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Electronegativity Equalization Method for the Calculation of Atomic Charges in Molecules

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Abstract: On the basis of the principle of electronegativity equalization, a formalism has been developed for the calculation of atomic charges in molecules which are connectivity and geometry dependent. The effective electronegativity of an atom in a molecule, which is equal to the molecular electronegativity, is given by eq 34 where $\chi_\alpha{}^\circ$ and $\eta_\alpha{}^\circ$ are the neutral atom electronegativity and hardness, respectively, q_α and q_β are the charges on atoms α and β, and $R_{\alpha\beta}$ is the internuclear distance. The parameters $\Delta\chi_\alpha$ and $\Delta\eta_\alpha$ are the corrections to the neutral atom electronegativity and hardness that arise as a consequence of bonding. A theoretical justification for the above formulation is provided within the framework of density functional theory. $\Delta\chi$ and $\Delta\eta$ are obtained by calibrating through small-molecule calculations and are transferable and consistently usable for calculating charges in any molecule. The formalism is tested through calculation of atomic charges in several small and large molecules including alanine dipeptide and riboses which are of biological importance. Atomic charges in interacting molecules viz. water dimers are also studied.

The principle of electronegativity equalization has led to the development of a formalism for the calculation of atomic charges in molecules which are geometry and connectivity dependent.[1] This formalism, which has a rigorous theoretical basis in the Hohenberg and Kohn theorem,[2] invokes the concept of an atom in a molecule through partitioning of the molecular density into atomic-like densities. Parr et al.[3] have shown that the electronegativity, χ, of any chemical species[4] is nothing but the negative of its chemical potential, μ, obtained from density functional theory as in eq 1 and 2 where E is the exact Hohenberg and Kohn energy

$$\mu = \left(\frac{\delta E[\rho]}{\delta \rho}\right)_v \tag{1}$$

$$\mu = \left(\frac{\partial E}{\partial N}\right)_v \tag{2}$$

functional for an N-electron system characterized by an external potential $v(\vec{r})$. Thus, density functional theory[5] provides a quantum mechanical justification for electronegativity, a concept used intuitively for a long time by chemists, and validates Sanderson's postulate[6] that when two or more atoms combine to form a molecule, their electronegativities get equalized. Moreover, not only the atomic electronegativities but also those of all arbitrary portions of the total number of electrons are the same in the equilibrium state as shown by Politzer and Weinstein,[7] independent of any density functional framework. The question as to at what distance of separation between atoms do the chemical potentials equalize is very fundamental[8] and has been shown to be related to the EPR paradox in quantum mechanics.[9] This is not of concern here since equilibrium configurations are considered where no ambiguity arises regarding the equalization.

Electronegativity equalization is fundamental for possible quantitative applications. A knowledge of the variation of the electronegativity with charge together with a formalism simulating the equalization of the chemical potentials of the different charge clouds upon bond formation should be sufficient for calculating atomic charges in molecules. To a first approximation, this was attempted by Huheey[10] and Parr and Pearson.[11] Atomic "hardness", η, was defined by Parr and Pearson as eq 3 from the expansion of energy in terms of the number of electrons (eq 4).

$$\eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_v = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_v \tag{3}$$

$$E = E^\circ + \left(\frac{\partial E}{\partial N}\right)_0 \Delta N + \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_0 (\Delta N)^2 + \ldots \tag{4}$$

To first order, the derivative of energy with respect to the number of electrons, μ, of an atom in a molecule is given by eq 5 where the zeroeth-order quantities belong to the neutral atom

$$\mu = \left(\frac{\partial E}{\partial N}\right)_v = \mu^\circ + 2\eta^\circ \Delta N \tag{5}$$

and ΔN is the number of electrons transferred in bond formation. In a diatomic molecule AB, equalizing the chemical potentials of the two atoms A and B yields eq 6.

$$\Delta N = (\mu_B{}^\circ - \mu_A{}^\circ)/2(\eta_A{}^\circ + \eta_B{}^\circ) \tag{6}$$

Difference in electronegativities drives the electron transfer, while the sum of hardnesses attenuates this. However, application of this approach to polyatomic molecules results in connectivity-independent charges, which is contrary to chemical intuition.

The importance of the neighbouring atoms for the chemical potential of the electrons becomes clear when examining the expression for μ in the density functional theory[5,12] eq 7 where

$$\mu = v_{ne}(\bar{r}) + \frac{\delta F[\rho]}{\delta \rho} \tag{7}$$

$v_{ne}(\bar{r})$ is the nuclear–electron potential and $F[\rho]$ is the functional containing the kinetic energy $T[\rho]$ and the electron–electron

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repulsion term $V_{ee}[\rho]$. For an atom in a molecule, the external potential to the electrons, i.e., v_{ne}, for the isolated atom will be supplemented by the potentials arising from the interactions with all other nuclei and their charge clouds. At the same time, we cannot expect $T[\rho]$ and $V_{ee}[\rho]$ to remain unaffected if the shape and the dimension of the charge cloud change. The effect of the external potential changes has been recently considered by Nalewajski.[13]

