the role of the solvent cage; rapid interconversion among Eigen complexes that allows reaction partners to explore many geometries within this well; and locked-rotor critical configurations that present entropic barriers to reaction, which permit ion–molecule complexes to live long enough to play a major role in selection of product channels. The similarities in dynamics between acid–base reactions in the gas phase and in solution reinforce the expectation that mechanistic insights from one realm will be pertinent to the other.

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The Use of Global and Local Molecular Parameters for the Analysis of the Gas-Phase Basicity of Amines

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Abstract: It is demonstrated that the variation of the gas-phase basicities of amines can be analyzed by using two parameters: one global and one local (that is, site-dependent). Two global quantities (the average "effective" electronegativity and the geometric average of the isolated-atom electronegativities) and two local quantities (the fukui function and the residual charges) are tested. A two-parameter linear model containing one global and one local quantity produces satisfactory correlations with the experimental gas-phase basicities. It is shown how to express the fukui function, which reflects the site reactivity in density functional theory ($f(\bar{r}) = [\partial\rho(\bar{r})/\partial N]_{v(\bar{r})}$), in terms of the variation of the Mulliken gross charges (q_i) of an atom in a molecule, which is accompanied with a change in the total number of electrons (N) in this molecule: $f_i^+ = q_i(N+1) - q_i(N)$; $f_i^- = q_i(N) - q_i(N-1)$ and $f_i^\circ = {}^1/_2[q_i(N+1) - q_i(N-1)]$.

The electron density distribution is fundamental for understanding chemical reactivity and naturally leads to explaining nucleophylic and electrophylic attack on the basis of electrostatic interactions. However, the electron density by itself does not explain everything, and it was recognized that the change in electron density under the influence of an approaching reagent is also of importance. The frontier-electron theory of chemical reactivity by Fukui[1,2] recognizes the key role of the valence electrons in forming molecules and considers therefore the distribution of the highest energy orbital electron density as being most important for electrophilic attack and the lowest energy vacant orbitals in nucleophilic substitution reactions. In reactions with radicals both orbitals become important. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are in this way considered as the principal factors governing the easiness of chemical reactions and the stereoselective path.

It was recently demonstrated by Parr et al.[3,4] that most of the frontier-electron theory of chemical reactivity can be rationalized from the density functional theory of the electronic structure of molecules.[5,6] For a system of N electrons with ground-state energy $E[n,v]$, where v is the potential energy acting on an electron due to the presence of all nuclei, several quantities of fundamental importance can be defined. The chemical potential μ of the electrons, i.e., the negative of the electronegativity χ, is given by $\mu = (\partial E/\partial N)_{v(\bar{r})}$ and has the same value everywhere. The change of μ with the number of electrons was defined by Parr and Pearson[7] as a measure for the "absolute hardness" as $\eta = (\partial\mu/\partial N)_{v(\bar{r})} = (\partial^2E/\partial N^2)_{v(\bar{r})}$. The frontier function or fukui function for a molecule, reflecting the reactivity of a site, was defined by Parr and Yang[3] as

$$f(\bar{r}) = [\delta\mu/\delta v(\bar{r})]_N = [\partial\rho(\bar{r})/\partial N]_{v(\bar{r})} \qquad (1)$$

i.e., the functional derivative of the chemical potential with respect to a change in the external potential or, because of the Maxwell relations, identical with the change in electron density accompanied with a change in the number of electrons. The hardness and the fukui function are local quantities and reflect the properties of the different sites within the molecule.

Probing the reactivity of the different sites within a molecule, being of importance for understanding reaction mechanisms, only partially meets the chemists aspirations. A comparison of different molecules is also of importance. The object of the present study is to explore different ways to make this comparison by using easily obtainable parameters. Substituent group properties have been used extensively in this context. However, as the atomic properties change from molecule to molecule, so will substituent groups be subject to variations. Alkyl groups, e.g., may act either as electron donors or as electron acceptors, depending on the substrate. One of the properties of interest of substituent groups is their tendency to attract electrons, i.e., their electronegativity. Depending on the actual molecular configuration, this may qualify a group as electron donor or electron acceptor. In a study of the gas-phase

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acidities of alcohols, however, Huheey[8] came to the conclusion that two parameters are necessary to consider the effect of groups: (i) the "inherent" electronegativity and (ii) the relative "charge capacity". This charge capacity, reflecting the delocalization of the charges, is a quantity typical for the reaction site, and in this respect it is related to the previously mentioned reactivity concepts. The inherent electronegativity is a global quantity by virtue of the electronegativity equalization principle.

