzoate anions.[115] The most significant correlation ($r$ = 0.921; $S$ = 0.17; $n$ = 18) for $\sigma$ was with the calculated electronic charge on the oxygen of the anion ($q_O-$). A nearly equally good linear correlation for $\sigma$ ($r$ = 0.899; $S$ = 0.19; $n$ = 18) was observed with the reciprocal of the highest occupied molecular orbital energy ($1/\epsilon_{HOMO}$) of the corresponding substituted benzoate anion. Since $\sigma$ and $\sigma^o$ are well correlated with each other, it was not surprising that $\sigma^o$ also regressed well against the same two parameters although the preferred parameter was $1/\epsilon_{HOMO}$:

$$\sigma^o = 34.38(1/\epsilon_{HOMO}) + 7.87$$

$$r = 0.946 \quad S = 0.12 \quad n = 18$$

These correlations indicate that the Hammett and Taft constants for substituted benzenes and also the equilibrium constants for the ionization of substituted benzoic acids are controlled by the anion structure. An analogous result was obtained using ab initio calculations with STO-3G basis sets augmented by diffuse functions for all oxygen atoms.[116] The correlations obtained are remarkably good, considering the neglect of solvation effects which are known to be of considerable importance in acid-base equilibria.[108] However, from electrostatic considerations, both $\epsilon_{HOMO}$ and $q_{O^-}$ can be considered as the "enthalpic" descriptors and therefore, as the ionization equilibria of carboxylic acids is known to be an isoentropic reaction series, the correlation of the p$K_a$ with this type of molecular characteristics is not completely unexpected. Notably, AM1 calculated partial charges on the oxygen atom $q_O-$ of benzoate anions correlate even better with a somewhat different set of Hammett $\sigma$-constants.[117] Good correlations of the inductive substituent constants with more elaborate enthalpic (energetic) descriptors have also been reported. P. Politzer et al.[118,119] invented the average local ionization energy ($\bar{I}(\mathbf{r})$) of a molecule as useful characterstics of atomic energetic properties in molecule. It was defined as the average energy required to remove an electron from any point **r** or region d**r** in the molecule. An excellent correlation was found between the lowest of $\bar{I}(\mathbf{r})$ value, $\bar{I}_{s,min}$ on a ring carbon atom of a monosubstituted benzene and Hammett $\sigma$-constant.[120] A good relationship was also demonstrated to exist between the $\bar{I}_{s,min}$ for the conjugated bases of substituted acetic acids and the inductive substituent constants $\sigma_I$:[120]

$$\sigma_I = -3.6467 + 0.4962\bar{I}_{s,min}$$

$$r = 0.97$$

In conclusion, despite numerous attempts to ascribe definite physical meanings to empirical substituent constants through secondary (multi)linear correlation analysis with quantum-chemically derived molecular descriptors, a comprehensive theoretical treatment of these constants is still absent. Notably, these empirical constants may possess substantial entropic components and thus in principle cannot be described solely by essentially energetic quantum-chemical descriptors (cf. also discussion in section V).

## G. Solvational Characteristics

The solvent effects play a key role in many chemical and physical processes in solution, and therefore it has been of the highest interest to develop quantitative structure property/activity relationships which reflect intermolecular interactions in dense media. Because of the complexity of solvent effects, such QSAR/QSPR correlation equations are usually multiparametric, involving descriptors corresponding (1)

to the polarity and the polarizability of the solvent, (2) to the solvent's ability to act as a hydrogen bond acceptor or donor, and (3) to short-range dispersion and repulsion interactions.[121] Indeed, the log *P* hydrophobicity parameter discussed above can also be considered as a solvational characteristic since it is directly related to the change of the free energy of solvation of a solute between two solvents (water and octanol).

The linear solvation energy relationship (LSER) descriptors based on LFER (linear free energy relationships) are demonstrated to be successful in correlating a wide range of chemical and physical properties involving solute−solvent interactions as well as biological activities of compounds.[122,123] The coefficients of the descriptors in the correlation equation are expected to provide insight into the physical nature of the solute−solvent interactions related to the experimentally observed plenomena or data. The original LSER descriptors (also called the solvatochromic descriptors) were derived from UV−vis spectral shifts of indicator dyes. Thus their ability to make *a priori* predictions has been somewhat limited because of their empirical origin. Although there exist tables of LSER parameters and predictive relationships to help in their estimation, LSER descriptors for new materials are not easily defined. Attempts to correlate computationally derived structural and electronic descriptors with the solvatochromic parameters have met with only moderate success.[124]

In an attempt to circumvent the problems associated with the LSER parameters, Famini and coworkers have developed a new set of computationally derived descriptors, called the theoretical LSER (TLSER).[125,126] The TLSER attempts to maintain the same relationship between property and parameters, that is, they incorporate steric, polarizability, and hydrogen bonding terms. However, each of these terms has been derived from semiempirical molecular orbital methods, permitting a much greater degree of *a priori* prediction once a correlation is derived, than does LSER. Like LSER, TLSER uses a single set of descriptors (six for the TLSER) and each parameter describes a single, orthogonal molecular event or characteristics.

