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Empirical Energy−Density Relationships for the Analysis of Substituent Effects in Chemical Reactivity

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Abstract: Electronic substituent effects may be rationalized in terms of Hammett-like linear relationships between global energy-dependent quantities and local electronic descriptors of reactivity. These linear relationships are framed on a local hard and soft acids and bases (HSAB) principle in accord with previous results reported by Li and Evans [*J. Am. Chem. Soc.* **1995**, *117*, 7756]. Chemical substitution is indirectly assessed as local responses at the active center of the substrate, with the Fukui function and local softness as the key quantities within the present approach. This model of chemical substitution has a potential advantage with respect to models based on group properties using the electronegativity equalization principle (EEP), since the transferability of group properties is not required. The formalism is illustrated for the gas-phase basicity of alkylamines, and the gas-phase acidity of alkyl alcohols and alkyl thioalcohols. Our results based on the local HSAB rule agree well with those obtained from group properties analysis based on the EEP, suggesting that both empirical rules consistently complement each other.

1. Introduction

Electronic substituent effects have been an important example of structural effects on reactivity from the early days of physical organic chemistry. Discussion of these phenomena through the use of empirical linear free energy relationships, with all their limitations, is the preferred language in the experimental literature.[1] From a theoretical point of view, recent work using the electronegativity equalization principle (EEP) in the context of density functional theory (DFT) has been proposed by Komorowski et al[2] and Geerlings et al.[3−5] The convenience of developing a common language between the theoretical and experimental approach to the substituent effects on chemical reactivity is stressed in their work. Following their proposal, our main objective in this paper is to provide simple relationships between energy-dependent properties and electronic descriptors of reactivity and selectivity, in the form of Hammett-like equations.

In our approach, chemical substitution is viewed as a global perturbation that changes the number of electrons from N to $N + \Delta N$. The local response of the system, encompassing the changes in the external potential, may then be probed by the derivative of the electronic distribution with respect to the number of electrons in the system (i.e. the Fukui function $f(\mathbf{r})$), condensed at the active atomic site, or the derivative of the electronic chemical potential with respect to the external potential (i.e. the local softness $s(\mathbf{r})$). Within this framework, we intend to define linear energy−density relationships by using the Fukui function and the local softness as genuine regional electronic indices associated with atoms or groups to discuss electronic substituent effects.

The approach follows Li and Evans complete discussion of the relationships between global and local indices in DFT, and the concepts of reactivity and selectivity in a chemical reaction.[6] Their results framed on a generalized HSAB principle can be condensed to simple and very useful criteria. In the first place, while global quantities determine reactivity, local quantities determine selectivity. Global softness and hardness are then pertinent quantities to define the reactivity pattern of a molecule.[7,8] Selectivity, on the other hand, is related to the active sites in a molecule that show the highest propensity to react in a form consistent with the reactivity pattern dictated by the global properties. In terms of the HSAB principle, Li and Evans[6] proposed the following rule: in hard−hard reactions, the preferred site of reaction will be the one showing the minimum value of the Fukui function condensed to that atom or group. For the case of soft−soft interactions it is expected that the site displaying the highest value of the condensed Fukui function will determine selectivity. Even though the selectivity concept is normally used in polyfunctional systems presenting more than one active site for reaction, it may also be applied within a family of related molecules to assess for instance, the electronic

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effect of substituents on the local reactivity pattern of a unique active site embedded in different chemical environments. Under these considerations, the Fukui function and local softness remain as valid criteria to discuss changes in local reactivity patterns induced by chemical substitution.

The article is organized as follows: In Section 2, we present the model equations leading to working formulas to analyze substituent electronic effects on the reactivity pattern in a series of related molecules. In Section 3, we illustrate the usefulness of the model to explain the gas-phase basicity of alkylamines and the gas-phase acidity of alkyl alcohols and alkyl thioalcohols. A general discussion is presented in Section 4. Section 5 contains our main conclusions. The justification of some of the approximations made is presented in an Appendix.