Quantitative empirical relations were established which require local as well as global properties for an adequate comparison of molecules. A two-parameter model based on a substituent polarizability (local) and an inherent "residual" electronegativity was developed by Hutchings and Gasteiger[9] to quantitatively predict the proton affinities of amines. Gasteiger and Hutchings[10] showed that the same two-parameter model applies to alcohols, ethers, and their thio analogues. It was demonstrated by Van Genechten and Mortier[11] that the geometric average electronegativity and the residual charges at the reaction center equally reflect the global and local quantities of the molecule necessary to explain the gas-phase protonation energies of amines and ethers and the acidity of alcohols. The residual charges and the possibility to delocalize the charges at the reaction center are indeed closely related.

These empirical relations suggest that the pertinent information, necessary to compare the properties of molecules, may be obtained in a number of different ways. As far as local properties are concerned, the fukui function and the residual charges both contain valuable information. The "inherent" or average electronegativity of a molecule may also be obtained in a number of ways. This could, in principle, be evaluated for a molecule from the ionization potential I and the electron affinity A of the molecule by using Mulliken's[12] definition of electronegativity: $(I + A)/2$, which is the finite-difference approach to $(\partial E/\partial N)_{v(\vec{r})}$. An equalization of the "effective" electronegativity[13] of all atoms in a molecule is an alternative. The effective electronegativity corrects the isolated-atom electronegativity for charge transfer and for a change in the external potential. The geometric average of the isolated-atom electronegativity (Sanderson's[14,15] compound electronegativity) was found[16] to correlate well with the average effective electronegativity for a homologous series of compounds.

In this paper a phenomenological analysis of the variation in the gas-phase protonation energy[17] for a series of amines will be given, which illustrates the importance of the use of local and global molecular properties for comparing reactivities of different molecules. We ignore zero-point energy and entropic effects, as has been rationalized for such species by Lias, Liebman, and Levin.[17]

Table I. Condensed Fukui Function for CH_2O[a] by Gaussian 82[20]

	STO-3G			STO-6-311G		
	f^+	f^-	f^0	f^+	f^-	f^0
C	0.3182	0.1590	0.2386	0.3568	0.0398	0.1983
O	0.3016	0.4128	0.3572	0.2685	0.5050	0.3869
H	0.1901	0.2141	0.2021	0.1874	0.2276	0.2075

[a] A standard geometry for CH_2O is used: planar; bond length: O–C 0.121 nm, C–H 0.109 nm, and 120° for the bond angles.

Table II. Gas-Phase Basicities[17] ($\Delta G°$/kJ/mol), Charges on Nitrogen (q_N), Fukui Function (f_N^-), Average Compound Electronegativity[a] ($\bar{\chi}_{at}$), and Average Effective Electronegativities[b] ($\bar{\chi}_{mol}$) for a Series of Amines

amine[c]	$\Delta G°$	q_N(STO-3G)	f_N^-(STO-3G)	$\bar{\chi}_{at}$	$\bar{\chi}_{mol}$
CH_3NH_2	–861	–0.4122	0.3173	2.693	2.657
$CH_3CH_2NH_2$	–872	–0.4145	0.3105	2.677	2.634
$(CH_3)_2CHNH_2$	–883	–0.4172	0.3091	2.669	2.596
$(CH_3)_3CNH_2$[d]	–891	–0.4191	0.3077	2.664	2.562
$(CH_3)_2NH$	–890	–0.3479	0.3017	2.677	2.669
$(CH_3)_3N$[d]	–909	–0.2876	0.2902	2.669	2.665

[a] Sanderson scale[15] used throughout. [b] $\Delta\chi_H = 0.0$. [c] Standard geometries: ref 22. [d] Molecules used for calibration of $\Delta\chi$ and $\Delta\eta$ for C, H, and N.

