Molecular Electrostatics

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Contents

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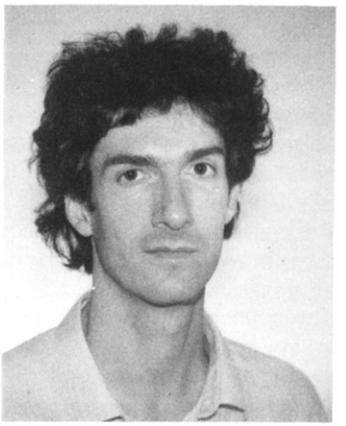

György G. Ferenczy was born in Budapest, Hungary, in 1960. He obtained his M.S. and Ph.D. degrees from the Eötvös University Budapest. His Ph.D. thesis addressed electrostatic interactions in chemical and biochemical systems. He has been working in the Molecular Modelling Group of the Chemical Works of Gedeon Richter Ltd. since 1988. He worked on a British Council grant at the Oxford University in 1989 and as a postdoctoral fellow at the University of Nancy in 1991 in the field of theoretical chemistry of extended systems.

I. Introduction

In principle, quantum mechanics describes molecular interactions with sufficient accuracy but at the cost of extremely complicated and time-consuming numerical calculations, especially for large systems. It is therefore desirable to find approximations that lead to a simplified, yet accurate, description of the interaction process. For polar molecules it is classical electrostatics that fulfills the aforementioned goal. In the electrostatic approximation it is the charge density of the isolated molecules that has to be calculated quantum mechanically or by some other approximation. The interaction energy and its dependence on the relative position of the partners is then obtained from these unperturbed charge densities classically. More sophisticated, yet classical, methods treat mutual polarization of the molecular charge distributions, as well, but in the present review we do not deal with this aspect. The electrostatic treatment provides fair to excellent results especially at large intermolecular distances and at a computational cost that is only a fraction of the quantum mechanical one. It is thus not surprising that molecular electrostatics is an increasingly popular field of computational chemistry.

In the early days quantum chemistry provided mostly equations, tables, and numbers that were difficult to interpret by chemists and other experimentalists. An important step toward domestication through visualization was done by to two Italians, Eolo Scrocco and Jacopo Tomasi, who introduced and widely advocated the concept of molecular electrostatic potentials (MEP).[1,2] The MEP is a quantity observable physically (e.g. by X-ray diffraction) and can be derived directly from the wave function. Its

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interpretation is easy in terms of classical electrostatics: the molecule provides a potential around itself that is seen by a pointlike positive probe charge approaching or avoiding regions where the MEP is negative or positive, respectively. In more general terms, we may represent one of the two interacting molecules by its MEP and the other by a point-charge distribution. Calculation of the potential from the wave function is relatively fast so it is possible to obtain values in a manifold of spatial locations around the molecule and represent the MEP as a three- or two-dimensional isopotential map or, by color, on the molecular envelope.

It is not surprising that the MEP plays an increasingly important role in theoretical chemistry and it has a widespread use in many different areas. From reactivity to crystal packing, solvation and molecular recognition several studies apply molecular electrostatics to interpret, even predict, molecular phenomena. Following early surveys[3,4] relatively few reviews have been published, especially in the last five years when they were devoted to some special applications, like multipole representations,[5] chemical reactivity,[6] or biomolecular structure and dynamics.[7] We feel that it is time now to review recent progress in methodology and, primarily, in applications. In the following we report mostly on papers published in the 1990s and, besides broader aspects of molecular electrostatics, discuss all fields of MEP applications of which we are aware.

II. Methodology

Noncovalent molecular interactions are governed, besides entropy effects, by the energy of association between interacting partners. Calculation of the total interaction energy, E_{int}, is in most cases quite laborious therefore it is a very useful feature that the dominant part of E_{int} is in most cases the electrostatic contribution, E_{elst}. We define this quantity as the interaction energy between the charge densities representing the isolated molecules. It can be derived formally e.g. via perturbation theories[8] or interaction energy decomposition schemes.[9] Although the terms appearing in a decomposition are not physical observables their definition offers both conceptual and computational advantages. E_{elst} is the term that vanishes quite slowly with increasing intermolecular separations; thus it approximates the total interaction energy at large distances. Due to the fortunate cancellation of other terms E_{elst} may prove to be useful for deriving qualitative or even quantitative conclusions at shorter intermolecular separations; as well. The calculation of E_{elst} is almost exclusively associated with approximations; either it is used as a substitute for E_{int} or for its components, and therefore, a wide range of approximate schemes have been developed. Most of them can be deduced from the multipole expansion which is the subject of the next subsection. The MEP concept can also be treated in the framework of multipole expansion; however, it deserves a separate discussion due to the various methodological aspects associated with the calculation and application of the electrostatic potential. Although electrostatics, as defined above, and polarization are sometimes treated together, we concentrate on electrostatics in the more restrictive sense.

A. Approximate Electrostatics by Multipoles

The approximate evaluation of the electrostatic interaction energy is often based on multipole expansions. One may use either a Cartesian multipole expansion[8] or spherical moments.[10] It is worth mentioning that the multipole expansion of the electrostatic interaction energy is formally divergent at any intermolecular separations due to the fact, that the molecular charge distributions extend to infinity. Nevertheless, E_{elst} can be separated into two parts. One part can be described by a multipole expansion and the other one relates to the overlap of the charge distributions. This latter decreases exponentially with increasing distance and is proposed to be regarded as part of the short-range interactions.[10,11]

It is often required to evaluate E_{elst} at intermolecular separations where molecular multipole expansions do not converge. To overcome this difficulty the molecular charge distribution can be partitioned into several fragments, each of which is described by multipole moments of its own center. Such a distributed multipole description[10,11] assigns several multipole series to a molecule at different sites. Stone advocates the use of spherical moments by arguing that a fundamental disadvantage of the Cartesian tensor formalism is that the evaluation of E_{elst} requires the transformation of the multipole moments referring to the molecule-fixed frames to those referring to a global coordinate system.[10] In contrast, the electrostatic interaction energy can be calculated efficiently by using local spherical multipole moments and an interaction function describing the relative orientation of the coordinate systems fixed to the molecules. Assuming that the electronic charge distribution is expressed in terms of Gaussians (as it is usually the case in quantum chemical applications) it can be described by a finite set of distributed multipole moments. However, for practical reasons, it is customary to use some selected sites (often those of the nuclei) and truncated multipole series. The reduction of the sites is possible by reexpressing some multipoles at new centers,[12,13] but various other proposals, not directly based on multipole expansions, appear in the literature. Here it is worth noting that no physical observable can be attributed to atomic (or in general many-center) multipole moments. Therefore, *any* assignment of moments to atoms is inherently arbitrary. Nevertheless, multipole moments reflect to a physical or a chemical property (molecular multipole moments, electrostatic potentials, IR intensities, etc.) via some models and the quality of the multipole moments can be valued by their ability to correctly describe that property. Due to the great number of models appearing in the literature we do not intend to give a full review. Apart from some "classical" charge models emphasis is laid on those methods intending to produce multipole sets suitable for the quantitative evaluation of the electrostatic interaction energy.

The method of cumulative atomic multipole moments[14,15] can be considered as a variant of the

distributed multipole analysis. A cumulative moment of atom a is obtained as a sum of three terms:

$$M_a^{klm} = Z_a u_a^k v_a^l w_a^m - \sum_{I\epsilon a}\sum_J P_{IJ}\langle I|u^k v^l w^m|J\rangle - \sum_{0<k'<k}\sum_{0<l'<l}\sum_{0<m'<m}\binom{k}{k'}\binom{l}{l'}\binom{m}{m'} \times u_a^{k-k'} v_a^{l-l'} w_a^{m-m'} M_a^{k'l'm'} \quad (1)$$

where Z denotes the nuclear charge, $\langle I|u^k v^l w^m|J\rangle$ is the multipole moment integral and P_{IJ} is an element of the first-order reduced density matrix. The first two terms are the expectation values of the multipole moment operator. In the calculation of these terms we consider only the atomic charge density. We use a "molecular origin" to obtain the atomic moment but this is moved to the atom in question. This transformation generates nonzero higher moments. The contributions of transformed lower moments represent the third term in eq 1 and are subtracted from the expectation value of the multipole operator. A virtue of the method is that lower order moments of any source can be complemented with higher order cumulative atomic multipole moments, thus improving the distributed multipole representation of the molecular charge density. The cumulative atomic multipole moment formalism is applied to study the effect of electron correlation and of different basis sets on the electrostatic interaction energy. The use of a 6-311G basis set with at least a double set of polarization functions (2s/2p) is found to prevent basis set incompleteness that may overshadow the contribution of electron correlation. For most molecules the correlation contribution to the molecular dipole moments is found to be essential. On the other hand, electron correlation is less significant in the calculation of quadrupole moments. Since the basis set dependence of ab initio calculations mainly affects the electrostatic component of the interaction energy it is suggested to calculate the latter with multipole moments obtained with extended basis sets. At this point it is worth recalling the observation[16] that electrostatic potentials calculated from smaller basis sets can be scaled to improve their agreement with more accurate calculations.