Reliable calculated charge transfers can only be expected from a formalism simulating the equalization of the chemical potentials upon bond formation if it not only accounts for the change of μ with charge (eq 6) but also corrects for the external potential as well as size and shape effects. Connectivity-dependent charges will then result from this. Since the energy of a many-electron system in a given potential is a unique function of the density of the system (Hohenberg and Kohn theorem[2]), this is exactly what we expect to find: with a given charge distribution, there can exist only one unique external potential. Atoms in a different position are subject to different external potentials, and they should therefore have distinct effective charges. Mortier et. al[1] were able to obtain atomic connectivity-dependent charges by using an empirical formalism (electronegativity equalization method, EEM), correcting the isolated-atom electronegativity for the external potential and including an atomic correction term. In this way, excellent correlations were obtained between the calculated atomic charges and C_{1s} binding energies (ESCA shifts). At the same time, it was demonstrated that an equally successful formalism for calculating charges in organic molecules[14] (partial equalization of orbital electronegativity, PEOE) simulates the process of bond formation.

The present paper has two objectives: (a) to find theoretical support based on density functional theory for the EEM and (b) to portray the importance of this scheme in the calculation of atomic charges in macromolecules. The latter has become extremely important in recent years due to the large interest generated in molecular mechanics and dynamics simulations.[15] Atomic charges are essential for calculating force fields for these simulations, and obtaining charges from ab initio calculations is nearly impossible. In this paper we demonstrate the utility of EEM by calculating atomic charges in a dipeptide and a nuecleotide, besides other molecules, with a view to extending the calculations to proteins and nucleic acids. The general validity of the parametrization scheme is thereby established.

Effective Chemical Potential of an Atom in a Molecule. Since electronegativity represents[4] the derivative of energy with respect to the number of electrons, N, one way to obtain an expression for effective electronegativity is through expressing energy as a function of N. On the other hand, one can directly obtain the electronegativity of an atom in a molecule from perturbative considerations.

The total molecular energy is a function of the number of electrons N, the external potential arising from all nuclear charges Z_α, Z_B, etc., and the internuclear distances $R_{\alpha\beta}$, etc. In the molecule, chemical potentials of individual atoms (identical with the chemical potential of the molecule) can be calculated following Politzer and Weinstein[7] by evaluating the energy derivatives with respect to the number of electrons N_α, N_β, etc., associated with the corresponding atoms, viz., eq 8. In order to obtain these

$$\mu = \left(\frac{\partial E}{\partial N_\alpha}\right)_{N_\beta \ldots R_{\alpha\beta} \ldots} = \left(\frac{\partial E}{\partial N_\beta}\right)_{N_\alpha \ldots R_{\alpha\beta} \ldots} \tag{8}$$

derivatives in a simple manner, it is convenient to express the total molecular energy as a sum of atomic-like contributions which constitute the energy of an atom in a molecule. This is achieved by a proper partitioning of the interatomic interaction terms into individual atomic contributions.

The total molecular energy consists of the kinetic (T), nuclear–electron (V_{ne}), electron–electron (V_{ee}), and nuclear–nuclear (V_{nn}) potential energy contributions, viz., eq 9–13. Here ψ, γ,

$$E_{mol} = T + V_{ne} + V_{ee} + V_{nn} \tag{9}$$

where

$$T = \left\langle \psi_{mol} \right| -\frac{1}{2}\sum_i^N \nabla_i^2 \left| \psi_{mol} \right\rangle = -\frac{1}{2}\int \nabla^2 \gamma_{mol}(\vec{r},\vec{r}')|_{r=r'}\, d\vec{r} \tag{10}$$

$$V_{ne} = \left\langle \psi_{mol} \middle| -\sum_i \sum_\alpha \frac{Z_\alpha}{|\vec{r}_i - \vec{R}_\alpha|} \middle| \psi_{mol} \right\rangle = -\sum_\alpha \int \frac{Z_\alpha}{|\vec{r} - \vec{R}_\alpha|} \rho_{mol}(\vec{r})\, d\vec{r} \tag{11}$$

$$V_{ee} = \left\langle \psi_{mol} \middle| \frac{1}{2}\sum_i \sum_j \frac{1}{|\vec{r}_i - \vec{r}_j|} \middle| \psi_{mol} \right\rangle = \frac{1}{2}\int\int \frac{\Gamma_2^{mol}(\vec{r}_1,\vec{r}_2)}{r_{12}}\, d\vec{r}_1\, d\vec{r}_2 \tag{12}$$

$$V_{nn} = \frac{1}{2}\sum_\alpha \sum_\beta \frac{Z_\alpha Z_\beta}{R_{\alpha\beta}} \tag{13}$$

ρ, and Γ_2 denote the molecular wave function, first-order density matrix, electron density, and the two-particle density, respectively. Z_α and $\vec{R}_\alpha$ denote the nuclear charge and coordinates of the αth atom, and $R_{\alpha\beta}$ is its internuclear distance from the βth atom.