The most general form of TLSER is as follows[126]

$$\log(\gamma) = c_o + c_1 V_{mc} + c_2 \pi^* + c_3 \epsilon_a + c_4 \epsilon_b + c_5 q^+ + c_6 q^-$$

where $V_{mc}$ is the molecular van der Waals volume calculated according to the method of Hopfinger,[127] and the polarizability term $\pi^*$ is derived from the polarization volume computed by the method of Kurtz.[128] The hydrogen-bonding effects are separated into donor and acceptor components. The covalent contribution to Lewis basicity, $\epsilon_b$, is represented as the difference in energy between the lowest unoccupied molecular orbital ($\epsilon_{LUMO}$) of water and the highest occupied molecular orbital ($\epsilon_{HOMO}$) of solute. The electrostatic basicity contribution, denoted as $q^-$, is simply the most negative atomic charge in the solute molecules.

Analogously, the hydrogen-bonding donating ability is divided into two components: $\epsilon_a$ is the energy difference between the $\epsilon_{HOMO}$ of water and $\epsilon_{LUMO}$ of solute, whereas $q^+$ is the most positive charge of a hydrogen atom in the solute molecule. The advantage of using this single set of descriptors has been demonstrated in the ability to compare disparate properties and data sets.

TLSER has been demonstrated to be useful in three regards. First, its ability to calculate easily the parameters of almost any chemical species significantly increases the correlative ability of this method by increasing the number of compounds that can be used in the data set, and by increasing the ease in which the parameters can be computed. Second, the resulting correlations relate an empirical (macroscopic) property to molecular (microscopic) parameters. In this way, how molecular structures, or more accurately, how changes in molecular structures affect the observed property, can be deduced, identified, and rationalized. Further, because the parameters are orthogonal, problems of cross correlation between independent variables are usually minimized. Last but not least, as discussed above, because TLSER descriptors are computed, it is not necessary to synthesize a new compound and measure specified descriptors in order to generate a prediction.

TLSER regressions have been developed for over 100 solute/solvent-based properties. These properties, like the LSER before it, runs the gamut of physical, chemical, spectral, and toxicological properties. The TLSER descriptors have led to good correlations and physical interpretations for variety of biological activities of chemical compounds: nonspecific toxicities,[126] activities of some local anesthetics,[129] opiate receptor activities of some fenantyl-like compounds,[130] six physicochemical properties,[131] gas-phase acidities,[132] acute toxicities,[133,239] and others.[134]

Several TLSER correlations have been reported for the chemical and physical properties of substances in solution, including adsorption on charcoal, Hafkensheid retention indices, octanol/water partition coefficient, supercritical carbon dioxide solutions, hydrolysis rates of organophosphorus compounds, and p$K_a$ of organic acids.[135,222−224]

In LSER, it is assumed that the solvent does not change significantly the geometrical and electronic structure of the molecules. However, it has been observed that in numerous cases this assumption is no longer valid. In particular, the intramolecular resonance effect can be substantially affected by the different dielectric media.[136−139]

Also, the predominant structure of a tautomeric molecule may be altered in different solvents and in the gas phase.[140−148] Therefore, it is important to apply in these cases the quantum-chemical descriptors, calculated by using one of the available methods to account for the solvent effects. The specific, hydrogen-bonding or solute−solvent charge-transfer effects on the solute molecular structure can be usually satisfactorily accounted for by using the supermolecule approach, i.e. by the quantum-chemical calculation of the solute molecule together with the first solvent coordination sphere or with the

solvent molecules attached to the hydrogen-bonding centers of the solute.[149] The nonspecific solvent effects can be described using one of the possible dielectric reaction field models.

### H. CoMFA

Since its introduction in 1988,[150] comparative molecular field analysis (CoMFA) has become rapidly one of the most powerful tools for three-dimensional quantitative structure−activity relationship (3D-QSAR) studies.[151−169] Because the molecular conformation optimization and charge density calculations to obtain the molecular field are often performed by using quantum-chemical methods, we feel it appropriate to include a short overview of this methodology in the present review.