Multipole moments can be represented by multicenter point-charge models as it is done e.g. in current semiempirical (MNDO AM1 and PM3) methods.[17] The advantage of such a treatment is the reduced computational cost and the preservation of the anisotropy of the electrostatic properties. Such models are proposed for the representation of multicenter multipole moments[18] and also for the reproduction of AM1 electrostatic potentials.[19]

Atomic charges derived from Mulliken population analysis[20] have traditionally been used to characterize qualitatively the charge distribution in molecules. Although they are often criticized for being unable to reproduce higher molecular moments and also for their heavy basis set dependence they are suitable to recognize trends in the deformation of electron distributions. The Mulliken population analysis can be considered as a particular case of a generalized population analysis defining the atomic charge as

$$q_a = Z_a - \sum_{\mu\epsilon a}(\mathbf{S}^t\mathbf{P}\mathbf{S}^{1-t})_{\mu\mu} \quad (2)$$

where Z_a is the charge of nucleus a and $\mathbf{S}$ and $\mathbf{P}$ are the overlap and first-order density matrices, respectively. An infinite number of choices for t are possible in eq 2. $t = 0$ corresponds to the Mulliken and $t = 0.5$ to the Löwdin charge definition.[21] The extended Mulliken analysis[22] calculates point charges due to electrons and to nuclei. The former set consists of charges emerging from atomic and overlap populations. The locations of the charge centers are also calculated thus, in general, off-atomic centers for the atomic electron populations are obtained. This model preserves the quantum mechanical electric dipole moment. The charges are found to reproduce the quantum mechanical electrostatic potential around the molecule.[23]

Potential-derived charges[24-26] are designed for the quantitative reproduction of electrostatic interaction energies between molecules. These are the charges which best reproduce, in least-square sense, the quantum mechanical electrostatic potentials in some points around the molecule. Their calculation includes the determination of the wave function, the evaluation of the MEP from the wave function in suitably chosen points, and the calculation of the charges at some predefined positions by fitting their MEP to the quantum mechanical one. Several variants of this method have been proposed. Points where the potentials are calculated are most often selected either on an extended van der Waals surface or on a cubic grid. The search for different point generation methods[27-30] was initiated by the observation that the magnitude of fitted charges heavily depends on the choice of the points. Although different sets of charges may create similar MEP around a molecule, inadequate point sampling may result in physically unacceptable charge sets. The sum of fitted charges may differ from the molecular charge and different charges may be assigned to symmetrically related centers. To overcome these difficulties constraints can be introduced into the fitting procedure, e.g. the sum of fitted charges can be constrained to be equal to the molecular charge. Potential-derived charges have the important feature that they describe molecular electrostatics better than do charges calculated from a multipole expansion. These charges are, in fact, effective ones including the effect of higher moments. They seem to represent the best compromise between accuracy and computational efficiency, and they find widespread use in molecular mechanics and dynamics studies.

Methods of calculating potential-derived charges can be classified according to the way of determining electrostatic potentials. Since potential calculating methods will be discussed in a separate section, here we mention only those models which are designed explicitly for the charge derivation rather than for the study of the MEP itself. Tasi et al. suggested[23] that charges from an extended Mulliken population analysis[22] generate the potential suitable for charge derivations. Another method[31] finds charges that best reproduce the MEP due to Hartree–Fock densities at atomic sites and offers an alternative to the debated point generation. The method of fitting the potentials of charges to quantum mechanical values

can be generalized to fit to electrostatic fields[32] and to calculate higher moments, e.g. charges and dipoles, or dipoles alone.[33]

A related method,[34,35] giving charges termed as multipole fitted charges, also requires the reproduction of the MEP but avoids the explicit evaluation of the potential. The starting point of this charge derivation is a set of distributed multipole series (reference moments) which represents the molecular charge distribution. Each reference series is considered separately, and charges reproducing the MEP of a series are calculated from a least-square procedure. The reproduction of the potential is required in a spherical shell centered on the multipole series. Then the difference between the potentials of the multipole series and those of the charges can be expressed as an analytical integral formula rather than as a sum over points. The charges are calculated by minimizing this potential difference written as

$$\sum_{\lambda\mu} 4\pi/(2\lambda+1) W_{r_1 r_2 \lambda} [Q_{\lambda\mu}(i) - \sum_j q(j) R_{\lambda\mu}(r_{ji})]^2 \quad (3)$$

with $W_{r_1 r_2 \lambda} = 1/(1-2\lambda)[r_2^{(1-2\lambda)} - r_1^{(1-2\lambda)}]$. $Q_{\lambda\mu}(i)$ is the multipole moment at the ith site; $q(j)$ is the charge at the jth site; $R_{\lambda\mu}(r_{ji})$ is a regular solid harmonic; r_1 and r_2 define the boundaries of integration. The formula shows that those charges reproduce the MEP whose multipole moments reproduce those of the reference multipole series. The final charge set is obtained as the sum of charges fitted to different reference multipole series. The comparison of potential derived and multipole-fitted charges shows that the two methods give similar charge sets. It has been found that, at least in the case of hydrocarbons, the transferability of multipole-fitted charges is superior to that of potential-derived charges.[35] This is an important finding since the charge set of a larger system is usually built from charges obtained for fragments of the system. It is also worth mentioning that it is 10−100 times faster to calculate multipole-fitted charges than to calculate potential-fitting charges. This difference in speed is primarily attributed to the fact that the former method does not require the explicit evaluation of the MEP. The multipole-fitted procedure is exempt from difficulties like the inequality of symmetry-related charges or the dependence of charges from the orientation of the coordinate system. Just like the method of potential-derived charges the multipole-fitting procedure can be extended to derive higher order moments.

It was shown that atomic charges determined through a least-square fit to the MEP are highly correlated.[36] It means that the number of atoms is larger than the number of point charges necessary to reproduce molecular electrostatic potentials and the magnitude of individual charges has little significance, rather does the potential of the whole set of charges. The redundancy in the number of charge centers offers the possibility to impose further constraints on the charges reproducing the MEP. One can fix the magnitude of some charges, especially that of those centers which are not exposed, to achieve chemically more acceptable and more transferable atomic charges.[37] Reynolds et al. suggest that charges reproducing the electrostatic potentials in several molecular conformations can be calculated.[38] One of their proposals includes the fit to potentials in one conformation while constraining the dipole moment of the charge set to an alternative conformation. Their other proposal is to determine the MEP for several conformations and weighting them with the appropriate Boltzmann factors.

For larger molecules the direct derivation of charges from the MEP is prohibited by the rapid increase of computational work. Then, charges calculated for model molecules similar to the fragments of the larger system can be used. Lee and Friesner[39] propose the building of the density matrix from ab initio self-consistent field density matrices of smaller molecules.

Density functional theory is not only able to generate MEPs for charge derivations but it also provides the theoretical basis for the electronegativity equalization method[40] which gives atomic charges at a negligible computational effort. Another simple way to derive atomic charges is based on the inductive effect and on Hückel molecular orbital calculations.[41]

The interaction energy method to calculate atomic charges from semiempirical wave functions was proposed by Cummins and Gready.[42] In their method the interaction energy between a molecule and a set of point charges is calculated in two ways: quantum mechanically (in the neglect of diatomic differential overlap, NDDO, approximation) and by representing the molecule by point charges. These latter charges are considered as atomic cores and hydrogen core parameters are assigned to them. The magnitude of these charges are obtained by minimizing the difference in energies obtained in the two ways. This derivation of charges from interaction energies allows the retention of the approximations of the semiempirical methods.

Atomic charges and dipoles can also be calculated from the Cartesian derivatives of the molecular first and second moments, respectively.[43,44] The interpretation of the derivatives of molecular dipoles as atomic charges is discussed in the literature primarily in connection with infrared intensities. It was also shown, that these quantities appear in the second derivatives of the energy with respect to the coordinates of distant atoms. The extraction of atomic charges from these derivatives is complicated by the fact that charges themselves do depend on Cartesian coordinates or, stated another way, intramolecular distortions induce charge flux. However, in planar molecules the charge flux is zero in the direction perpendicular to the molecular plane. This fact makes it possible to define atomic multipoles as Cartesian derivatives of molecular moments in the case of planar molecules.

B. The Molecular Electrostatic Potential

Since the work of Scrocco and Tomasi[1,2] the MEP has been applied in the study of electrostatic interactions in various ways. Electrostatic charges interact with electrostatic potentials and it is customary to model one of the interacting molecules by a set of point charges. Then the potential arising from the other molecule is calculated either by the same model

(i.e. from point charges) or by a more sophisticated but usually still approximate manner. As described in the previous section electrostatic potentials are particularly useful for deriving atomic charges. Since MEPs are often required to be calculated in a great number of points (cf. MEP maps and MEP-derived charges) their computational requirement is comparable to that of the determination of a Hartree–Fock wave function. In order to reduce the computational work associated with subsequent calculations of an ab initio wave function and the MEP various approximate computational schemes have been proposed.

The molecular electrostatic potential is the expectation value of the $1/\mathbf{r}$ operator. Thus, for a wave function, written in terms of atomic basis functions, the MEP is given by the formula

$$V(\mathbf{r}) = -\int|\Psi(\mathbf{r}')|^2|\mathbf{r}-\mathbf{r}'|^{-1}\,\mathrm{d}^3\mathbf{r}' + \sum_a Z_a|\mathbf{r}_a-\mathbf{r}|^{-1} = -\sum_{mn}P_{mn}\langle\varphi_m(\mathbf{r}')||\mathbf{r}\text{-}\mathbf{r}'|^{-1}|\varphi_n(\mathbf{r}')\rangle + \sum_a Z_a|\mathbf{r}_a-\mathbf{r}|^{-1} \quad (4)$$

where $\Psi(\mathbf{r}')$ is the electronic wave function, Z_a is the nuclear charge, $\mathbf{r}_a$ is the position vector of the nucleus, P_{mn} is an element of the first order density matrix, and φ_m is an atomic basis function. Approximations to $V(\mathbf{r})$ may involve the use of an approximate density matrix, approximate integral evaluation, or even the neglect of some of the integrals.