2. Model Equations

The well-known Hammett linear free energy relationship was formerly proposed to have the form:[9]

$$\log\left[\frac{K}{K^\circ}\right] = \rho\sigma \tag{1}$$

where K and K° are the equilibrium constants of the substituted molecule and the reference, respectively, ρ is the slope of the regression, and σ is the substituent constant. Similar relationships involving kinetic parameters such as reaction constant instead of equilibrium constants have been proposed.[10]

To set up similar energy−density relationships framed on global and local reactivity indices, we start by considering that chemical substitution in a molecule will result in a change in the number of electrons from N to $N + \Delta N$. ΔN is the difference in the number of electrons between the reference molecule and the substituted one. If we further assume that the changes in ΔN will be reflected in the electronic population changes ΔN_A or atomic charge variations Δq_A along all the atomic centers A in the molecule, satisfying the normalization conditions:

$$N = \sum_A N_A \tag{2a}$$

and

$$\Delta N = \sum_A \Delta N_A \tag{2b}$$

the corresponding change in the electronic chemical potential, μ, at constant external potential, $v(\mathbf{r})$, will be given up to first order by:

$$\mu[N + \Delta N] = \mu^\circ[N] + \sum_A \left[\frac{\partial\mu}{\partial N_A}\right]_v \sum_B \Delta N_B = \mu^\circ[\mathrm{N}] + \sum_{A,B} \eta_A \Delta N_B, \tag{3}$$

where $\eta_A = [\partial\mu/\partial N_A]_v$ is the global hardness.[7,8] Equation 2 may be viewed as a generalization of the Politzer equation for atoms.[11]

The generalization of Politzer's eq 3 to the case of molecules, in terms of the fluctuation of the electron population ΔN_A at every atomic center in their valence state, is just the recognition that ΔN_A can still be regarded as one of the factors upon which the molecular electronegativity (the electronic chemical potential of chemistry) depends.[11] It is important to stress here that the quantity η_A represents the change in chemical hardness of the whole molecule due to the change in the electron number at site A. It is not to be understood as the value of the chemical hardness at that site, due to the global nature of this property.

On the other hand, as was shown by Bartolotti and Parr,[12] the electronic chemical potential for atoms displays an exponentially decreasing behavior with ΔN:

$$\mu[N + \Delta N] = \mu^\circ[N] \exp(\gamma\Delta N) \tag{4}$$

where γ is a falloff parameter. We will assume that a similar relationship holds for the case of atoms in molecules, so that we may write:

$$\mu[N + \Delta N] = \mu^\circ[N] \exp(\gamma(\Delta N)) \approx \mu^\circ[N] \exp(\gamma f(\Delta N)) \tag{5}$$

where $\mu^\circ[N]$ is the electronic chemical potential of the unsubstituted molecule, and $f(\Delta N)$ is any well-behaved function of the change in the number of electrons. If we make the *ansatz* that $f(\Delta N)$ may be represented by the variations of the regional Fukui function Δf_A at site A, namely,

$$f(\Delta N) \approx \sum_A \Delta f_A \tag{6}$$

then we may immediately write the following Hammett-like equation:

$$\ln\left[\frac{\mu[N + \Delta N]}{\mu^\circ[N]}\right] = \rho\sigma = \gamma \sum_A \Delta f_A \tag{7}$$

Equation 7 is a genuine energy−density relationship, in the sense that it contains on the left-hand side a quantity that corresponds to the first variation of the electronic energy under a change in the number of electrons promoted for instance by chemical substitution, whereas the right-hand side contains the variations in electron density with N. Within the present approach, the substituent constant is indirectly assessed as local responses at the active site, described by the variations of the Fukui function at that site. The physical meaning of the γ parameter, which corresponds to the reaction constant ρ within the present approach, will be discussed in detail in Section 4.

3. Applications

3a. Gas-Phase Basicity of Aliphatic Amines. In the preceding Section 2 we have presented an empirical energy−density relationship that relates energy-dependent quantities with electronic indices of chemical reactivity. Following the proposal of Li and Evans[6] the Fukui function may be used as the natural local descriptor of reactivity within a generalized HSAB context. This local property is expected to describe local reactivity within a series of related molecules that do not differ too much in their global reactivity.