The CoMFA approach is based on the assumption that since most drug−receptor interactions are noncovalent, changes in the biological activity of compounds should correlate with the steric and electrostatic fields of these molecules. In order to develop the numerical representation of those fields, all molecules under investigation are first structurally aligned and the steric electrostatic fields around them sampled with probe atoms. Usually a $sp^3$ carbon atom with a positive unit charge (+1) is moved on a rectangular grid that encompasses the aligned molecules.[152] A CoMFA QSAR table of thousands of columns is formed thereafter from the numerical values of the fields at each grid point which is subsequently analyzed using special multivariate statistical analysis procedures, such as partial least-squares (PLS) analysis[155,156] and cross-validation.[157] A cross-validated $R^2$ ($q^2$) obtained as a result of this analysis serves as a quantitative measure of the predictability of the final CoMFA model. It should be noted that the $q^2$ is different from the cross-validated correlation coefficient in multilinear regression and a $q^2 > 0.3$ is already considered significant.[158]

In most cases the molecular field is developed from the quantum-chemically calculated atomic partial charges of the molecule under investigation. MNDO, AM1, and PM3 calculated Mulliken charges have been used most widely for this purpose. The fields arising from the charge distribution on the frontier molecular orbitals (HOMO-s) have also been suggested for CoMFA analysis.[159]

CoMFA has been used for the quantitative description of enzyme inhibition activities of compounds,[160−162] receptor antagonist and agonist activities,[163−170] antiviral activities,[171−177] and carcinogenic and toxicological properties of compounds.[178,179] The CoMFA approach has been mostly used in biomedical QSAR studies; however, it has also been applied for the description of the chemical reactivity of compounds.[180−183] Notably, CoMFA has been used to correlate log $k$ for the $S_N2$ reaction of benzyl benzenesulfonates and *p*-methoxybenzylamines.[184]

## V. Conclusions

We have demonstrated above that the molecular descriptors derived from the quantum-chemically calculated molecular total wave function and charge distribution have wide applicability for the development of quantitative structure activity/property relationships in numerous areas of physical, organic, analytical, and biomedical chemistry. In most cases the quantum-chemically derived descriptors have definite physical meaning, and thus they have proven to be especially useful in the clarification of the detailed intra- and intermolecular interaction mechanisms determining the molecular property or chemical process under study. Also, in contrast to empirical substituent and solvent effect constants, quantum-chemical descriptors can be derived solely from the theoretical structure of the molecule, provided it has been geometry optimized. This enables applications of QSAR/QSPR correlation equations involving quantum chemical descriptors to hypothetical structures that have been never synthesized or are otherwise unavailable.

However, it should be mentioned that these descriptors are not completely universal and, depending on the nature of the chemical structures or processes involved, may have serious drawbacks. First, it should be kept in mind that a quantum chemical calculation is performed for a single structure at an energetic minimum. Thus it corresponds to the hypothetical physical state of the gas at 0 K and infinitely low pressure. Also, the zero-point vibrations of the molecule are neglected. Therefore, the quantum chemical descriptors cannot in principle account for entropic and temperature effects. When such effects are dominant for a given property or process, quantum-chemical descriptors are not adequate for their description and any correlation obtained using them can be regarded as accidental. However, most standard quantum-chemical program packages (AMPAC,[199] MOPAC,[200] Gaussian92[201]) have an option to calculate the vibrational, rotational, and translational partition functions of the molecule at the given temperature and their respective contributions to the molecular enthalpy, entropy, and other thermodynamic functions. Whereas examples of the use of those theoretically calculated thermodynamic molecular characteristics in QSAR/QSPR are practically unknown, this is to be encouraged in future studies of thermodynamically complex and presumably temperature-dependent properties of compounds. However, the thermodynamic functions provided by the quantum-chemical program packages mentioned above still refer to but a single conformation of a single molecule. Thus, for the conformationally flexible molecules with several energetically close conformational minima, a preliminary averaging of the molecular descriptors is therefore advisable. Different schemes (arithmetic average, Boltzmann average) could be used for this purpose. However, in some applications, particularly in the studies of biological activity of the compounds, only one conformation of the compound may be active in the given process. In such cases, the use of descriptors applying to a singular conformation is required.

Finally, as most chemical reactions and all biochemical reactions refer to condensed (mostly liquid) media, it should be advantageous to use molecular descriptors calculated using some quantum-chemical scheme which accounts for specific and nonspecific

(bulk) solvation effects in these media. Specific effects, primarily hydrogen bonding, on the molecular structure can be accounted for using the supermolecule approach where the solute molecule is treated together with the specifically coordinated solvent molecules. A number of different calculation schemes[202−221] are available for the description of the solvent bulk (reaction field) effects on the solute geometrical and electronic structure. Several of them are available in the standard program packages,[199−201] but it is advisable to consult the original papers before doing the calculations since most of the quantum chemical reaction field models involve empirical parameters (dielectric permittivity of the medium, cavity size, and shape of the solute molecule).

In summary, it is clear that quantum chemical descriptors have tremendous applicability and potential in QSPR/QSAR studies in diverse areas of chemistry and biomedicine provided that their use is critically analyzed and justified for a given property or phenomenon.

## VI. References


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