Early approximate quantum chemical methods for the MEP evaluation[45–47] are based on the semiempirical complete neglect of differential overlap (CNDO) method. Although these early methods have been replaced by newer ones, they deserve some attention because they clearly show the basic dilemma one faces when electrostatic potentials are calculated from semiempirical wave functions. Semiempirical methods apply approximations and the adaptation of these approximations in the calculation of the MEP is by no means straightforward. The best quality electrostatic potentials were obtained with deorthogonalized CNDO wave functions. The deorthogonalized coefficients, C^χ are calculated as

$$C^\chi = \mathbf{S}^{-1/2}C^\lambda \quad (5)$$

where C^λ and $\mathbf{S}$ are the CNDO coefficient and overlap matrices of the basis functions, respectively. Thus all integrals in eq 4 are evaluated. Another CNDO-based method uses the coefficient matrix without deorthogonalization and neglects the contribution of two-center charge distributions in accordance with the approximations inherent in semiempirical methods. It was found that in the case of CNDO wave functions, the former method is superior in reproducing ab initio potential maps. On the other hand, the latter method requires significantly less computer time. At this point it is worth mentioning a recent CNDO-based method which calculates directly E_{elst} rather than the MEP. It uses deorthogonalized wave functions and is able to calculate E_{elst} for large systems rapidly with a limited accuracy.[48]

An even more simple scheme calculates the MEP from bond increments.[49] The molecular wave function is built from localized molecular orbitals whose coefficients are determined for small model systems. Thus the electrostatic properties are calculated without a previous self-consistent field process. The MEP is evaluated with the neglect of the contribution of two-center charge distributions, an approximation common in semiempirical methods. In spite of the drastic approximations the method is able to reproduce the essential features of MEP maps. This very fast procedure can be applied to calculate the electrostatic properties of very large systems, like zeolites[50] or proteins.[51,52]

Recent potential evaluation schemes based on semiempirical methods utilize NDDO-type (MNDO, AM1, or PM3)[17] wave functions. A method which retains the basic features of the NDDO approximation uses the NDDO coefficient matrix without deorthogonalization and neglects three-center integrals.[53] The core potentials are calculated from point charges and the integrals of the electronic contribution to the electrostatic potential are evaluated with Slater-type orbitals. This computational scheme is motivated by the fact, that the MNDO, AM1, and PM3 methods use semiempirical expressions for calculating the core–core, core–electron and electron–electron interactions and no unambiguous extraction of the core or electron potentials from these expressions is possible. It was found that AM1 MEP maps represent a significant improvement with respect to the CNDO ones, in particular, they are able to reproduce the negative region under and above aromatic rings.[54]

Another method,[55] also using the native AM1 coefficient matrix, evaluates the electronic contribution to the electrostatic potential similarly to the AM1 core–electron attraction integrals and introduces a semiempirical function for the core contribution. This function is of similar form as that of the AM1 core–core repulsion term and its parameters are optimized to reproduce ab initio Hartree–Fock MEP values.

Alternatively, the NDDO coefficient matrix can be deorthogonalized and then all integrals (including three-center ones) in eq 4 are evaluated.[56,57] To facilitate the calculation of three-center integrals the Slater-type orbitals, used as basis functions in semiempirical methods, are replaced by sets of fitted Gaussians. Both the method using the native NDDO coefficient matrix and the one using deorthogonalized density matrix were shown to yield potential-derived charges of comparable quality to ab initio potential-derived ones. A recent comparison of the two methods[58] reveals that the latter is able to better reproduce MEPs within the van der Waals surface, while the two methods perform similarly beyond the van der Waals surface. The comparison of different NDDO wave function-based methods led to the unexpected observation that MNDO is superior to AM1 which, in turn, is superior to PM3 in calculating electrostatic properties.[59–63] The most usual way to compare the quality of the results of different approximate methods is the statistical analysis of MEPs or MEP derived charges, however, several other

possibilities to assess the quality of potentials and charges were proposed.[54] It was also shown that MEPs and MEP derived charges can be efficiently scaled to represent ab initio values.[64]

MEPs can be calculated from distributed multipoles accurately and efficiently over the van der Waals surface of molecules, in regions where the electron penetration is negligible.[65] Efficiency can be further improved by approximate multipole expansions.[66] Koster et al.[67] use a simple function with parameters for approximating the electronic density of an atom and replace the electronic contribution to the MEP by the potential of the approximate density. Their asymptotic density model is required to satisfy certain conditions, among them the potential of the asymptotic density model must be exact at the nucleus and must asymptotically approach the multipole potential. The virtue of the asymptotic density model is that it describes the electrostatic potential correctly near nuclei, in regions where the multipole expansion fails. MEPs of large molecules can be calculated by a method in which the idea of building the molecular wave function from smaller units is complemented by a replacement of the potential of the orbitals by simple analytical functions.[68,69]

Besides searching simplified methods for evaluating MEPs progress is also made in increasing the efficiency of the ab initio potential calculation. These technics include the separation of the integral evaluation into a point dependent and independent part and the elimination of those products of Gaussians which do not contribute significantly to the MEP.[65,70,71]

Efforts are also made to clarify the effect of electron correlation on the MEP. Price et al.[16] found that it is necessary to use a correlated wave function to reproduce the MEP of a peptide on the water-accessible surface within a few kilojoules per mole. Confronting conclusions are reported on the relative significance of the correlation effects on the MEP inside and outside of the van der Waals surface of molecules. Electron correlation is found to be relevant near nuclei and insignificant outside the van der Waals surface.[72] In another study, electron correlation, introduced by second-order many-body perturbation theory, is found to be important beyond the van der Waals surface only.[73]

Gadre et al. studied the topography of the MEP by locating its critical points.[74-76] They found a correlation between the position of critical points and molecular structure, in particular, that bonded pairs of nuclei are associated with a critical point in between, that the size and shape of negatively charged molecular ions can be estimated from the location of critical points, and that bond ellipticities can be determined in terms of curvatures of bond critical points. They conclude that the topography of the MEP exhibits enhanced features with respect to that of the molecular charge distribution. An electrostatic charge model including point charges and spherical Gaussians is also developed by employing the critical topological features as fitting criterion.[77]

MEPs can be calculated within the framework of the density functional theory. A study of the MEPs by the local density approximation suggests that the key features of the MEPs by ab initio molecular orbital calculations are reproduced.[78] Since calculations of density functional MEPs may have reduced computational requirements they can be applied advantageously for larger systems.[79]

In large asymmetrical systems a simplified study of electrostatics is possible with continuum models, in which case some molecules are not treated explicitly. This approximation is typical in biomolecular systems, where the biomolecule is immersed in a continuous medium (solvent) whose effect on the electrostatics is mimicked by some dielectric models.[7] Among them, the Poisson–Boltzmann equation is probably the most widely used to calculate electrostatic energies and ion distributions. The Poisson–Boltzmann equation is based on the Poisson equation and on the supposition that the distribution of mobile ions follows the Boltzmann distribution law. Furthermore, approximating the potential of mean force by the mean electrostatic potential the Poisson–Boltzmann equation is written as

$$-\nabla[\epsilon(x)\nabla\phi(x)] = \varrho^{f}(x) + \lambda(x)\sum_i q_i c_i \exp[-q_i\phi(x)/(k_B T)] \quad (6)$$

where $\epsilon(x)$ is the permittivity, $\phi(x)$ is the electrostatic potential, $\varrho^{f}(x)$ is the fixed charge density, $\lambda(x) = 1$ for ion-accessible regions and 0 otherwise. c_i is the bulk concentration k_B is the Boltzmann factor and T is the absolute temperature. The advantage of this equation is that it is applicable to arbitrary geometries and nonuniform dielectrics. To facilitate the numerical solution of the Poisson–Boltzmann equation it is often solved in its linearized form or with the inclusion of a finite number of nonlinear terms. Numerical technics for solving the Poisson–Boltzmann equations have already been reviewed[7] and recent developments are reported in refs 80 and 81. Luty et al.[82] suggest that the nonlinear Poisson–Boltzmann equation be solved by finding the stationary value of the function

$$G[\phi(x)] = \int[-\phi(x)\varrho^{f}(x) + {}^{1}/_{2}\phi(x)\nabla\epsilon(x)\nabla\phi(x)] - -k_B T\lambda(x)\sum_i c_i \exp[-q_i\phi(x)/(k_B T) - 1] \quad (7)$$

This function represents a free energy functional for the Poisson–Boltzmann equation. The $\phi(x)$ which makes $G[\phi(x)]$ stationary satisfies eq 6. Note that the approximation of the potential of mean force by the mean electrostatic potential creates theoretical difficulties in the definition of the energy expression of the Poisson–Boltzmann equation. However, several equivalent energy formulae, including eq 7, are derived[83] by invoking the calculus of variations.

In order to perform molecular mechanics and dynamics calculations on a system governed by the Poisson–Boltzmann equation the forces in the system have to be evaluated. By finding the variations of G in eq 6 with respect to ϱ, ϵ, and λ the electrostatic force is obtained as the sum of three terms.[84] The effect of electric field on charges includes the Coulombic forces and the reaction field forces. The other two terms are the dielectric boundary pressure and the ionic boundary pressure, the former accounts for the tendency of the high dielectric solvent to displace

the low dielectric solute in the regions of electric field and the latter corresponds to the tendency of ions to move into regions of nonzero electric potentials. Other recent attempts to include hydration forces into molecular dynamics simulations are also reported.[85-88,179]

As was emphasized in the Introduction a key feature of the MEP is that it can be visualized, thus facilitating the extraction of the vast information included in MEP maps. However, the three-dimensional nature of the MEP requires a clever approach to visualize the spatial distribution and the magnitude of the MEP simultaneously. Electrostatic potential values can be represented in planes by contour lines or by color-coding. Another approach is to represent the MEP by color-coded points on a surface (often on an extended van der Waals surface) of the molecule. When this is done on a computer monitor, an interactive program can rotate and shift the molecule and the surface to obtain a full picture of the MEP distribution. Several programs are available which are able to perform various related functions like the building of molecular structures, the calculation of their wave functions and properties and the visualization of properties like electron density or MEP.[89,90] A new approach to the display of the three-dimensional MEP on a two-dimensional surface uses neural networks.[91]

It is important to know that molecular electrostatic potentials can be directly derived from experimental electron densities available from X-ray diffraction by crystals of small molecules,[92-95] even proteins.[96] However, if we compare these MEPs to those calculated for isolated molecules we may face several problems. One is that the diffraction experiment has to be done at low temperatures in order to reduce vibration effects that may considerably influence the potential. Furthermore, crystal packing effects also perturb the MEP therefore only main features of the experimental and theoretical maps can be compared. The numerical evaluation of the diffraction data is also limited; thus we may say that the quality of MEPs obtained from sophisticated ab initio calculations for a free molecule exceeds, in general, the one extracted from an X-ray diffraction experiment for the same molecule in the condensed phase.