The molecular electron density can now be partitioned as eq 14 where $\rho_\alpha(\vec{r})$ integrates to N_α, the number of electrons in the atomic fragment α in the molecule. V_{ne} can then be simplified

$$\rho_{mol}(\vec{r}) = \sum_\alpha \rho_\alpha^{mol}(\vec{r}) \tag{14}$$

as eq 15 and 16 where the approximation in the last term corresponds to the assumption of a spherically symmetric "atomic" charge cloud $\rho_\beta(\vec{r})$.

$$V_{ne} = -\sum_\alpha Z_\alpha \int \frac{\rho_\alpha{}^{mol}(\vec{r})}{|\vec{r} - \vec{R}_\alpha|}\, d\vec{r} - \sum_\alpha \sum_{\beta \neq \alpha} Z_\alpha \int \frac{\rho_\beta{}^{mol}(\vec{r})}{|\vec{r} - \vec{R}_\alpha|}\, d\vec{r} \tag{15}$$

$$V_{ne} \approx -\sum_\alpha Z_\alpha \int \frac{\rho_\alpha{}^{mol}(\vec{r})}{|\vec{r} - \vec{R}_\alpha|}\, d\vec{r} - \sum_\alpha \sum_{\beta \neq \alpha} \frac{Z_\alpha N_\beta}{R_{\alpha,\beta}} \tag{16}$$

It may be noted here that the density partitioning of eq 14 is not unique. In fact, several such partitioning schemes[16,17] have been proposed in the literature. For example, the virial partitioning of Bader et al.[16] separates the atomic regions by boundaries defined through the zero-density gradient criterion, while in some others[17] the atomic densities extend over the entire molecule. Although the rigorous regional partitioning based on virial criterion[16] yields atomic-like densities which are not truly spherical, the molecular electron density has been known to be well represented[18] by using spherical atomic fragments.

Such a spatial partitioning is helpful in simplifying the other terms in the energy expression. Integrating over the atomic region Ω_α, the kinetic energy T can be written as[19] eq 17.

$$T = \sum T_\alpha{}^{mol} = \sum_\alpha \int_{\Omega_\alpha} -\frac{1}{2}\nabla^2 \gamma(\vec{r};\vec{r}')|_{\vec{r}=\vec{r}'}\, d\vec{r} \tag{17}$$

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[18] Francl, M. M.; Hout, R. F., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 563–570.

[19] It may be noted that the partitioning of the kinetic energy into atomic terms is not trivial since the density partitioning given by eq 14 does not imply an analogous partitioning of the single-particle density matrix. However, the kinetic energy decomposition of eq 17 is possible when spatial partitioning is followed to decompose the density (see, e.g.: Bader, R. F. W.; Nguyen-Dan, T. T. *Adv. Quantum Chem.* **1981**, *14*, 63–124), although the density martix is not partitioned even in this case.

The electron–electron repulsion term V_{ee} can also be separated into intra- and interatomic contributions as eq 18. The last term

$$V_{ee} = \frac{1}{2}\sum_{\alpha}\int_{\Omega_\alpha} d\vec{r}_1 \int_{\Omega_\alpha} d\vec{r}_2 \frac{\Gamma_2(\vec{r}_1,\vec{r}_2)}{r_{12}} + \frac{1}{2}\sum_{\alpha}\sum_{\beta\neq\alpha}\int_{\Omega_\alpha} d\vec{r}_1 \int_{\Omega_\beta} d\vec{r}_2 \frac{\Gamma_2(\vec{r}_1,\vec{r}_2)}{r_{12}} \quad (18)$$

can again be simplified by approximating Γ_2 as a product of $\rho(\vec{r}_1)$ and $\rho(\vec{r}_2)$ where $\vec{r}_1$ and $\vec{r}_2$ belong to different atomic regions. Assuming further spherical atomic densities, we obtain eq 19.

$$V_{ee} = \frac{1}{2}\sum_{\alpha}\int_{\Omega_\alpha} d\vec{r}_1 \int_{\Omega_\alpha} d\vec{r}_2 \frac{\Gamma_2(\vec{r}_1,\vec{r}_2)}{r_{12}} + \frac{1}{2}\sum_{\alpha}\sum_{\beta\neq\alpha}\frac{N_\alpha N_\beta}{R_{\alpha\beta}} \quad (19)$$

When the first terms in eq 16 and 19 are denoted by $\sum_\alpha v_{ne}^{\alpha,mol}$ and $\sum_\alpha v_{ee}^{\alpha,mol}$, respectively, the energy expression is explicitly written as eq 20. The total energy is thereby factorized into

$$E_{mol} = \sum_{\alpha}[T_\alpha^{mol} + V_{ne}^{\alpha,mol} + V_{ee}^{\alpha,mol}] + \sum_{\alpha}\left[-N_\alpha\sum_{\beta\neq\alpha}\frac{Z_\beta}{R_{ab}} + \frac{1}{2}\sum_{\beta\neq\alpha}\frac{N_\alpha N_\beta}{R_{\alpha\beta}}\right] + \frac{1}{2}\sum_{\alpha}\sum_{\beta\neq\alpha}\frac{Z_\alpha Z_\beta}{R_{\alpha\beta}} \quad (20)$$

typical "atomic" terms (intraatomic, i.e., the first sum in (20)) and atom–atom interaction terms (interatomic) and can as such be written as a sum of effective atomic energies (E_α^{mol}) (eq 21).