Methods

a. Local Properties: The Fukui Function and the Partial Charges. For an atom or molecule, the derivative in eq 1 is discontinuous,[3] with $f^-(\vec{r})$ governing electrophilic attack, $f^+(\vec{r})$ governing nucleophilic attack, and their average governing radical attack. The rigorous evaluation of $f(\vec{r})$ can be quite complicated.[4,18] Here, we present a simple procedure to calculate $f(\vec{r})$, condensed to individual atoms in the molecule. This is based on a Mulliken population analysis[19] and a finite-difference approximation to eq 1. For a system of N electrons, independent calculations were made for the corresponding $(N - 1)$-, N-, and $(N + 1)$-electron systems with the same molecular geometry. A Mulliken population analysis (gross charges) yields $q_i(N - 1)$, $q_i(N)$, and $q_i(N + 1)$ for all atoms i. The values reported here were calculated by using ab initio methods (Gaussian 82).[20] In a finite-difference approximation, the "condensed" fukui functions are then given by[21]

$$\text{for nucleophilic attack} \quad f_i^+ = q_i(N + 1) - q_i(N) \tag{2a}$$

$$\text{for electrophilic attack} \quad f_i^- = q_i(N) - q_i(N - 1) \tag{2b}$$

$$\text{for radical attack} \quad f_i^0 = \tfrac{1}{2}[q_i(N + 1) - q_i(N - 1)] \tag{2c}$$

The justification for the above procedure lies in the commutability of parameter differentiation (finite-difference here) and integration (condensation here). The basis-set dependence was investigated by STO-3G and STO-6-311G approximations for formaldehyde (Table I). For a series of amines, only f^- was calculated, and only f_N^- is reported in Table II together with the charges q_N for nitrogen, calculated by using STO-3G. The amines were deliberately chosen so as to fall in two different homologous series: $MeNH_2$, $EtNH_2$, i-$PrNH_2$, and t-$BuNH_2$ on one hand and $MeNH_2$, Me_2NH, and Me_3N on the other, for reasons given below.

b. Global Properties: The Average Electronegativity. The change in chemical potential for an atom or a molecule due to a change in electron transfer (dN) and a change in external potential also contains a global quantity

$$d\mu = \mu - \mu^0 = 2\eta dN + \int f(\vec{r})\delta v(\vec{r})\, d\vec{r} \tag{3}$$

The chemical potential μ^0 will differ from molecule to molecule and is therefore the natural (global) companion parameter to the (local) fukui function.

A direct determination of the molecular electronegativities of the molecules we are interested in from the ionization potentials and the electron affinities is difficult. More elaborate calculations than the STO-3G level would certainly be required if the values were calculated by ab initio methods. Whole sets of experimental values of I and A for molecules are not easily accessible. We therefore obtain the average electronegativities indirectly from the values of the "effective" atomic electronegativities after equalization. Mortier, Ghosh, and Shankar[13] defined the effective electronegativity of atom α in a molecule as

$$\chi_\alpha = (\chi_\alpha{}^\circ + \Delta\chi_\alpha) + 2(\eta_\alpha{}^\circ + \Delta\eta_\alpha)q_\alpha + \sum_{\beta\neq\alpha} q_\beta/R_{\alpha\beta} \tag{4}$$

with $\chi_\alpha{}^\circ$ and $\eta_\alpha{}^\circ$ the isolated-atom electronegativity and hardness, respectively, q the partial charges of the atoms in the molecule, $R_{\alpha\beta}$ the