III. Applications

A. Reactivity and Electrostatic Catalysis

1. Small Molecules

One of the first applications of the MEP was to use it as a reactivity map for the electrophilic attack on a molecule by pointlike reagents in charge-controlled reactions.[1-3,97-99] The electrophile, bearing a positive charge, prefers negative regions thus the potential map can be used e.g. for the prediction of potential protonation sites of a polar molecule.[100-102] For a series of related molecules absolute values of MEP minima may correlate with protonation energies although this is not always the case.[103] The electrostatic potential provided by a substituent correlates fairly with the electrostatic component of the Hammett constant determining electrophilic and nucleophilic reactivity.[104,105]

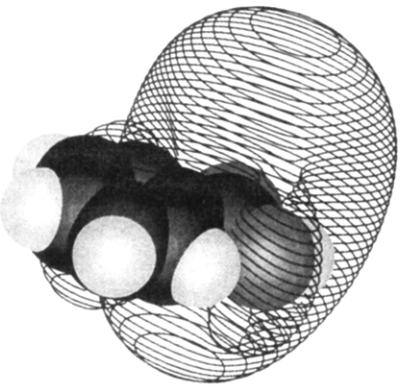

Figure 1. The −4.0 kJ/mol potential contour for benzoic acid calculated from atomic monopoles after Gasteiger and Marsili.[274] The figure was produced with the SYBYL software.[275] Shades: carbon, black; oxygen, gray; hydrogen, light grey.

The MEP does not provide direct information on nucleophilic reactions since it becomes infinitely large at nuclei and because of the absence of core−core repulsion the reagent−reactant system will collapse for small internuclear separations. However, it is still possible to treat nucleophilic reactivity on the basis of the MEP alone. Politzer and co-workers considered the MEP on the molecular van der Waals envelope and thus avoided the aforementioned collapse for the interacting partners.[106,107] Another way is to consider negative regions around the molecule that are avoided by a nucleophilic attack. We provide a simple example by the rationalization of the rear-side attack of carbonyl groups by nucleophiles that was found to occur in a wide variety of compounds consisting the >C=O moiety.[108] The MEP, as displayed on Figure 1 for benzoic acid, has a negative region near the oxygen atom of the carbonyl group. This hinders the approach of the negatively charged nucleophile; thus it is plausible that the attack will occur from the carbon (rear) side. Owing to the approximate transferability of the electronic distribution providing similar electrostatic potentials near the carbonyl group, in the absence of steric effects, a nucleophilic attack should take place in all carbonyl compounds exclusively from the carbon side.

Molecular electrostatics is a useful tool in the interpretation, even design, of regioselectivity.[109-111] The MEP yields information on those molecular regions that are preferred or avoided by an electrophile or a nucleophile. In the following we present an example for the computer-aided design of the steric preference in a nucleophilic attack of a hydride anion on the sterically unbiased carbonyl group of substituted 5,6-norbornen-7-ones.[112] Our goal was to design substituents in these positions that are quite distant from the attacked carbonyl group, yet influence selectivity. We constructed a geometric model for 2,3-bis(bromomethyl)-5,6-norbornen-7-one (**1**) on the basis of a search in the Cambridge Structural Database[113] and calculated its MEP contour (cf. Figure 2). It is seen that the negative region around bromine atoms is unfavorable for a nucleophilic attack from this side; the incident reaction channel is slightly reduced even if it is open in the middle. On the basis of this calculation we postulated that bromomethyl substituents in the 2 and 3 position will

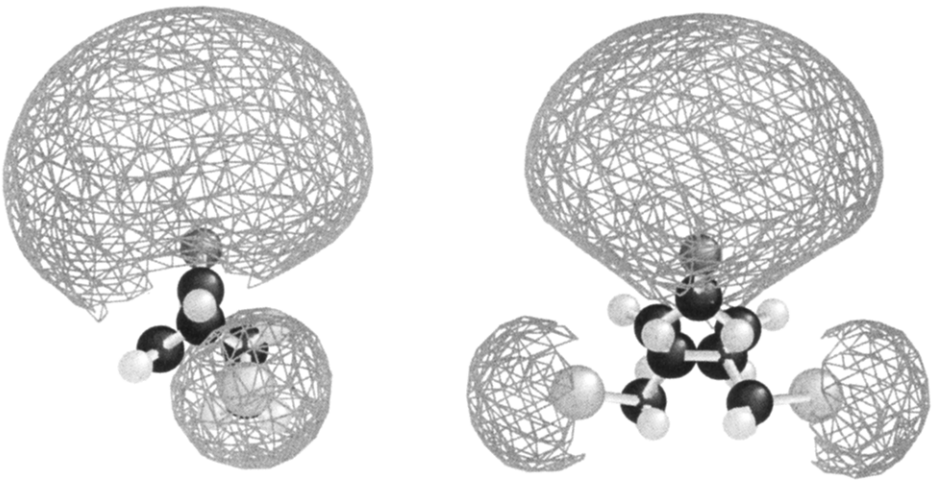

Figure 2. The −4.0 kJ/mol potential contour for 2,3-bis(bromomethyl)-5,6-norbornen-7-one calculated from atomic monopoles after Gasteiger and Marsili:[274] (left) side view and (right) front view. The figure was produced with the SYBYL software.[275] Shades: carbon, black; oxygen and bromine, gray; hydrogen, light gray.

prefer the *anti* product **2a**. In fact, checking our prediction by the reduction of **1** with $NaBH_4$ we found the **2a**:**2b** ratio to be 76:24. To our knowledge, this is the first example for the successful application of the MEP to computer-assisted synthesis.

An important case where electrostatics is crucial in the reactivity of small molecules was discussed recently by Jiao and Schleyer.[114] They reported on the electrostatic acceleration of the 1,5-hydrogen shifts in cyclopentadiene by Li^+ complexation and showed that the energy barrier to the rearrangement is reduced by the greater electrostatic stabilisation of the transition over the ground-state structure. While the ground state is symmetric and binds the lithium cation on both sides of the ring with an energy of 103 kJ/mol, the transition state is asymmetric and binds the cation by 97 and 137 kJ/mol at *cis* and *trans* sides with respect to the moving hydrogen, respectively. Accordingly, the *trans*-complexed form of the transition state is stabilized by an extra 34 kJ/mol as compared to the ground state, i.e. a catalytic rate acceleration takes place that is completely due to the electrostatic effect of the complexing cation. This is maybe the simplest example for *electrostatic catalysis*, where the catalyst acts through its electrostatic potential on the reactant by stronger stabilizing the transition than the ground state. Since the higher level ab initio calculations by Jiao and Schleyer reproduce the measured kinetics of the 1,5-hydrogen shifts in cyclopentadiene accurately, the conclusions on lithium complexation should be also valid. Similar effects will be discussed for enzymes and crystal cavities and surfaces in subsequent sections.

Differences in Li^+ complexation energies are reflected by the MEPs calculated both for the ground and transition states (cf. Figure 3). The −8.0 kJ/mol potential contours are symmetric above and under the cyclopentadiene ring, representing the ground state, but they extend above and diminish under the ring in the transition state, indicating the increase and decrease of the binding energy of the positively charged pointlike metal. This is an example for the successful application of the MEP to metal−ligand complexation stressed also by others.[115,116,117,118]

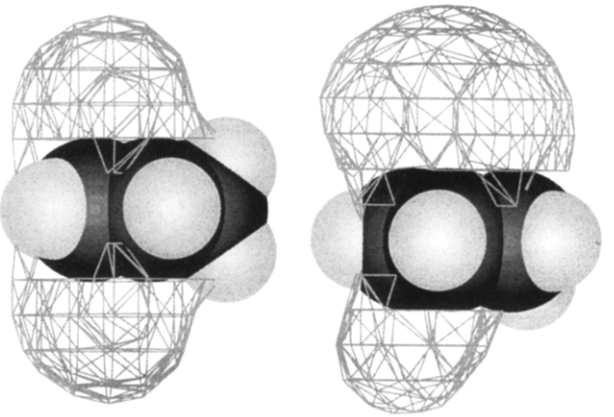

Figure 3. The −8.0 kJ/mol potential contour for the cyclopentadienyl ring in the ground state (left) and in the transition state for the 1,5-hydride shift (right). Atomic monopoles are from semiempirical AM1 calculations,[17] the figure was produced with the SYBYL software.[275] Shades: carbon, black; hydrogen, light gray.

2. Enzymes

It has been known for a long time that proteins provide strong electrostatic potentials both in their interior and around themselves;[49,119−124] however, it was not recognized at once that the MEP has an important effect on enzyme reaction mechanisms. In 1974 Thoma[120] argued that electrostatic effects are not important in catalysis. Since the effect of charged groups around the protein is very small because of strong shielding by counterions and bulk water the real problem was the inadequate evaluation of the MEP emerging from the protein core. Early calculations used inappropriate values of the dielectric constant (varying from unity to 40 from author to author) and thus provided only vague estimates for electrostatic energetics. This is a crucial problem, treated correctly first by Warshel and Levitt,[122] who called the attention to the essential importance of water as solvent in the quantitative treatment of protein electrostatic effects.

With the development of gene manipulation techniques it became possible to study protein electrostatic effects, at least in part, directly through the

replacement of one or more charged side chains by neutral ones or by altering their lengths (e.g. Asp to Glu). Drastic changes in substrate binding power (K_M) and in enzyme activity (k_{cat}) indicate the importance of electrostatics.[125-128] Present day computation methods are reliable enough to reproduce the protein MEP to a sufficient accuracy, comparable to experiment; thus theory gives new insight in protein electrostatics and its role in activity.[7,129,130]

Long-distance electrostatic effects may be important for charged substrates. For example, in the encounter of triose phosphate isomerase with glyceraldehyde phosphate the protein MEP orients the substrate in the best position for binding even at relatively large distances thus increasing the diffusion-controlled rate constants.[131] A similar effect was found in the case of the reaction of super oxide dismutase with the super oxide anion.[132-134] However, it has to be mentioned that the effects of changing the diffusion rate are very small relative to the enormous effect of the protein active sites.[130b] Clearly, after the protein increases the rate by more than 10 orders of magnitude and the reaction becomes diffusion controlled the small effect of surface charges can modulate the diffusion.