$$E_{mol} = \sum_{\alpha} E_\alpha^{mol} = \sum_{\alpha}(E_{\alpha,mol}^{intra} + E_{\alpha,mol}^{inter}) \quad (21)$$

The intraatomic contribution depends on the number of electrons as well as the shape factor[20] for the density function. In a molecule, this contribution differs from the isolated atom value due to the change in the number of electrons ($\Delta N_\alpha = N_\alpha - N_\alpha^\circ$) as well as a change of the shape factor due to molecule formation. The latter depends on the details of the electron density profile, i.e., the shape and size or the nature of confinement of the atom in the molecule, and includes covalent bonding effects.

Expanding E_α^{intra} in Taylor series around the spatially confined neutral atom energy value analogous to the expansion for the neutral atom in eq 4, we obtain eq 22. The final total energy expression is then given by eq 23.

$$\begin{aligned} E_\alpha^{intra} &= E_\alpha^* + \left(\frac{\partial E_\alpha^*}{\partial N}\right)\Delta N_\alpha + \frac{1}{2}\left(\frac{\partial^2 E_\alpha^*}{\partial N^2}\right)(\Delta N_\alpha)^2 \\ &= E_\alpha^* + \mu^*\Delta N_\alpha + \eta^*(\Delta N_\alpha)^2 \end{aligned} \quad (22)$$

$$E_{mol} = \sum_{\alpha}\left(E^* + \mu_\alpha^*\Delta N_\alpha + \eta_\alpha^*(\Delta N_\alpha)^2 - N_\alpha\sum_{\beta\neq\alpha}\frac{Z_\beta}{R_{\alpha\beta}} + \frac{1}{2}N_\alpha\sum_{\beta\neq\alpha}\frac{N_\beta}{R_{\alpha\beta}} + \frac{1}{2}\sum_{\beta\neq\alpha}\frac{Z_\alpha Z_\beta}{R_{\alpha\beta}}\right) \quad (23)$$

The chemical potential of the atom α in the molecule is now obtained by using eq 8 and 23 and replacing eq 24. Thus we obtain eq 25. This expression for the effective chemical potential of the

$$\mu_\alpha^* = \mu_\alpha^\circ + \Delta\mu_\alpha \qquad \eta_\alpha^* = \eta_\alpha^\circ + \Delta\eta_\alpha \quad (24)$$

$$\mu_\alpha = \left(\frac{\partial E_{mol}}{\partial N_\alpha}\right)_{N_\beta \ldots R_{\alpha\beta}\ldots} = (\mu_\alpha^\circ + \Delta\mu_\alpha) + 2(\eta_\alpha^\circ + \Delta\eta_\alpha)\Delta\eta_\alpha - \sum_{\beta\neq\alpha}\frac{Z_\beta - N_\beta}{R_{\alpha\beta}} \quad (25)$$

atom in the molecule explicitly refers to the isolated atom (μ_α° and η_α°) but includes correction terms for the change in size and shape of the atom in the molecule ($\Delta\mu_\alpha$ and $\Delta\eta_\alpha$), the charge transfer (ΔN_α), and the external potential ($\sum_\beta(Z_\beta - N_\beta))/R_{\alpha\beta}$).

While eq 25 has been obtained from the energy derivative through wave function approach, the same can alternatively be arrived at by evaluating the correction to isolated atom chemical potential due to molecule formation from perturbation theoretic consideration within a density functional framework.

For this purpose, consider the chemical potential as a function of the number of electrons N and the external potential $v(\vec{r})$ which characterizes the system. We can then express the change in chemical potential by eq 26 and 27 where $f(\vec{r})$, the Fukui function, is defined through the relation[21] eq 28.

$$\Delta\mu_\alpha = \int \frac{\delta\mu_\alpha}{\delta v(\vec{r})}\Delta v(\vec{r})\, d\vec{r} + \frac{\partial\mu_\alpha}{\partial N}\Delta N_\alpha \quad (26)$$

$$\Delta\mu_\alpha = \int f_\alpha(\vec{r})\,\Delta v(\vec{r})\, d\vec{r} + 2\eta_\alpha\Delta N_\alpha \quad (27)$$

$$\frac{\delta\mu}{\delta v(\vec{r})} = \frac{\delta\rho(\vec{r})}{\delta N} = f(\vec{r}) \quad (28)$$