On the other hand, the energetics of gas-phase protonation equilibria is governed by the proton affinity (PA), defined as the negative of the enthalpy for the protonation reaction:[13,14]

$$\mathrm{B} + \mathrm{H}^+ \Rightarrow \mathrm{BH}^+, \qquad \mathrm{PA} = -\Delta H^\circ \tag{8}$$

Proton affinities are measured from data recorded from ion−

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Table 1. Experimental PA Values, Fukui Function Differences, Global Softness, and Atomic Charges on the Basic Center for a Series of Alkylamines[a]

Brönsted base (B)	exptl PA	Δf_N^-	S	q_N	
				MPA	NBO
NH_3	204.0	0.0000	3.17	−0.9959	−1.1112
CH_3NH_2	214.1	0.1243	3.35	−0.8332	−0.9121
$CH_3CH_2NH_2$	217.0	0.1498	3.32	−0.8304	−0.9128
$(CH_3)_2CHNH_2$	218.6	0.1813	3.38	−0.8293	−0.9154
$(CH_3)_2NH$	220.6	0.1860	3.40	−0.6757	−0.7266
$(CH_3)_3CNH_2$	220.8	0.1946	3.44	−0.8244	−0.9170
$(CH_3)_3N$	225.1	0.2200	3.54	−0.5313	−0.5580

[a] Proton affinity values (in kcal/mol); global softness in atomic units. For definition of Δf_N^-, see the text.

molecule collision experiments using the bracketing technique,[15,16] and they are commonly referred to as relative proton affinities with reference to a Brönsted base of known PA.

In the case of alkylamines considered here, the global reactivity pattern as probed by global softness, *S*, shows a relatively low variation within the series ($\Delta S = 0.37$ units which is about 10%, see Table 1). The global softness has been calculated as the inverse of the HOMO-LUMO gap. Therefore, according to the Li−Evans rule, we can make use of the Fukui function difference to build up a Hammett-like relationship with the proton affinity variations ln[PA(B)/PA(B°)] in a logarithmic scale. The Fukui function difference is defined as $\Delta f_N^- = f_N^-(B°) - f_N^-(B)$ for an electrophilic attack by a proton, and corresponds to the variation of the regional Fukui function at the basic center N of the unsubstituted Brönsted base B°, and the corresponding Fukui function of the substituted derivative B, respectively. The general energy−density expression 7 will now take the following particular form:[17]

$$\ln\left[\frac{\mathrm{PA(B)}}{\mathrm{PA(B°)}}\right] = \rho\sigma = \rho\Delta f_N^- \tag{9}$$

The quantity ρ represents the slope of our linear regression 9. We will consider here all the calculations and data with reference to ammonia (i.e., B° = NH_3 in eq 9). Nitrogen-containing bases will be considered then as substituted ammonia, making our approach easier to compare to the usual experimental analysis using Hammett-like equations. Our energy−density relationship 9 refers to the proton-transfer reaction:

$$NH_3 + BH^+ \Rightarrow NH_4^+ + B; \qquad \delta\mathrm{PA} = \mathrm{PA(B)} - \mathrm{PA}(NH_3) \tag{10a}$$