Desideri et al.[135] reported on the evolutionary conservativeness of the MEP near enzyme active sites. Calculating the electrostatic potential by solving the Poisson–Boltzmann equation[133] for six different Cu–Zn super oxide dismutase species from various sources, with different protein electrostatic charges and various degree of sequence homology they found that in the proximity of the active site the MEP was similar for all species. This indicates that the electrostatic potential pattern is conserved in the evolution of this protein family. Further confirmation for this hypothesis was provided by X-ray diffraction studies.[136] Earlier we drew the same conclusion for eight serine proteases.[137] The MEP provided by the protein environment around the transition-state complex stabilizes the (− + −) charge pattern both in chymotrypsin and subtilisin families in spite of the lack of sequence homology near the catalytic triad. Thus, the goal of convergent evolution of these enzyme families was not only to bring the Ser-His-Asp catalytic triad together, but also to provide similar electrostatic patterns along it.

Electrostatic catalysis is effective in several enzymes. Generalizing semimacroscopic results for lysozyme,[122] we state that in enzymatic mechanisms where the polarity of the transition state is much higher than that of the ground state the major source of catalytic rate acceleration is the electrostatic stabilization of the transition state by the protein environment. Trypsin,[138,139] α-chymotyrpsin,[140] subtilisin,[139,140,141] and D-xylose isomerase[142,143] are examples where the above hypothesis works. In serine proteases the MEP provided by the protein environment stabilises the (− + −) charge pattern of the transition state better than the (− 0 0) one representing the ground state, thus the protein core acts like a super solvent providing stronger stabilization than by water and this is the main source of enzymatic rate acceleration.[130]

Point mutation studies extended by electrostatic calculations helped to clarify the somewhat mysterious role of the buried aspartate of the Asp–His–Substrate triad in serine protease catalysis.[139,140,141] For the Asp/Asn-102 mutant of trypsin and the Asp/Ala-32 mutant of subtilisin the catalytic rate decreases by 4 orders of magnitude (i.e. the activation energy increases by 25 kJ/mol) as compared to the wild-type enzymes.[125,127] This is plausible if we consider that the energy of the (0 + −) charge distribution of the triad in the mutant (Asn–His–substrate in trypsin and Ala–His–substrate in subtilisin) is higher than that of the (− + −) one since the extra stabilization of the (+ −) dipole at its positive end by a negative charge is absent. Beyond this qualitative argumentation our calculations with the semimacroscopic protein dipoles Langevin dipoles method[130] on the mutants, considering exclusively electrostatic effects, reproduced the experimental rate reduction semiquantitatively.

The success of the calculations allowed us to distinguish between two possible mechanisms of serine protease catalysis. Earlier the so-called "charge-relay" mechanism proposed by Blow et al.,[144] stating that a proton transfers during catalysis from His to Asp, was widely accepted but later this was questioned on the basis of speculation,[145] molecular orbital calculations,[138,146] nuclear magnetic resonance,[147] and neutron diffraction studies.[148] The quoted works supported the opposite hypothesis: there is no proton transfer during catalysis, the role of the buried Asp is just the electrostatic stabilization of the transition-state complex. We considered both the charge-relay and electrostatic mechanisms and found that the activation energy is 42 kJ/mol higher for the former. The large increase in the activation energy for the "charge-relay" mechanism, a value that is even higher than that calculated for the mutants and reproducing experiment semiquantitatively, allows one to rule out this mechanism as a possible route for serine protease catalysis.

An interesting example for the role of protein electrostatics is the two-step reaction catalysed by D-xylose isomerases.[142,143] These enzyme catalyze the isomerization of D-xylose and D-glucose from aldose to ketose. They require divalent cations (e.g. Mg^{2+}), a histidine, and a carboxylate (Asp or Glu side chain) for activation of the substrate that loses a proton in the transition state thus providing a similar (− + −) charge distribution as in serine proteases (cf. Figure 4). X-ray diffraction and computer modelling studies support the hypothesis that the reaction proceeds via two distinct steps: ring opening of the sugar ring followed by a 1,2-hydrogen shift the latter being rate limiting.[149,150] Our semiempirical quantum chemical MNDO calculations with the PM3 parametrization[17] also support this finding. If we consider a model including xylose, His-54, Asp-57, the first Mg^{2+} ion, and three structural water molecules, the energy barrier is by 54 kJ/mol higher for the hydrogen shift than for ring opening.[143] Extending the model with further neighboring side chains (Trp-16, Phe-94, Trp-137, Glu-181, Lys-183, Glu-217, His-220, Asp-245, Asp-255, Asp-257, Asp-287, and the second Mg^{2+} ion) we get 29 kJ/mol as a difference.

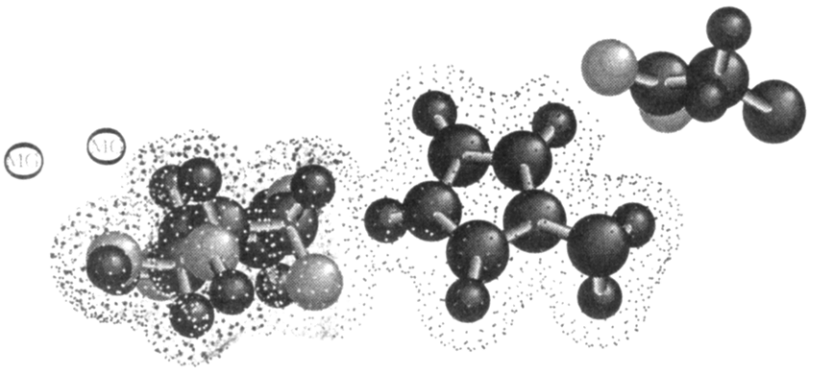

Figure 4. The protein MEP, displayed on the molecular van der Waals envelope, near the Asp−His−substrate triad of D-xylose isomerase in the transition state of the ring opening step. Positive regions (shaded) are indicated by larger, while negative ones by smaller dots. The figure was produced by the SYBYL software.[275] Shades: carbon and nitrogen, large black spheres; oxygen, large gray spheres; hydrogen, small black spheres. Magnesium cations are encircled.

Electrostatic catalysis, similar to that in serine proteases, takes place for the ring-opening step. The MEP provided by Asp-57 and the two metal ions stabilizes the (− +) charge distribution formed by the deprotonated sugar ring and protonated imidazole side chain in the transition state (cf. Figure 4). Since ring opening is not rate limiting, acceleration for this step has no effect on the whole reaction. This explains why, in contrast to serine proteases, no catalytic rate decrease is observed in the Asp/Asn mutant of D-xylose isomerase.[151] k_{cat}/K_M is 17.3 and 10.1, while $1/K_M$ is 4.8 and 4.7 for the wild-type and mutant enzymes, respectively. Mutation affects only the faster ring opening step and it is probable that activation energy of this step is increased by around 25 kJ/mol, like in serine proteases.[125,127] Consequently, the activation energy difference between the ring opening and hydride shift reaction steps may not be smaller than this value in good agreement with ours (29 kJ/mol). Replacing magnesium cations with zinc we obtain higher activation energies for both reaction steps (by 21 kJ/mol for ring opening and by 67 kJ/mol for the hydride shift) and this is in agreement with the observation that zinc inhibits catalysis by D-xylose isomerase. A possible reason for the increased activation energy is the considerable difference in charge transfer to the metal cations. Our calculations on the extended models indicate that for the hydride shift the net charge on magnesium and zinc is roughly one-half and one-quarter of an electron both in the ground and transition states, respectively.

3. Crystal Surfaces and Cavities

Zeolites and crystal surfaces are two important classes of catalysts that essentially influence gas-phase reaction paths through interaction with the reacting partners. It is an interesting question whether electrostatics plays a role for reactions taking place with the participation of these systems or not.

Zeolites are structures composed of highly polar SiO_4 and AlO_4 tetrahedra bearing a net negative charge that is compensated by cations. Tetrahedra are connected within the pores by sharing corners to form channels throughout the crystal. While zeolite electrostatics did not receive much attention earlier,[152−154] the interest has grown in the last few years.[50,155−161] It has been shown that the proton affinity of bridging hydroxyl groups is affected by MEP changes at the acid site,[158,160] and that ion pairs formed in zeolite-catalyzed reactions are stabilized by the MEF in the channels.[152] Although another study states that the field is small near the center of the channel in mordenite[160] our bond-increment calculations[49] on faujausite models gave MEF values as high as 50 V/nm at a distance of 200 pm from bridging oxygen atoms, while the average field does not exceed 10 V/nm and tends to zero at 400 pm from the atoms.[50,156a] Electrostatic calculations on the acidity and the vibrational frequency sequence of skeletal OH groups in faujausite support the conclusions derived from experiments.[156a] These results indicate that high electrostatic fields inside zeolite cavities, emerging mostly from long-range contributions,[50,156,160,161] are essential factors of their reactivity.