Equation 27 should be, in principle, sufficient to calculate the effective chemical potential of an atom (αth) in a molecule. However, the external potential variation $\Delta v(\vec{r})$ which arises because of interaction with the other nuclei as well as electrons belonging to them can, in practice, be evaluated only approximately. We assume $\Delta v(\vec{r})$ to be equal to the interaction potential, at any point within the atom α, with the electrostatic potential of the other atoms, say β, i.e., eq 29. Assuming now spherically symmetric densities for each atom and writing $\vec{x} = \vec{r} - \vec{R}_{\alpha\beta}$ and $\vec{x}' = \vec{r}' - \vec{R}_{\alpha\beta}$, we obtain eq 30 where N_β is the number of electrons enclosed in a sphere of radius x around nucleus β. Since we are interested in finding $\Delta v(\vec{r})$ at points $\vec{r}$ within the αth atomic sphere, the minimum value of $|\vec{x}| = r_\beta$, the radius of the βth atom. The last integral in eq 30 is therefore neglected, and N_β is the total number of electrons in atom β. Equation 27 then becomes eq 31. Again, assuming a spherically symmetric $f_\alpha(\vec{r})$ around nucleus α, we can write eq 32 where the second integral has been neglected (the Fukui function integrates to unity).

$$\Delta v(\vec{r}) = -\sum_{\beta}\frac{Z_\beta}{|\vec{r} - \vec{R}_{\alpha\beta}|} + \sum_{\beta}\int\frac{\rho_\beta(\vec{r}')}{|\vec{r} - \vec{r}'|}d\vec{r}' \quad (29)$$

$$\begin{aligned} \Delta v(\vec{r}) &= -\sum_{\beta}\left(\frac{Z_\beta}{x} - \int\frac{\rho_\beta(\vec{x}')}{|\vec{x} - \vec{x}'|}d\vec{x}'\right) \\ &= -\sum_{\beta}\left(\frac{Z_\beta}{x} - \frac{1}{x}\int_0^x \rho_\beta(\vec{x}')\, d\vec{x}' - \int_x^\infty \frac{\rho_\beta(\vec{x}')}{x'}d\vec{x}'\right) = -\sum_{\beta}\left(\frac{Z_\beta - N_\beta}{x}\right) \end{aligned} \quad (30)$$

$$\Delta\mu_\alpha = -\sum_{\beta}(Z_\beta - N_\beta)\int\frac{f_\alpha(\vec{r})}{|\vec{r} - \vec{R}_{\alpha\beta}|}d\vec{r} + 2\eta_\alpha\Delta N_\alpha \quad (31)$$

$$\begin{aligned} \Delta\mu_\alpha &= -\sum_{\beta}(Z_\beta - N_\beta)\left(\frac{1}{R_{\alpha\beta}}\int_0^{R_{\alpha\beta}} f_\alpha(\vec{r})\, d\vec{r} + \int_{R_{\alpha\beta}}^\infty \frac{f_\alpha(\vec{r})}{r}d\vec{r}\right) + 2\eta_\alpha\Delta N_\alpha \\ &= -\sum_{\beta}\frac{(Z_\beta - N_\beta)}{R_{\alpha\beta}} + 2\eta_\alpha\Delta N_\alpha \end{aligned} \quad (32)$$

The contribution due to detailed intraatomic variation in the profile of the electron density due to molecule formation and concomitant confinement of the atom has not, however, explicitly been incorporated in deriving eq 32. Considering the reference state to be this confined atom (with chemical potential μ_α^* and

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(20) Parr, R. G.; Bartolotti, L. J. *J. Phys. Chem.* **1983**, *87*, 2810–2815. These authors define a shape factor, σ, by factorizing the explicit N dependence of the density; $\rho^{mol}(\vec{r}) = N^{mol}\sigma^{mol}(\vec{r})$, where $\sigma^{mol}(\vec{r})$ integrates to unity.

(21) Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049–4050.

hardness η_α^*) rather than the free isolated atom (characterized by μ_α° and η_α°), eq 32 becomes eq 33. With μ_α^* and η_α^* given by eq 24, one recovers eq 25 from eq 33.

$$\Delta\mu_\alpha^* = \mu_\alpha - \mu_\alpha^* = -\sum_\beta \frac{(Z_\beta - N_\beta)}{R_{\alpha\beta}} + 2\eta_\alpha^*\Delta N_\alpha \qquad (33)$$

Recently, Nalewajski[22] has also obtained an expression for the effective chemical potential of an atom in a molecule through expansions in terms of N and $v(\bar{r})$ as well as $\rho(\bar{r})$ and $v(\bar{r})$. His treatment for a diatomic molecule takes into account the contribution due to $\Delta v(\bar{r})$ through a model potential. In the present expression, generalized for polyatomic molecules, we consider the external potential effects explicitly (within a spherical atomic density approximation) and incorporate the confinement or covalent contributions to the change in μ and η as well. (Notice that the term $2\Delta\eta_\alpha q_\alpha$ in eq 24 and 33 is essential for the calculation of meaningful charges.[1])