where

$$\Delta f_N^- = f_N^-(NH_3) - f_N^-(B) \tag{10b}$$

In Table 1 the Fukui function differences Δf_N^- are displayed, together with the global softness values and the experimental PA values for the alkylamines series.[13] The Fukui function difference is evaluated from the condensed quantities at the Nitrogen center by a procedure described elsewhere.[18,19] This method approaches the condensed to atom Fukui function for an electrophilic attack f_k^-, by the density of the highest occupied frontier molecular orbital (HOMO). Within this approach, the f_N^- quantities for the substituted and unsubstituted alkylamines are obtained in terms of the MO coefficients and the overlap matrix. The reference value for the Fukui function at the basic nitrogen center is 0.9659 at the HF/6-31G(d) level of theory, using the Gaussian94 package.[20] From the Δf_N^- values shown in Table 1, it may be seen that increasing the PA results in a decrease in the absolute Fukui function at the basic center N. Because the Fukui function is a normalized softness, we may expect that a decrease in the Fukui function entails a decrease in local softness. A decrease in local softness also may be associated with an increase in the local hardness at the basic center (see Appendix). In Figure 1, the linear relationship proposed in eq 9 for the series of alkylamines is presented. It may be seen that a good correlation exists between relative proton affinities and the Fukui function difference, with a regression coefficient of 0.9918 and a regression slope $\rho = 0.42$. In classical physical organic chemistry, the sign of ρ is meaningful. It measures the susceptibility of a reaction to a substituent effect (relative to the standard basicity of NH_3 in the present case) as the response in the PA values to the changes promoted by substitution. A positive value of ρ means that there will be a greater electron population at the reaction center (i.e. the nitrogen atom). The interaction of the basic center with the proton is hard, and therefore charge controlled.[21] The variations of atomic charges at the basic nitrogen center q_N, within the series of alkylamines are also shown in Table 1. Both Mulliken population analysis (MPA) and natural bond orbital (NBO) population analysis were considered, at the same HF/6-31G(d) level of theory. No apparent correlation between PA and q_N quantities is observed within the whole series. However, our HSAB analysis based on the Fukui function does explain the gas-phase basicity pattern within this series: the molecule

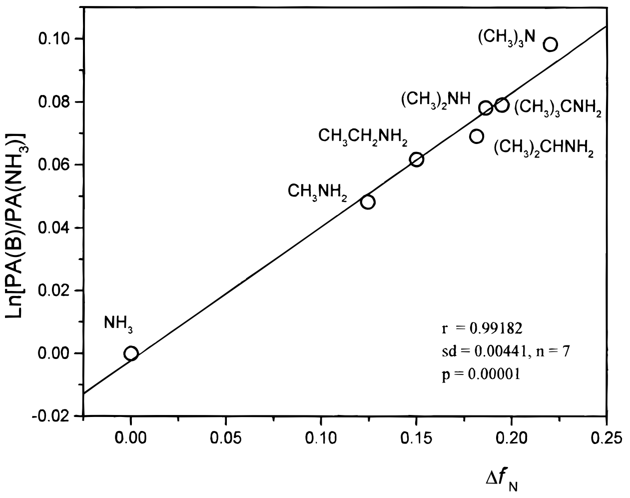

Figure 1. Correlation between relative proton affinity of alkylamines (with reference to ammonia) and the Fukui function difference at the Nitrogen site. **r** is the regression coefficient, **sd** is the standard deviation, **n** is the number of points, and **p** is the probability that the observed correlation is randomly obtained.

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displaying the higher value of PA($(CH_3)_3N$) corresponds with the minimum value of the absolute Fukui function at the basic nitrogen center, in agreement with the Li−Evans interpretation of Pearson's HSAB rule. It is also interesting to note that the molecule presenting the lower value of PA(NH_3) displays the higher value of the absolute Fukui function.

The HSAB explanation for the observed PA variations in the series of alkylamines may be further understood as follows: consider for instance that the Brönsted base B is more basic than the reference ammonia molecule: PA(B) > PA(NH_3). From the results shown in Figure 1 we have:

$$\ln \mathrm{PA}(\mathrm{B}) > \ln \mathrm{PA}(\mathrm{NH_3}) \Rightarrow f_{\mathrm{N}}^{-}(\mathrm{NH_3}) > f_{\mathrm{N}}^{-}(\mathrm{B}) \qquad (11)$$

in close agreement with the Li−Evans rule.[6] To bring our analysis closer to the HSAB context, we can use the exact relationship between the Fukui function and local softness, namely, $s_N^- = f_N^- S$.[7,8] Since the global softness S within the series of alkylamines falls within a narrow range ($\Delta S = 0.37$ units, see Table 1), we can safely multiply the second inequality in (11) by S without changing the order relationships to obtain:

$$\ln \mathrm{PA}(\mathrm{B}) > \ln \mathrm{PA}(\mathrm{NH_3}) \Rightarrow s_{\mathrm{N}}^{-}(\mathrm{NH_3}) > s_{\mathrm{N}}^{-}(\mathrm{B}) \qquad (12)$$

or

$$\ln \mathrm{PA}(\mathrm{B}) > \ln (\mathrm{NH_3}) \Rightarrow \eta_{\mathrm{N}}^{-}(\mathrm{NH_3}) < \eta_{\mathrm{N}}^{-}(\mathrm{B}) \qquad (13)$$

i.e., the HSAB principle. Inequality 13 is obtained by invoking the inverse relationship $s_N^- \eta_N^- = \Delta N_N / \Delta N$ between the local softness and hardness condensed at the basic center N (see Appendix).

In summary, it seems that the enhanced basicity at the nitrogen site shown by alkylamines almost results from the electron-donating substituent effects that increase the hardness at the basic site. This is indeed a very useful result in the sense that the well-known inductive effects of the substituent may now be expressed in terms of local electronic descriptors of chemical reactivity (i.e., on a more quantitative basis). Moreover, since the protonation reactions may be regarded as hard−hard interactions, the enhanced basicity shown by the alkylamine series seems to be framed on a local HSAB principle (hards like hards).

3b. Gas-Phase Acidity of Alkyl Alcohols and Alkyl Thioalcohols. The gas-phase acidity of alcohols and thioalcohols may be quantitatively represented by PA values, defined in this case as the enthalpy change for the heterolytic cleavage reaction 14:

$$\mathrm{RXH} \rightarrow \mathrm{RX}^{-} + \mathrm{H}^{+}; \qquad \mathrm{PA} = \Delta H \qquad (14)$$

for X = O, S and R = alkyl group.

The series considered to evaluate gas-phase acidity contains a first subset of alkyl−alkoxide ions with PA values, ranging from 379.2 (CH_3O^-) to 371.8 kcal/mol ($(CH_3)_3CCH_2O^-$), and a second subset of alkyl−thioalkoxide ions of significantly lower PA values, ranging from 359.0 (CH_3S^-) to 354.7 kcal/mol ($(CH_3)_3CS^-$).[22] The experimental PA values are summarized in Table 2. To validate the HF/6-31G(d) level of theory used, we compared the theoretical and experimental δPA quantities obtained by subtracting the PA of CH_3X^- (reference) from each PA(RX^-) value. This last quantity is obtained as the difference in total energy of the RX^- and RXH species, namely, PA(RX^-) = $E(RX^-) - E(RXH)$. Inspection of Table 2 shows that this choice gives confidence, in the sense that the relative PA values are correctly assessed at this level of the theory for both subsets of molecules. Since our model to explain the gas-phase acidity of alcohols and thio derivatives within the HSAB framework focuses mainly on the local nature of the acid−base interactions, no attempts to reach higher chemical accuracy in the energetic aspects involved in process 14 will be made here.

Table 2. Experimental and Theoretical Proton Affinity Values, and Proton Affinity Differences from HF/6-31G(d) Calculations for RX^- Ions (X = O, S; R = Alkyl Group)

RX^- ion	PA(exp), kcal/mol	δPA(exp), kcal/mol	δPA(theor), kcal/mol
CH_3O^-	379.2	0.0[a]	0.0[a]
$CH_3CH_2O^-$	376.1	−3.1	−3.1
$(CH_3)_2CHO^-$	374.1	−5.1	−5.1
$(CH_3)_3CO^-$	373.3	−5.9	−6.6
$(CH_3)_3CCH_2O^-$	371.8	−7.4	−9.4
CH_3S^-	359.0	0.0[b]	0.0[b]
$CH_3CH_2S^-$	357.4	−1.6	−1.0
$(CH_3)_2CHS^-$	355.6	−3.4	−2.1
$(CH_3)_3CS^-$	354.7	−4.3	−2.7

[a] Relative values with reference to CH_3O^-. [b] Relative values with reference to CH_3S^-.