Metallic and other surfaces have reactive atoms and groups (adatoms, steps, kinks) on their reconstructed structure that are linked by specific bonds and have no analogues among classical molecules.[162] Although recently a few papers have been published on crystal surface electrostatics,[163−166] surface−adsorbate interactions are treated mostly in terms of molecular orbital calculations.[167] McCarthy and Hess were able to predict adsorption sites of Cl_2 on the MgO(001) surface by inspection of the MEP and concluded that the interaction is dominated by electrostatics.[166] We studied the MEF near the reconstructed Si(111) surface[168] applying the semiempirical NDDO AM1 molecular orbital method.[17] By using atom coordinates given by Tong et al.[169] and modeling the surface by adatoms, two double layers and hydrogen atoms that saturate dangling bonds and thus represent the bulk, we calculated the MEF from net atomic charges as obtained from the molecular orbital calculation. (cf. Figure 5 for a color representation). We see that the field is strongest in the triangular regions with rest atoms in the center and surrounded by center and corner adatoms (for notations see Figure 5a). This parallels the chemisorption ability observed experimentally for ammonia near these sites[170] and is also in agreement with the finding that water[171] and acetylene[172] adsorb easiest

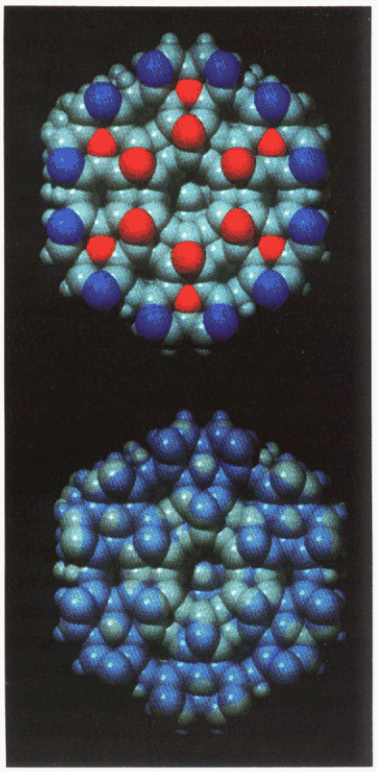

Figure 5. Space-filling representation of the hexagonal unit cell of the Si(111) surface: Center adatoms, blue; corner adatoms, red; corner holes; red triangles (top). The MEF displayed on the van der Waals surface (bottom). Colors denote the following: gray, <2 V/nm; blue, between 2 and 5 V/nm; deep blue (near center adatoms), >5 V/nm. The figure was produced with the MolIdea software.[276]

near rest atom−adatom pairs. The MEF is smaller near the central atom in the corner hole (in the center of Figure 5) indicating reduced adsorption ability here. We conclude that the enhanced reactivity of adatoms on the Si(111) surface is at least partly determined by the high MEF in their vicinity (up to 5 V/nm in our case). The strong field attracts dipolar molecules, polarizes apolar molecules approaching the surface, and thus enhances their chemisorption and dissociation ability.

B. Solvation

Solvent, especially hydration, effects have been recognized as important factors in molecular phenomena. Electrostatics plays an essential role in solvation by polar media influencing solute properties and solution reactions through the MEP and MEF provided by solvent molecules. Solvation theories consider electrostatics either directly, by including some averaged electrostatic term in the solvation energy or indirectly in the force field applied to the description of solute−solvent interactions. We briefly treated some recent solvation theories in section II.B others have been extensively reviewed earlier.[130,173,174]

In protic solvents hydrogen bonding is one of the most important determinants of solvation. While the accurate reproduction of energetics, intermolecular distances, and vibration properties of hydrogen-bonded systems needs high-level ab initio molecular orbital calculations, a simple analysis based on electrostatics can provide excellent predictions of the intermolecular orientations.[175] This is why several successful electrostatic models could be constructed for a qualitative or semiquantitative description of solvation, in particular hydration. Electrostatic hydration models[7,83,87] are especially important for proteins[130,176] and nucleic acids[177] because of their relative simplicity and sometimes surprising success in the interpretation, sometimes even prediction, of experimental information. Such models produce excellent agreement with experiment in case of the study of interactions between two surface side chains of a protein by determining the pK shift induced at one site by the modification of the charge through site-directed mutagenesis at another one.[178] Calculation of the actual pK_a of a side group in a protein is much more challenging, but was done successfully using a microscopic model.[179] Ionic strength dependence of enzyme(super oxide dismutase)−ligand association rate in water is also correctly reproduced.[133]

Hydration effects were studied in detail for charge transfer reactions.[180−183] Despite the crucial role of the solvent in these processes, it is not obvious how to include the solvent in molecular orbital calculations. Attempts to represent the solvent by a cavity around the solute could not be used for a quantitative study, since the solvation energy depends very strongly on the cavity radius. Supermolecule models, including the solute plus a limited number of solvent molecules, could not treat a sufficient portion of the hydration sphere thus neglected significant electrostatic contributions. More demanding studies introduced ab initio solute potentials interacting through the calculated gas-phase charge distribution with an all-atom water model.[180] Other works were based on ab initio solute surfaces and empirical potential functions.[181,182] Warshel and co-workers proposed a semimacroscopic model combining the empirical valence bond method[130] and a free-energy perturbation technique.[183] Incorporating the effect of the solvent reaction field on the polarization of the solute they explored the general relationship between the reaction free energies and the solvent contribution to the activation free energies. Their simulated free energy relationship is similar to Marcus' macroscopic formula.[184]

In general, polar solvents increase dipole moments of the solute, as compared to the gas phase,[185] and stabilize structures with higher dipole moments more than those with lower ones. Accordingly, if the dipole moment of the transition-state complex is larger than that of the reactants it is stabilized more by hydration than the initial state; therefore the activation energy decreases as compared to the gas phase process. This is true for conformational changes[185,186] as well as for charge separation (e.g. proton transfer) reactions where the dipole moment change is large.[187,188] For such reactions the solvent has an electrostatic effect increasing reaction rate which corresponds to the concept of electrostatic catalysis treated in section II.A. On the other hand, it is also possible that the reactants are stronger stabilized by the solvent than the transition state like in the S_N2 reaction of $ClCH_3$ with Cl^-.[180] Computer modeling studies beautifully showed that the electrostatic interaction of hydrating water molecules is stronger

with the chlorine monopole than with the symmetrically polarized transition-state complex, $[ClCH_3Cl]^-$. This makes the solution reaction many times slower than in the gas phase.

Politzer and co-workers proposed to use the MEP on the molecular van der Waals envelope to estimate solvent hydrogen-donating and -accepting ability.[189,190] They interpreted the so-called solvatochromic parameters extensively used to quantify solvent effects on various experimentally measurable quantities, like rate constants, equilibrium constants, absorption maxima and intensities in infrared, nuclear magnetic resonance, electron spin resonance, and ultraviolet and visible spectra.[191] Two of these solvatochromic parameters, α and β have been interpreted as providing measures of the solvent ability to donate or accept a proton, respectively, in solute−solvent hydrogen bonding.[192] It was found that good relationships exist between β and the most negative MEP value associated with the H-bond accepting heteroatoms in four families of compounds, taken separately: 10 azines, four primary amines, four alkyl ethers, and 15 molecules containing double-bonded oxygens.[193] The correlation coefficients were found to vary between 0.94 and 0.98.

In view of the good correlation between β and the minimum of surface MEP it was suggested that relationships might exist between the hydrogen-bond-donor parameter α and positive regions of the MEP. Politzer and co-workers computed the MEP on well-defined molecular surfaces, defined by the 0.002 electron/bohr^3 contour of the electronic density encompassing at least 95% of the electronic density of the molecule and, providing physically meaningful molecular dimensions. They found that good linear relationships exist between α and the most positive surface MEP value for two groups of hydrogen-bonded donors taken separately, the correlation coefficients were 0.96 and 0.97.[194]

These relationships between the solvatochromic parameters and the extrema of surface MEP confirm that the potential in the space around a gas-phase molecule is a key (even if not the sole) factor in determining its ability to accept a proton in a hydrogen bond. In the light of the success of electrostatic theories of hydrogen bonding, this is not surprising.

Recently we proposed to correlate the average molecular electrostatic field, F, with the hydration ability of a molecule.[195−199] The idea is based on the fact that the MEF near a molecule is proportional to the binding energy of a point dipole, e.g. a water molecule in this region, the larger is its value, the stronger binds a water molecule to the solute.[200] This concept can be used for a pictorial and qualitative description of hydration, location of hydrophilic and hydrophobic regions near a small molecule,[201] a protein,[202] characterization of molecular similarity,[203] and structure−property relationships.[204,205]

We derived quantitative relationships containing F, the molecular surface, S, its saturated apolar (S_{sa}), unsaturated apolar (S_{ua}), and polar (S_p) components, and other quantities to estimate various molecular properties. For the Hansch hydrophobicity indices of small molecules we have[198]

$$\log P = -0.190F - 0.010S_{ua} - 0.054S_p + 0.020S + 0.0014S_pF + 2.77 \quad (8)$$

$$r = 0.9098 \qquad n = 110 \qquad F = 99.0 \qquad s = 0.63$$

The Wolfenden hydrophobicity scale for amino acid residues can be estimated from the following equation with $R_{p/a} = S_p/(S_{sa} + S_{ua})$:[199]

$$HP(\mathrm{W}) = -0.756F - 0.251S_p + 3.25R_{p/a} + 22.0 \quad (9)$$

$$r = 0.9614 \qquad n = 18 \qquad F = 63.0 \qquad s = 1.83$$

The above equations indicate that there is a significant correlation between the average MEF and the hydration ability of molecules or parts of them, thus F is an appropriate descriptor to be used in quantitative structure−property relationships. Politzer and co-workers proposed another quantity, derived from the surface MEP, to describe molecular hydration and they applied it as a descriptor in an equation estimating solubility of various molecules in supercritical fluids with success.[206]

C. Complementarity and Similarity

1. Principles

Since the formulation of the lock-and-key analogy by Emil Fischer just 100 years ago[207] molecular recognition is one of the most important concepts in structural biology having influence on the theory of host−guest complexes and crystal packing, too. If we neglect dynamic aspects and remain in the framework of the rigid-body approximation we may consider the association between host and guest molecules as fitting a key into its lock. It has to be mentioned that enzymes may change their conformation due to the interaction with the substrate thus the static lock-and-key model is not perfect, in some cases it is better to speak about a hand-and-a-glove analogy. The lock-and-key model is best applied in cases where neither the biopolymer, nor the ligand changes its conformation essentially during association. Another possibility is to consider the biopolymer in its active conformation that is preformed to accommodate its more-or-less rigid partner. We should mention here a recent paper by Tapia et al. with a different view of complementarity.[208]

Within the static model a theory of molecular recognition must be able to define the terms "lock", "key", and "fit". The definition of the first two terms is straightforward. The "lock" refers to the crevice inside or on the surface of a molecular entity (biopolymer, pharmacophore, crystal, host) accommodating the "key", a whole molecule or part of it (ligand, pharmacon, asymmetric unit, guest). The definition of the term "fit" is more complicated.