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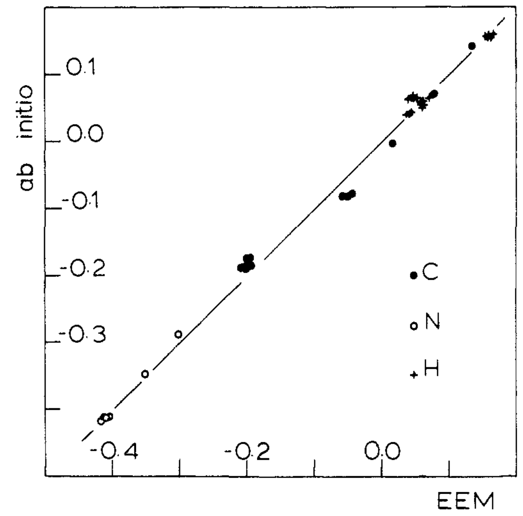

Figure 1. Correlation between the charges on C, H, and N for the molecules in Table II, as evaluated by ab initio and by the EEM method using Sanderson's electronegativity scale[15] and a single set of $\Delta\chi$ and $\Delta\eta$ values for C, H, and N, calibrated to the ab initio charges of $(CH_3)_3C$-NH_2 and $(CH_3)_3N$. The same geometry was used in both methods.

internuclear distance, and $\Delta\chi_\alpha$ and $\Delta\eta_\alpha$ corrections to the isolated-atom electronegativity and hardness because of the change in size and shape of this atom in a molecule. An equalization of the effective electronegativity for all atoms in the molecule, subject to a conservation of the total molecular charge producing the average electronegativity $\bar{\chi} = \chi_\alpha = \chi_\beta ...$ and the partial charges q_α, $q_\beta ...$, was called the EEM formalism (electronegativity equalization method). $\chi°$ and $\eta°$ are given by an electronegativity scale (Sanderson's scale[15] was used throughout), and $\Delta\chi$ and $\Delta\eta$ for C, H, and N were calculated by a least-squares fit so as to reproduce the charges on all atoms in $(CH_3)_3CNH_2$ and $(CH_3)_3N$ by using the same molecular configurations as for the ab initio calculations above. With the same calibrated values for $\Delta\chi$ and $\Delta\eta$ of C, H, and N, atomic charges are calculated for all molecules in Table II and compared with the ab initio charges (Figure 1). Considering the excellent agreement and therefore also the transferability of $\Delta\chi$ and $\Delta\eta$ to varying atomic environments, the average effective atomic electronegativity obtained in this way should be a reliable estimate for the molecular electronegativity. This value is reported in Table II ($\bar{\chi}_{mol}$), relative to the electronegativity of H for which $\Delta\chi$ was set to 0 ($\Delta\chi$ for one atom type can be chosen arbitrarily).

Sanderson[14,15] postulated that the electronegativity of a molecule is idential with the geometric average of the isolated-atom electronegativities. These values are also reported in Table II ($\bar{\chi}_{at}$). Because of an expected correlation between $\bar{\chi}_{at}$ and $\bar{\chi}_{mol}$ for homologous series,[16] it is important that the molecules chosen do not fall within the same homologous series if $\bar{\chi}_{at}$ is to be tested as a valuable global parameter, characterizing the different molecules.

It was found that the EEM formalism is not suitable to estimate the fukui function (by eq 2) because of the first order expansion of χ with respect to q, which produces the same absolute value for f^+ and f^-. (See Appendix for a straightforward proof.)

c. A Two-Parameter Linear Model. $\Delta G°$ for the reaction $B + H^+ \rightleftharpoons BH^+$ for the molecules in Table II were taken from ref 17.

Neither one of the global ($\bar{\chi}_{at}$ or $\bar{\chi}_{mol}$) or the local (q_N, f_N^-) quantities correlate with the gas-phase basicity. A satisfactory relation (Figure 2) between observed basicities and those calculated from a two-parameter linear model, the coefficients of which are given below, was obtained

$$\Delta G° = 1875.6 f_N^- + 125.54\bar{\chi}_{mol} - 1788.7 (\Sigma\Delta^2/n = 3.5) \qquad (5a)$$

$$\Delta G° = -198.99 q_N + 1046.89\bar{\chi}_{at} - 3760.8 (\Sigma\Delta^2/n = 4.0) \qquad (5b)$$

The other combination of a local and global quantity was somewhat less satisfactory: $\Sigma\Delta^2/n$ 6.6 and 5.9 using (f_N^-, $\bar{\chi}_{at}$) and (q_N, $\bar{\chi}_{mol}$), respectively.