Table 3. Experimental PA Values (in kcal/mol), Fukui Function, Global Softness and Local Softness (in atomic units), and Electron Population (in electron units) at the Basic Center for RX^- Species (X = O, S; R = Alkyl Group)

					q_X	
RX^- Ion	PA(exp)	f_X^-	S	s_X^-	Mulliken	NBO
CH_3O^-	379.2	0.7572	3.6997	2.8014	−0.8940	−1.0266
$CH_3CH_2O^-$	376.1	0.7405	3.8561	2.8553	−0.8977	−1.0328
$(CH_3)_2CHO^-$	374.1	0.7381	3.9515	2.9165	−0.9096	−1.0376
$(CH_3)_3CO^-$	373.3	0.7550	4.0574	3.0631	−0.9285	−1.0423
$(CH_3)_3CCH_2O^-$	371.8	0.7416	4.2244	3.1330	−0.8945	−1.0303
CH_3S^-	359.0	0.9558	4.1584	3.9746	−0.7720	−0.7599
$CH_3CH_2S^-$	357.4	0.9515	4.2551	4.0488	−0.7639	−0.7530
$(CH_3)_2CHS^-$	355.6	0.9481	4.3258	4.1015	−0.7520	−0.7404
$(CH_3)_3CS^-$	354.7	0.9490	4.4085	4.1836	−0.7378	−0.7217

On the other hand, it is well-known that the increasing acidity of the RXH species is determined by the increasing stability of the conjugated RX^- base.[23] It also has been established that the stabilization of anions by alkyl substituents is mainly determined by the role played by polarization forces between the charged center and the alkyl group.[24,25] It is interesting to note that the opposite reaction to that described in eq 14 exactly matches with the spirit of Pearson's HSAB principle: the stability of the RX^- species entails a low PA of RX^-. While the PA values determine the acidity of RXH species in the gas phase, the stability of the RX^- species again may be explained within the HSAB rule. A low PA value should be therefore correlated with a high value of global softness of RX^-, since the interaction with the proton will be unfavorable, thereby stabilizing the RX^- conjugated base. Furthermore, the local reactivity picture at the X atom in RX^-, probed for instance by the Fukui function and local softness, also contains useful information about the substituent effect, which according to our model may be monitored as local responses at the active site.

In Table 3 the local and global quantities obtained from the approximate HF/6-31G(d) electron density, including the ex-

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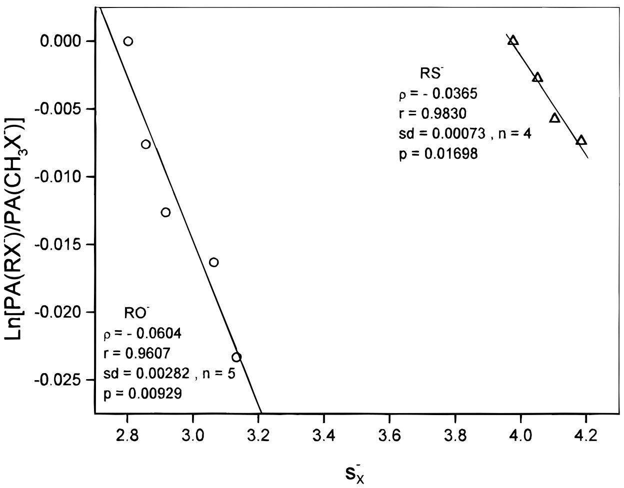

Figure 2. Correlation between relative proton affinity of RX^- alkoxyde ions, X = O, S (with reference to CH_3X^-), and the local softness at the X atom. **r** is the regression coefficient, **sd** is the standard deviation, **n** is the number of points, and **p** is the probability that the observed correlation is randomly obtained.