In our terminology "fit" means the combination of at least three types of interactions: steric, electrostatic, and hydrophobic.[209,210] Steric fit means that interacting atoms may not approach each other beyond their van der Waals radii and, simulta-

neously, the crevice should be filled densely by reducing the free space between interacting atoms to a minimum. Electrostatic fit requires the maximum ionic and polar (hydrogen bonding and other dipole–dipole-type attraction) interaction between host and guest atoms. The term "hydrophobic" corresponds to the association trend between apolar groups in an aqueous medium. We may define molecular similarity on the same basis as complementarity: in the following we call two molecules similar if they fit into the same crevice. In an ideal case only one molecule (the lead) can fit perfectly, for all other species the fit, thus the similarity to the lead, will be imperfect.

Let us discuss now the three main aspects of complementarity on a semiquantitative basis.[209] The free energy of the host–guest interaction can be written as follows:

$$\delta G_{int} = \delta H_{vac} - T\delta S_{vac} - (\delta H_{solv} - T\delta S_{solv}) \quad (10)$$

where δH_{vac} and δH_{solv} stand for gas-phase interaction and solvation energy changes upon association, $T\delta S_{vac}$ and $T\delta S_{solv}$ are the corresponding entropy terms. The interaction energy between parts of a noncovalent complex can be decomposed as follows:[211]

$$\delta H_{vac} = \delta H_{elst} + \delta H_{pol} + \delta H_{ct} + \delta H_{ex} + \delta H_{disp} + \delta H_{mix} \quad (11)$$

The shorthand notations in parentheses correspond to electrostatic (Coulombic), polarization (inductive), charge-transfer, exchange repulsion, dispersion, and mixed terms, respectively.

δH_{ex} and δH_{disp} determine the steric fit. The exchange repulsion energy increases exponentially if two nonbonded atoms get close to each other. On the other hand, δH_{disp} represents attractive and nondirectional dispersion forces depending on the inverse higher powers of the interatomic distance. Its value becomes optimal if the crevice is filled by the ligand atoms perfectly. In an aqueous medium this is explained in terms of density differences between water and the host, the latter being more dense.[212] Upon host–guest association atoms may get closer to each other than in case of hydration, i.e. δH_{disp} increases. Another explanation is macromolecular crowding, an entropy effect forcing to reduce the water-accessible surface of dissolved molecules in order to avoid unfavorable perturbation of water structure around the solute.[213] Combining the above two effects we find that the better is the steric complementarity, the larger is the free energy of steric interaction.

δH_{elst} and δH_{pol} of eq 11 account for the electrostatic fit. The first contribution plays the primary role since in most cases it is proportional to the polarization term. Accordingly, the electrostatic interaction between host and guest has to be optimal, or put more simply, oppositely charged atoms should approach each other as close as possible. The trend may be visualized by the overlap between MEP regions of opposite sign as done first by Weiner et al.[214] for the trypsin–trypsin inhibitor and prealbumin–thyroxine complexes. This is not an exact treatment because in the power series derived in classical electrostatics the MEP interacts with point charges rather than with potentials. However, a phenomenological proportionality exists between the product of host and guest MEP values and electrostatic interaction energies.[215] This has been used as a basis for the quantitative definition of electrostatic complementarity at the level of molecular graphics.[216,217]

Hydrophobic complementarity is related mainly to the solvation- (hydration-) free energy term in eq 10, $\delta H_{hydr} - T\delta S_{hydr}$. As we already mentioned in section III.B, δH_{hydr} is approximately proportional to the magnitude of the MEF at the hydration site. Near small-field regions hydrophobic hydration takes place which means that the water molecules will be ordered more strongly than in the bulk and this leads to an unfavorable entropy loss. Association of such regions hinders hydrophobic hydration and leads to the increase of the free energy of interaction. Thus we have a simplified explanation for the observation that hydrophobic regions of host and guest tend to associate in aqueous solutions. On the other hand, hydrophilic groups also tend to associate because of the favorable electrostatic interaction between them. As a summary we may formulate the *similis simili gaudet* principle stating that electrostatically similar regions, characterized by MEF values of similar order of magnitude, tend to associate more than dissimilar ones.[126,195,209,210,218] An energetic analysis of complementarity, treating steric, electrostatic, and hydrophobic aspects, has been given by Warshel et al.[219] They found that electrostatic effects provide the largest contribution to antibody–antigen interactions.

While complementarity can be treated on a solid energetic basis, quantification of molecular similarity is more problematic.[220] Possible ways to consider electrostatic similarity are to compare MEP maps on the surface,[221,222] to perform shape group analysis,[223] to maximize electrostatic overlap,[224] to integrate the MEP and MEF numerically at points on a three-dimensional grid surrounding the molecules,[225,226] or to follow some other scheme.[227–229] These approaches allow the definition of similar indices finding application in quantitative structure–activity relationships and molecular graphics.[230]

2. Host–Guest Interactions

On the basis of the lock-and-key analogy electrostatic aspects of host–guest complementarity were discussed by several authors. Beyond cyclodextrins,[231,232] two-point adducts,[233] and crystal packing,[234–237] mostly protein–ligand[238–241] and nucleic acid–ligand[242–244] complexes have been studied. All three aspects of complementarity can be adequately visualized by molecular graphics. Graphic representations of steric complementarity are widely available, leading journals in chemistry and structural biology frequently publish beautiful, sometimes colored, illustrations provided by computers. Less is available on electrostatic and hydrophobic complementarity. In Figure 6 we display electrostatic complementarity between trypsin and basic pancre-

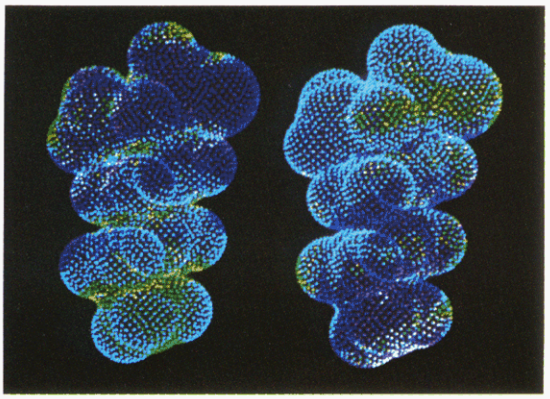

Figure 6. MEP on the van der Waals envelope of Lys-15 of BPTI emerging from the inhibitor (left) and the enzyme (right). Color (entries in kJ/mol) denote the following: MEP <-150, violet; $-150 <$ MEP < 0, blue; $0 <$ MEP < 150, cyan; $150 <$ MEP < 300, green; $300 <$ MEP, yellow. The figure was produced with the SYBYL software,[269] calculating the MEP by the neglect of diatomic differential overlap fragment self-consistent field method.[277]

atic trypsin inhibitor (BPTI). The MEP provided by the enzyme and the inhibitor on the van der Waals envelope of the BPTI Lys side chain is complementary, positive and negative regions match nicely. A similar representation of electrostatic complementarity for various protein-ligand associations has been given by Nakamura et al.[216]

In this review we discuss hydrophobic complementarity in terms of the MEF having the advantage over phenomenological representations[245,246] that it is based on a sound physical basis even if it may not cover all aspects of hydrophobicity (e.g. entropy effects). Investigating the specificity of the Asp/Ser-189 mutant of trypsin toward various substrates it was found that log k_{cat}/K_M, a quantity proportional to $-\delta G^{\ddagger}$, the negative of the activation free energy of the enzymatic reaction, and to δG_{int}, the enzyme–substrate interaction free energy, is larger for charged–charged and polar–polar pairs of side chains than for charged–polar ones.[126] This is unusual, since in the gas phase the charged–polar (monopole–dipole) interaction is stronger than the polar–polar (dipole–dipole) one.[8] Another effect, a further manifestation of the *similis simili gaudet* hypothesis outlined in the preceding subsection, was the considerable increase of log k_{cat}/K_M (decrease of $\delta G^{\ddagger}$) for the Ser-189···Lys(P_1) pair with increasing pH. Experimental data for single and double mutants in the specificity pocket of trypsin[127] further support these findings. A graphic representation of the effect is given in Figure 7.[209] Molecular regions characterized by MEF values of the same order of magnitude tend to associate as it is illustrated by the MEF color coded on the van der Waals surface. In native trypsin the protonated positive Lys P_1 side chain of the substrate has a deprotonated negative Asp-189 counterpart in the specificity pocket, both producing strong fields. In the Asp/Ser-189 mutant the complementarity is absent because the field around Ser is much smaller than around Asp. Thus the interaction energy (and log k_{cat}/K_M) will decrease, the activation energy will increase and, in fact, it is larger in the mutant than in the wild-type enzyme by 28 kJ/mol.[126] If we deprotonate the Lys P_1 side chain of the substrate by raising the pH, the interaction energy increases in the mutant by 11 kJ/mol leading to an increase of log k_{cat}/K_M, too, according to the fact that both interacting side chains are of medium polarity thus tend stronger to associate.