Discussion

a. The Fukui Function: Probing the Reactive Site Within a Molecule. It is obvious from Table I that the qualitative results do not change with the basis set, although the more elaborate STO-6-311G calculations more clearly distinguish the reactive sites. Depending on the type of attack, different sites are indicated as the most reactive site for CH_2O, i.e., this site for which f is largest. This simplified approach by using a Mulliken population analysis does indeed meet all requirements and is in agreement with chemical intuition. The distinct mechanisms of acid-catalyzed and base-catalyzed hydration of aldehydes[23] may illustrate this: the acid-catalyzed hydration proceeds via an electrophilic attack by H^+ at oxygen (f^- largest for O) while the base-catalyzed mechanism occurs via a nucleophilic attack by OH^- on C (f^+ largest for C).

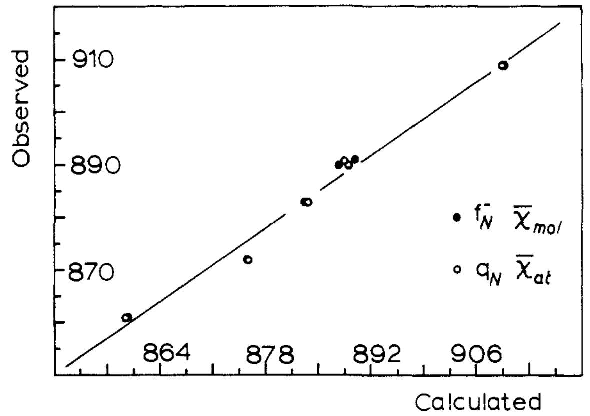

Figure 2. Correlation between the observed gas-phase basicities ($-\Delta G°$/kJ mol^{-1}) of the amines in Table II and those calculated from a two-parameter linear model (eq 5a or 5b).

It may therefore be concluded that the variation in gross charges is a convenient way to estimate the fukui function and that also for the comparison of amines f_N^- (Table II) will reflect the reactivity of this site for an electrophilic attack (protonation). This is also consistently the site in each molecule for which f^- is maximum.

b. The Use of Local and Global Molecular Properties. There is a distinction to be made according to the type of molecular properties that are compared: one might be interested in intrinsic properties only, or one may attempt to analyze reactivities and reaction energies. In the latter case, a successful comparison can only be made on the basis of the properties of one reactant if the second reactant (the proton for comparing the gas-phase basicities of amines) is constant. ESCA and NMR shifts are examples of intrinsic properties. Atomic charges correlate very well with ESCA shifts (see, e.g., ref 25) where originally these shifts were considered proportional to the charge of the emitting atom only. Reference to core binding energies has therefore been used repeatedly to test electronegativity-related formalisms for calculating partial charges: Jolly and Perry,[26] the modified Sanderson method,[27] partial equalization of orbital electronegativity,[28] and full equalization of orbital electronegativity,[29] which has found a theoretical justification in the EEM formalism.[13] Another example is the use of the geometric average compound electronegativity for rationalizing the compositional influences on zeolite properties,[24,30] all of which are comparisons limited to intrinsic properties or to homologous series.

The geometric average of the isolated-atom electronegativities has also been found to correlate extremely well with the gas-phase

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basicity of amines but only within a homologous series.[24] Similar correlations are also found (although not always linear) for all four quantities ($\bar{\chi}_{at}$, $\bar{\chi}_{mol}$, q_N and f_N^-). Consistently two distinct correlations exist for the two homologous series studied here: one being characterized by a methyl substitution on the carbon, the other by a methyl substitution directly on N.

Obviously more information is required if a comparison of molecules has to be made which involves molecules which cannot be considered as part of a homologous series or for which the properties do not depend on the intrinsic properties only. Reaction energies are an example. H NMR shifts, e.g., fail to place the bridging hydroxyls (Si–OH–Al) of zeolites in the proper place on the acidity scale:[31] the deprotonation energy also involves a reorganization of the deprotonated base. The two homologous series of this study also fail to obey a simple relation with either one of the global or local quantities tested.