perimental PA values obtained from ref 22, are given. As previously stated, the lower the PA of RX^- is, the greater is the acidity of the RXH species. In terms of the global HSAB rule, it is then expected that a high value of the global softness of RX^- should be associated to the highest acidity of the corresponding RXH molecule. This is shown to be true for both subsets considered here, by comparing columns 2 and 4 in Table 3. On the other hand, from the Li–Evans selectivity rule, one would expect a correlation between gas-phase acidity, represented by the PA values, and the Fukui function at the X atom in the conjugated base RX^-. From Table 3, second and third columns, it may be seen that such a correlation is not observed for both series of alcohols considered. A possible explanation is that for the Li–Evans selectivity rule to be satisfied, the additional prerequisite of common global reactivity should be fulfilled.[6] This criterion requires that at least a global descriptor of reactivity, namely the global softness of the RX^- species in this case, should remain approximately constant within the series. Inspection of Table 3 shows that this is not the case for this series. The variations in global softness fall within a wider range than the one displayed by the alkylamines ($\Delta S = 0.71$ units, which is approximately 20%, see Table 3). We can make use again of the product between global softness and the Fukui function at the basic site yielding exactly the local softness at that site. Local softness at the X atom in the RX^- species is also included in Table 3, fifth column. It is shown in Table 3 that local softness does show a qualitative correlation with the relative proton affinity with reference to CH_3X^-. On the basis of this result, the following Hammett-like equation between these variables may be proposed:

$$\ln\left[\frac{\mathrm{PA(RX^-)}}{\mathrm{PA(CH_3X^-)}}\right] = \rho\sigma = \rho s_X^- \ (\mathrm{X = O, S}) \qquad (15)$$

where ρ (=−0.0604 and −0.0365 for X = O and S, respectively, see Figure 2) are the regression slopes. The negative value in both cases means that there will be a smaller electron population at the reaction site in the product than in the reactant. Within our model based on the HSAB rule, where we are considering the acid–base process as the opposite to the one described in eq 14, the sign of ρ trivially matches this criterion. Changes in the electron density at the reaction center promoted by chemical substitution may be interpreted within the present approach, as changes in the electron density due to changes in the electronic chemical potential, which defines exactly what local softness is within the DFT/PPY formulation.[7,8]

The substituent constant σ, indirectly represented here by the local softness at the X atom in RX^-, enters the model in an implicit way, namely as a local response to the changes in electronic chemical potential induced by changes in the total number of electrons due to chemical substitution. This Hammett-like linear relationship between the relative proton affinity variations and the local softness may be explained again on the basis of both the global softness of the alkoxide and thioalkoxide ions and local softness at the basic site within the HSAB principle. What these results show is that the electronic substituent effect manifests itself here by rendering the basic X atom in RX^- less hard than the X atom in the reference (CH_3X^-), thereby giving less stable RXH products. It is also interesting to note that our model also discriminates well the gas-phase acidity pattern displayed by the short series of alcohols and thioalcohols considered here, as shown in Figure 2. Within the local softness scale, the subset of alkoxide ions appears at lower values of s_X^- than the corresponding thio derivatives, indicating again that the PA values of RO^- species (measuring gas-phase acidity) will be higher than the corresponding PA values of the RS^- species. This result is also consistent with a local HSAB rule.

4. General Discussion

It is quite surprising that the Hammett-like linear relationship may be successfully cast in the form of an energy–density relationship, framed on global and local HSAB rules. These relationships correctly assess the substituent electronic effects on both gas-phase basicity of alkylamines and acidity of alcohols, including the thio derivatives. Despite the fact that our model equations are not rigorously derived, they may be reasonably justified within an empirical model based on an expansion of the electronic chemical potential in a scheme of atoms in molecules. To give consistency to the model eqs 7, 9, and 15, we may assign to the γ parameter a physical interpretation within the present model. Let us rewrite eq 5 for the case of a hard–hard interaction (ΔN_A small). There results

$$\mu[N + \Delta N] = \mu^\circ[N] \exp(\gamma\sum_A \Delta f_A) \cong \mu^\circ[1 + \gamma \sum_A \Delta f_A] = \mu^\circ + \mu^\circ\gamma\sum_A \Delta f_A \qquad (16)$$