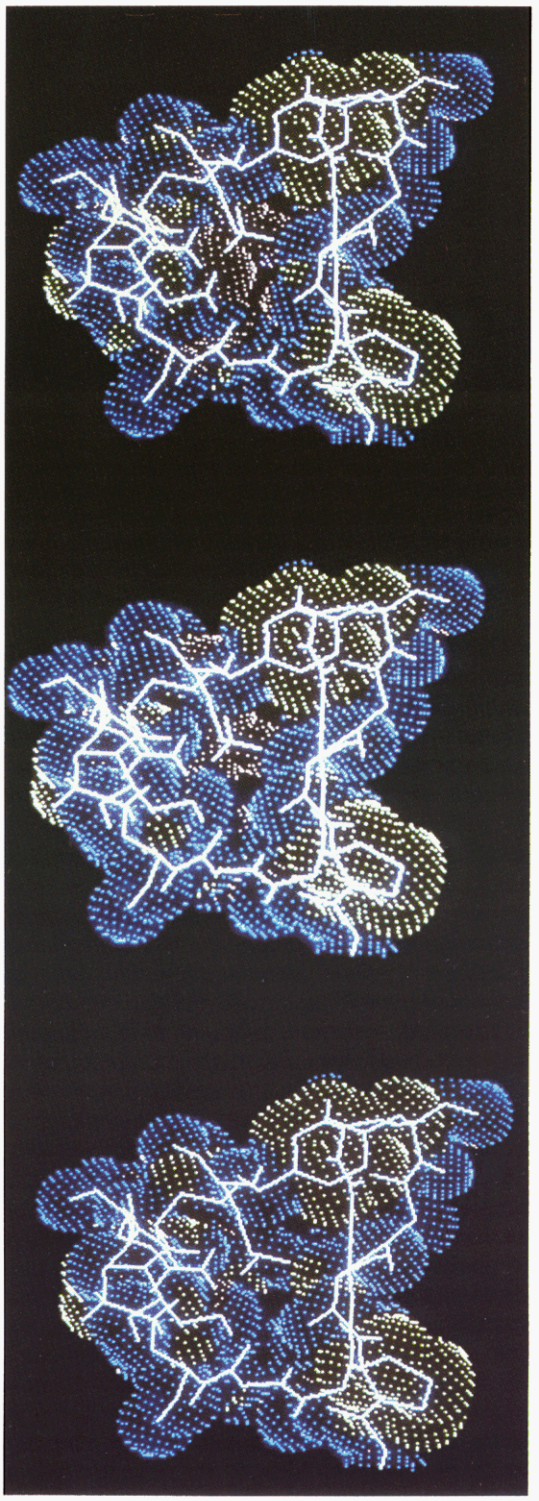

Figure 7. MEF displayed on the van der Waals surface of a model of the trypsin–substrate complex. Native trypsin–protonated substrate (at pH = 7) (top); Ser/Asp-189 mutant trypsin-protonated substrate (at pH = 7) (center); Ser/Asp-189 mutant tryspin-deprotonated substrate (at pH = 10.5) (bottom). Color (entries in V/nm) denote the following: $0 <$ MEF < 15, yellow; $15 <$ MEF < 25, blue; MEF > 25 pink. The figure was produced with the POTROT software.[278]

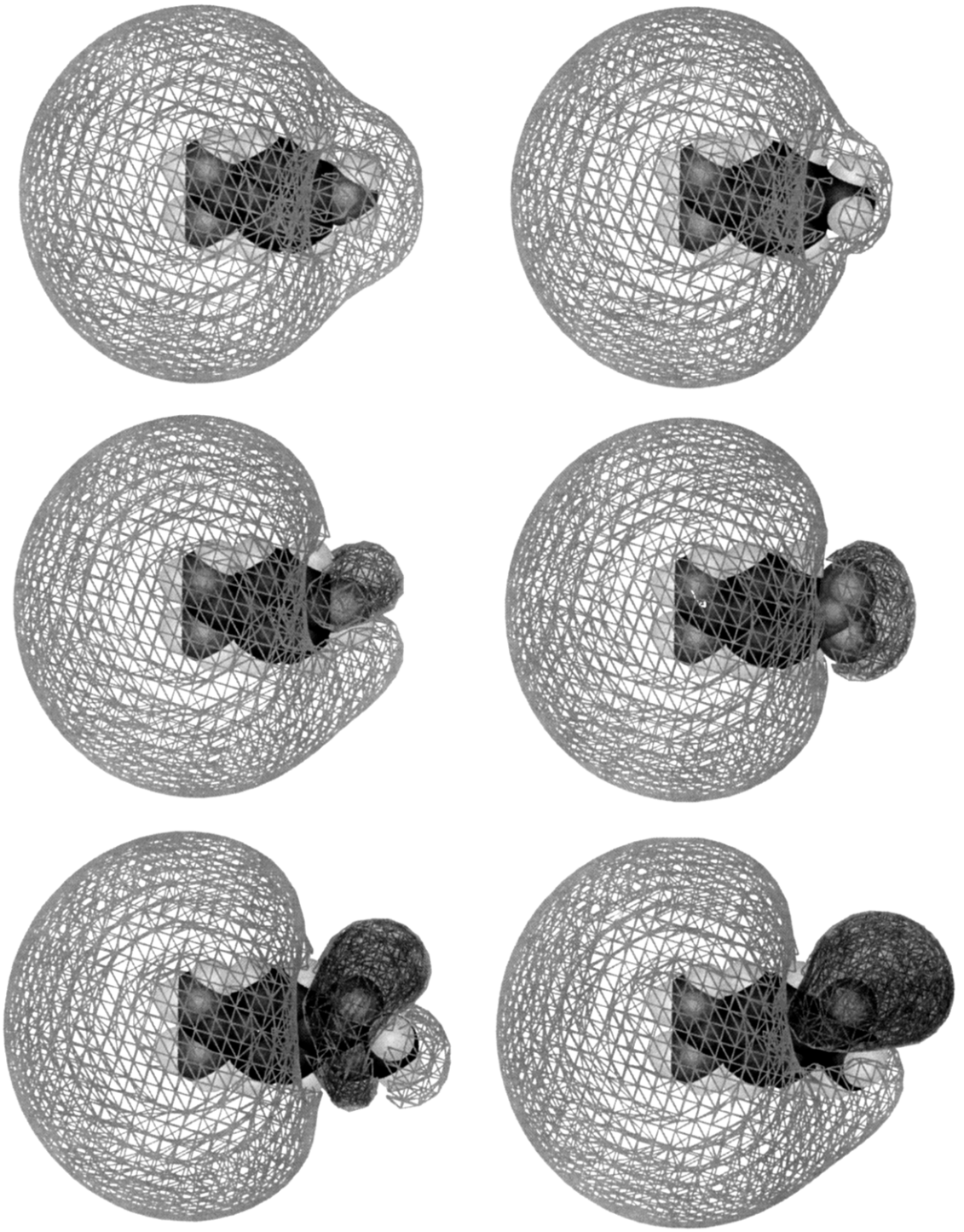

Figure 8. MEP contours (±8 kJ/mol) for substituted benzamidine derivatives (negative regions shaded): (top left) NH_2 (5.0), (top right) Me (4.5), (middle left) OH (4.3), (middle right) NO_2 (3.5), (bottom left) COOMe (3.5), (bottom right) COMe (3.5) (pK_i values for trypsin inhibition in parentheses). Figures were produced with the SYBYL software[275] using atomic monopoles after Gasteiger and Marsili.[274]

3. Structure–Activity Relationships

Since the MEP represents an aspect of molecular similarity, it finds wide application in structure–activity studies, as reviewed recently.[247,248] It has been related to dopaminergic activities,[249–252] H2 receptor antagonists,[253–255] benzodiazepine receptor ligands,[256,257] β-adrenoceptor activity,[258,259] toxicity,[260] and several other problems of pharmacological interest.[261–267] The MEP is used also in the CoMFA analysis[268–270] that became recently very popular in structure-based molecular design. It was also possible to design a transition-state analogue of nucleoside hydrolase on the basis of the MEP.[271]

In the following we illustrate how the MEP can be used to distinguish between two classes of benzamidine inhibitors (Figure 8). Earlier we have shown that differences in inhibitory potencies of substituted benzamidines to trypsin can be explained in terms of electrostatics.[272,273] The electrostatic interaction energies calculated from the protein MEP and the charge distribution of the inhibitor are in a fair linear correlation with the experimental binding free ener-

gies. Furthermore, we have shown that on the basis of the electrostatic patterns of the molecules they can be divided in two classes. As displayed in Figure 8 for six representative substituents the benzamidine moieties show perfect similarity, but the substituent regions are different. While the negative region is absent or is very small for NH_2, Me, and OH substituents, it is much more extended for NO_2, COOMe, and COMe substituents. Experimental inhibitory potencies are larger for the first class than for the second one and this rule can be extended to other substituents, also in the *meta* position, and to other serine proteases, like thrombin and plasmin.

We applied the average MEF, F, in some quantitative structure-activity relationships with success as in eqs 8 and 9. To put the *similis simili gaudet* principle on a more quantitative footing we tried to relate specificities of subtilisin mutants to F.[196,198] We derived the following equation:

$$\log k_{cat}/K_M = -0.1519F(P_1) - 0.0173S_{sa}(P_1) - 0.0027E_{Coul} + 8.33 \quad (12)$$

$$r = 0.915 \qquad n = 47 \qquad F = 73.8 \qquad s = 0.55$$

where P_1 stands for the corresponding side chain position in the substrate, E_{Coul} is the electrostatic interaction energy between a model of the enzyme and the substrate and other notations are equivalent to those in eqs 8 and 9. We derived another equation for the inhibitory potencies of triazine inhibitors of dihydrofolate reductase[195,197]

$$\log K_i = -0.1222F - 0.010S_{ua} - 0.054S_p + 0.020S + 0.0014S_p.F + 2.77 \quad (13)$$

$$r = 0.9098 \qquad n = 110 \qquad F = 99.0 \qquad s = 0.63$$

In the light of our conclusions in section 3B on the dependence of hydration on the MEF, the above relationships indicate that both substrate and inhibitor binding are essentially influenced by the hydration−dehydration process.

IV. Conclusions

In this paper we presented arguments that noncovalent bonding between polar and/or charged molecules (hydrogen bonding, host−guest association, solvation, etc.) is mainly governed by classical electrostatics. This allows one to treat such interactions at a simpler and computationally faster level than by quantum mechanics, which is necessary only for the determination of the charge distributions of the isolated species. We mentioned two important phenomena where electrostatics plays a crucial role:

(1) *Electrostatic catalysis* is effective for molecular processes where the dipole moment of the transition-state complex is considerably larger than that of the reactants in the initial state. The transition state can be stabilized electrostatically by a catalyst (metal ion, polar solvent, zeolite cavity, protein environment) leading to the increase in reaction rate.

(2) *Electrostatic molecular recognition* plays a crucial role in the interaction between polar hosts and guests and can be best formulated in molecular graphics by comparing molecular electrostatic potentials and fields. The requirement of electrostatic complementarity between interacting partners means the matching of MEP regions of the opposite sign, while hydrophobic complementarity means matching of MEF regions of the same order of magnitude.

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