Electronegativity Equalization and Partial Charges. The existence of a unique chemical potential everywhere in the molecule establishes the electronegativity equalization principle. Rewriting eq 25 as eq 34, the electronegativity equalization principle demands that eq 35 apply for all atoms α, β, γ, etc., in the molecule. This

$$\chi_\alpha = (\chi_\alpha^\circ + \Delta\chi_\alpha) + 2(\eta_\alpha^\circ + \Delta\eta_\alpha)q_\alpha + \sum_{\beta\neq\alpha}\frac{q_\beta}{R_{\alpha\beta}} \qquad (34)$$

$$\chi_\alpha = \chi_\beta = \chi_\gamma = \ldots \qquad (35)$$

yields $(n - 1)$ simultaneous equations for a molecule containing n atoms; these, along with the constraint equation on the net charge in the molecule, can be solved to give the charges on each atom in a molecule if all other parameters in eq 34 are known.

The electronegativity χ and the hardness η for most atoms are available from Sanderson[6] and Parr and Pearson[11] scales, respectively, and are used in this method. Other scales may also be consistently used with these equations as pointed out by Mortier et al.[1]

The parameters $\Delta\chi$ and $\Delta\eta$ merit discussion, since they portray the influence of the environment and connectivity on electronegativity and hardness of the free atom.

The correction to the free-atom electronegativity obviously contains two major effects: (i) corrections invoked by the change in size and shape of the atom in the molecule ($\Delta\chi_\alpha$ and $\Delta\eta_\alpha$) and (ii) the external potential originating from the surrounding molecules. The former effect, which may be called a volume-confinement effect, has its equivalent approach in quantum chemistry. It is known that the charges obtained by quantum mechanical ab initio calculations are considerably improved by treating the ζ exponents of the Slater-type orbitals as variational parameters (see, e.g., ref 23). These are directly related with the size of these orbitals. Examples and an extended discussion are given by Fliszar.[24] In an analysis of H_2^+, an orbital contraction with respect to the H atom is also found.[25] In the case of a heteropolar one-electron bond, Feinberg and Ruedenberg[26] observed a contraction of both orbitals. However, they emphasize the fact that there exists a tendency for the atomic orbitals of the two parent atoms to become more similar in size upon bond formation. This illustrates the importance of $\Delta\chi_\alpha$, since, although the relative offset only being of importance, the effect on two different atoms will not result in a cancellation. This volume-confinement effect being distinct for different atom types (and probably also subject to different surroundings) changes the atomic energies and therefore also their electronegativities.

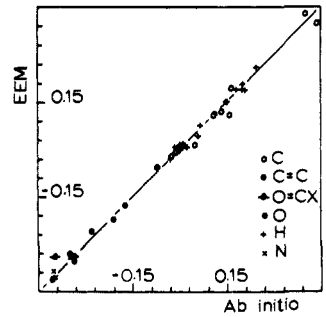

Figure 1. Calibration curve for $\Delta\chi$ and $\Delta\eta$ using Pople's ζ-optimized charges.

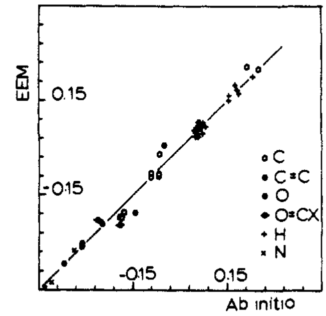

Figure 2. Calibration curve for $\Delta\chi$ and $\Delta\eta$ using ab initio STO-3G charges.

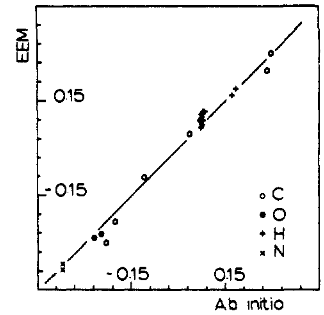

Figure 3. Comparison of EEM and ab initio charges for alanine dipeptide.

Table I. Values of $\Delta\chi$ and $\Delta\eta$ (in eV)

atom	$\Delta\chi$	$\Delta\eta$
A. Calibration with STO-3G Charges		
C	0.3303	0.5965
N	0.4739	0.7343
O	0.5081	1.0010
H	0.2541	0.4937
B. Calibration with ζ-Optimized Charges		
C	0.2633	0.6170
H	0.2817	0.4057
O	0.3552	0.6967
N	0.5122	0.9284

While theoretically it is possible to estimate these parameters from ab initio molecular wave functions, it is computationally a very difficult task. Since our primary objective is to calculate atomic charges, it is desirable to mode these parameters empirically such that they are transferable from molecule to molecule and are able to accurately reproduce atomic charges in molecules. With this objective, $\Delta\chi$ and $\Delta\eta$ are calibrated through a least-squares adjustment of the effective electronegativities of several small molecules with specified configurations and charges. To model these so as to reproduce charges in macromolecules containing H, C, N, and O, small molecules containing representative functional groups were used in the calibration. These included propane, ethene, propene, water, methanol, dimethyl ether, methylamine, dimethylamine, formaldehyde, formic acid, and for-

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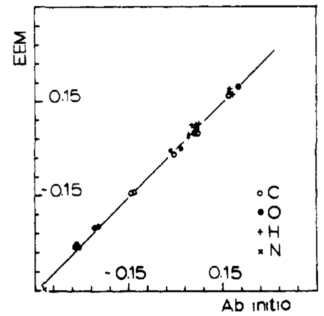


Figure 4. Comparison of EEM and ab initio charges for deoxyribose and 2-aminodeoxyribose.