For a protonation reaction, the general "tendency" of the molecule to attract electrons, i.e., its electronegativity ($\chi^\circ = -\mu^\circ$) will certainly be of importance. Different molecules will necessarily have different average electronegativities, which should inversely correlate with the proton affinity (and indeed do: see the positive coefficient of $\bar{\chi}$ in eq 5).

A knowledge of this "inherent" electronegativity is however not sufficient. The reaction energy not only involves the properties of the reactant but also those of the reaction products. In this particular case, this will largely involve a redistribution of the electron density or a delocalization of the positive charge after protonation. This will be site-dependent, i.e., a local property. A better delocalization of the charge created implies a stabilization of the reaction product and therefore also an increased reaction energy. As already introduced for the discussion of the acidity of alcohols by Huheey,[8] the "charge capacity" of the substituent group also plays a role here. The charge capacity has not been defined quantitatively, but it is obvious that several local properties will be related to it, allowing in some way or another a quantitative expression. Certainly, it will be related to the hardness of the site, and in a similar way that hardness has been defined for atoms.[7] The residual charges in the molecule will also depend on the charge capacity of the substituent groups attached to an atom. For amines, the reactive sites for protonation is the N atom. The residual charge on N is negative and will be more so if the substituent group is less polarizable. A smaller residual charge is consistent with an increased delocalization possibility, and therefore also with a more negative energy of formation, in agreement with the negative sign of the coefficient of q_N in eq 5b. Local softness has been recently defined[18] as $s(\vec{r}) = [\partial\rho(\vec{r})/\partial\mu]_{v(\vec{r})} = Sf(\vec{r})$, with S being the global softness: $S = 1/\eta = 1/I - A$. The fukui function as the normalized local softness might directly give a quantitative estimate of the charge capacity, since it is equivalent to the change of the charge on N for removing one electron from the molecule. The effect of the most polarizable group will be a smaller change. Henceforth, a larger value of the fukui function will be disfavorable for the protonation energy, again in agreement with the coefficient of f^- in eq 5a.

There remains the question of the choice of global and local quantities for use in the comparison. None of the quantities discussed here contain the same information (there is no single correlation between them). Empirically, the choice of the average compound electronegativity and the partial charges were found to produce very satisfactory relations and also give good agreement between calculated and observed basicities here. However, at the moment, there is no theoretical justification for this. The use of f^- and $\bar{\chi}_{mol}$ produces the best results and as already discussed before constitutes a more natural pair of molecular quantities, but this is certainly not the easiest way to proceed. It would be interesting to see how these ideas may be extended to other types of reactions.

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Appendix

The equations of the EEM formalism are written in matrix form as follows: $Y = X\beta$, with

$$X = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1m} & -1 \\ x_{21} & x_{22} & \cdots & x_{2m} & -1 \\ . & . & . & & . \\ . & . & . & & . \\ . & . & . & & . \\ x_{m1} & x_{m2} & \cdots & x_{mm} & -1 \\ 1 & 1 & & 1 & 0 \end{bmatrix}, \quad \beta = \begin{bmatrix} q_1 \\ q_2 \\ . \\ . \\ . \\ q_m \\ \chi \end{bmatrix}, \quad Y = \begin{bmatrix} y_1 \\ y_2 \\ . \\ . \\ . \\ y_m \\ \Sigma q_i \end{bmatrix}$$

for an m atom molecule where $x_{ii} = 2(\eta^\circ + \Delta\eta_i)$, $x_{ij} = {}^1/_{R_{ij}}$ for $i \neq j$ and $y_i = -(\chi^\circ + \Delta\chi_i)$. The charges q_i and the average electronegativity $\bar{\chi}$ are obtained as $\beta = X^{-1}\, Y$. Adding k to Σq_i in matrix Y will result in a change of the charge of atom i, q_i, by $[x^{-1}{}_{i,m+1}]\cdot k$. Column matrix Y is not changed for positively or negatively charged molecules; a change in q_i will have the same magnitude for the same absolute value of k and differ only in sign.

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