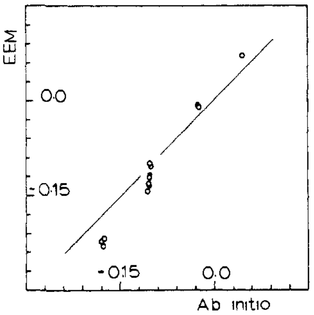


Figure 5. Comparison of EEM and ab initio charges on the carbon atoms in cyclohexane, methylcyclohexane, 1,3,5-trimethylcyclohexane, and 1,1,3-trimethylcyclohexane.

Table II. Comparison of Ab Initio and EEM Charges for Alanine Dipeptide[a] (CF Configuration)

atom	STO-3G	EEM
C1	−0.23	−0.29
C2	0.30	0.30
O3	−0.27	−0.28
H4	0.09	0.11
H5	0.08	0.10
H6	0.09	0.11
N7	−0.37	−0.38
C8	0.04	0.04
H9	0.19	0.19
C10	0.28	0.25
N11	−0.36	−0.36
C12	−0.10	−0.09
H13	0.07	0.07
C14	−0.20	−0.23
H15	0.08	0.10
H16	0.08	0.11
H17	0.08	0.10
O18	−0.24	−0.27
H19	0.17	0.17
H20	0.08	0.07
H21	0.07	0.07
H22	0.08	0.08

[a] See Figure 7.

mamide. Two sets of charges[27] one obtained from STO-3G calculations[28] and the other, obtained from Pople's exponent-optimized calculations,[23] were tested in the calibration. The calibration curves for the two cases are presented in Figures 1 and 2; $\Delta\chi$ and $\Delta\eta$ values thus obtained are reported in Table I. In both cases, charges which are consistent with the respective calculations are reproduced in small molecules that are not used in the calibration.

Table III. Comparison of ab Initio and EEM Charges for 2-Aminodeoxyribose[a]

atom	STO-3G	EEM
C1	0.06	0.05
C2	0.07	0.05
C3	−0.14	−0.14
O4	−0.32	−0.31
H5	0.04	0.04
H6	0.18	0.17
H7	0.08	0.08
C8	0.00	−0.01
O9	−0.31	−0.30
H10	0.07	0.07
H11	0.07	0.07
H12	0.20	0.20
H13	0.05	0.07
H14	0.05	0.07
O15	−0.25	−0.25
C16	0.17	0.17
H17	0.06	0.05
N18	−0.42	−0.44
H19	0.17	0.17
H20	0.18	0.19

[a] See Figure 7.

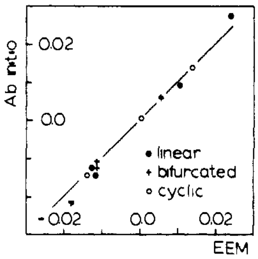
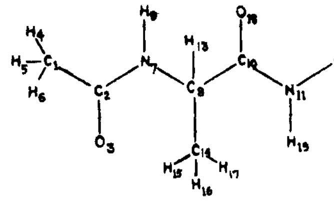
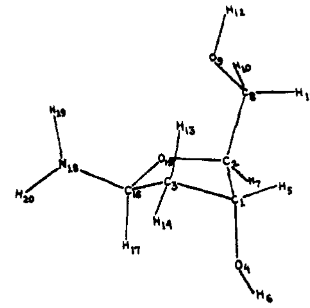


Figure 6. Comparison of EEM and ab initio charges for linear, bifurcated, and cyclic geometries of water dimers.



Alanine dipeptide



Amino deoxyribose

Figure 7. Schematic diagrams of alanine dipeptide and aminodeoxyribose.

The STO-3G-calibrated values of $\Delta\chi$ and $\Delta\eta$ are then used in the calculation of charges in alanine dipeptides, deoxyriboses, and a few substituted cyclohexanes. The calculated atomic charges for four different minimum energy configurations of the dipeptide,[29] two riboses, viz., deoxyribose, and 2-aminodeoxyribose, and four cyclohexanes are correlated with the ab initio charges

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[27] Although we have employed here the charges based on Mulliken population analysis, one can as well use charges corresponding to other definitions, some of which might seem to be more physical. It may, however, be noted that the Mulliken charges have recently been shown to correlate well with the ones obtained by regional integration. See, for example, ref 18 and: Grier, D. L.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 3556–3564.

[28] These calculations were done in a VAX 11/780 computer at the Chemistry Department, University of North Carolina, using the QCPE program GAUSSIAN 82. For EEM calculations and charges, see ref 39.

[29] Weiner, S. J.; Singh, U. C.; O'Donnell, T. J.; Kollman, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 6243–6245.

in Figures 3–5, respectively. To enable a better comparison, in Tables II and III, numerical values are also given for two representative molecules. In all cases, the EEM charges agree very well with the corresponding STO-3G ab initio charges.[28]

The EEM is also extended to study charge transfer in intermolecular interactions. Charges are calculated for water dimers in three different configurations based on a parametrization scheme used for water. The comparison with ab initio charges in both series of molecules is good. The correlation between the charges calculated by the EEM and the corresponding ab initio charges[30] is presented in Figure 6.

Good agreement is not limited to atomic charges alone. Thus, the effective electronegativities calculated through eq 34 using the EEM charges are also seen to agree very well with the Mulliken electronegativities of the corresponding molecules. A detailed discussion on the prediction of the molecular electronegativity using the present approach is given elsewhere (see ref 40).

Discussion

Atomic charges in molecules have long served as indexes of chemical reactivity[31] and have been correlated with a variety of properties like NMR chemical shifts and ESCA shifts.[1] They are also turning out to be extremely important in molecular mechanics and dynamics simulations of large biological molecules. The electrostatic force field calculations for such simulations use charges obtained from semiempirical or ab initio MO calculations of the molecule in its ground-state geometry.[32] The influence of the configuration changes on the atomic charges is neglected, owing to the near impossibility of performing MO calculations for every configuration obtained in the dynamics simulation. This approach is reasonable in vis-ã-vis simulation of neutral molecules in vacuum, where charges do not change appreciably with configuration changes. This is apparent from the EEM charges on the four minimum energy configuration of alanine dipeptide, where the largest changes are of the order of 10^{-2} electrons. However, in simulations of charged macromolecules, or those in highly polar solvents, and in binding of ligands to receptors, where electrostatic contribution to the force field becomes dominant, it would be essential to consider the influence of changes in atomic charges with environments. EEM calculations which involve negligible computation times could well be incorporated into such simulations for calculating charges with dynamical changes in configurations. Charge transfer in solvent–substrate interactions can also be effectively taken into account. EEM charge calculations on deoxyribose, the dipeptide, and water dimers indicate the utility of this method in protein and nucleic acid simulations.

The environment is particularly important in the study of molecular interactions. After calibration of $\Delta\chi$ and $\Delta\eta$ to H_2O and the cyclic $(H_2O)_2$ dimer, the charge shifts were correctly predicted for the bifurcated and the linear cluster (for the latter, only an intermolecular charge transfer of 0.006 was allowed, as for the ab initio calculations). The extra polarization of the bonds in molecular interactions is almost uniquely determined by a change in the electrostatic correction term, due to a change in the relative positioning of the water molecules. An increased ionicity is found with respect to the isolated water molecule. This is quite generally observed in molecular interactions,[33] and this might now be quantitatively understood. For an increase of the external potential (e.g., by bringing an extra positive charge close to an atom in a molecule), eq 28 predicts an increase of the effective electronegativity for this atom. The opposite is true for a lowering of the external potential. This is exactly equivalent with the "pileup" and "spillover" of electrons at the donor and the acceptor site, respectively, in donor–acceptor interactions, as defined by Gutmann.[33] At the same time, it will induce a charge rearrangement throughout the entire molecule, and all bonds will be affected (an increase in ionicity will usually be accompanied with a bond lengthening, a decrease with bond shortening). These changes can now be predicted quantitatively. For atoms in a crystal lattice, the Madelung constant is to be considered, which will result in an increased ionicity for a transition from the gas phase to a condensed phase.

The charge separation in polyatomic homonuclear compounds, such as the different properties of surface, and bulk atoms in metal clusters can also be understood in terms of an effective electronegativity. For example, $\Delta\chi$ will be more different for the central Ag atom in linear Ag–Ag–Ag clusters than for the terminal silver atoms. Evidently, this must result in a charge separation, which for this system was confirmed by EH-MO calculations;[34] the charge on the central Ag becomes −0.22.

The EEM formalism allows the calculation of two chemically important quantities: the average molecular electronegativity and the partial charges.[35] For the intrinsic properties of atom, such as those measured by ESCA or NMR, the variation of one of these will usually correlate with the experimental data. For the correlation of the C_{1s} binding energy shifts of a series of organic molecules with the EEM charges, see ref 1. For a rationalization of the influence of the composition on several physicochemical properties of zeolites, the average compound electronegativity was sufficient.[36-38] For reaction energies, however, neither the average compound electronegativity nor the charges correlate with the gas-phase basicities of alcohols, amines, and ethers, but a quantitative correlation is possible using both.[39] The partial charges in particular reflect the capacity to dissipate the charges through the molecule, and in this respect, these are related to the polarizability, a parameter of considerable importance in chemical reactions.

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Registry No. Alanine dipeptide, 19701-83-8; amino deoxyribose, 68290-03-9.

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