Comparison of eqs 3 and 16 yields:

$$\gamma = \frac{\Delta N}{\mu^\circ}\sum_A \frac{1}{\kappa_A} \qquad (17)$$

where

$$\Delta f_A = \frac{\Delta N_A}{\Delta N} \qquad (18a)$$

and

$$\eta_A = \left[\frac{\partial\mu}{\partial N_A}\right]_v \qquad (18b)$$

and

$$\kappa_A = \left[\frac{\partial N_A}{\partial \mu}\right]_v = \frac{1}{\eta_A} \tag{19}$$

is Huheey's group charge capacity.[26,27] Note that within the present approach, the parameter γ, which appears associated to the reaction constant ρ of Hammett eq 1 and the Hammett-like eqs 7, 9, and 15, contains the fundamental ingredients of the electronic substituent effect, namely, the group charge capacity k_A, and the intrinsic electronegativity of the substrate $\chi° = -\mu°$. This is a well-known result already proposed by Huheey,[26,27] who stated that when discussing the substituent inductive effect of groups, it was necessary to consider the relative charge capacity of the group together with the electronegativity of the substrate. In this sense, a group cannot be considered as an efficient electron donor or acceptor in absolute terms: their ability as good Lewis acids and bases will certainly depend on the substrate intrinsic electronegativity.[26−28] While for atoms the γ falloff parameter displays a nearly constant value, within the present approach it becomes a characteristic quantity dependent on the intrinsic electronegativity of the substrate and the effect of the charge capacity of the substituent. This last effect is indirectly encompassed in the responses of local electronic properties such as the Fukui function difference and the local softness at the active center.

In the case of the gas-phase basicity of alkylamines, the substituent constant appears related to the Fukui function difference, namely, $\sigma = \Delta f_k^- = f_k^-(\text{reference}) - f_k^-(\text{molecule})$ at the active site k. This result follows from the relatively small variations in the global softness within the series (i.e. Li−Evans HSAB reactivity rule[6]). In the case of alkyl alcohols and thio derivatives, the substituent constant σ appears closely related to the local softness at the active site, because of the greater variation pattern shown by global softness within this series. Both results match well with the local reactivity criterion encompassed in the Li−Evans selectivity rule. The gas-phase basicity of alkylamines as well as the gas-phase acidity of alcohols and the thio derivatives may be explained within a common electronic framework, i.e. the HSAB principle. However, as a reviewer correctly stated, the linear relationships between softness (hardness) and proton affinity reported here refer to a series of related molecules, and they could be lost within a series of different molecules presenting different chemical functionalities.

5. Concluding Remarks

The Politzer equation relating charge-dependent electronegativity with charge capacity, together with the Parr−Bartolotti model describing the variations of electronic chemical potential with the number of electrons in atoms, may be generalized to molecules. This empirical approach provides physical grounds allowing one to write useful energy−density relationships. These linear relationships correctly assess the electronic substituent effects in different gas-phase acid−base equilibria. They may be cast in the form of Hammett-like equations, relating variations in proton affinities and local descriptors of reactivity that explain the substituent effects on the gas-phase basicity of alkylamines and acidity of alcohols and thio derivatives. While for alkylamines the substituent effect manifests itself by an increase of local hardness at the basic center, the substituent effect on the gas-phase acidity of alkyl alcohols and thio alcohols may be explained by an increase in local softness at the basic center that stabilizes the conjugated bases RX^-. These empirical Hammett-like energy−density relationships are therefore framed on a local HSAB principle. The results obtained here are also consistent with the reactivity and selectivity rules recently proposed by Li and Evans.[6]

Even though the empirical energy−density relationships between energy-dependent quantities (PA values) and electron-density dependent ones cannot be derived from an exact and rigorous procedure (because the empirical nature of Hammett-like linear free energy relationships), we have shown that they can be reasonably justified within an approximate model for the variation of the electronic chemical potential by assuming that this quantity exponentially decays with the acquired charge of atoms in their valence state.

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Appendix: Inverse Relationship between Regional Hardness and Softness

Local softness and hardness obey the following inverse relationship:[7]

$$\int d\mathbf{r}\, s(\mathbf{r})\, \eta(\mathbf{r}) = 1 \tag{A.1}$$

The changes in electronic chemical potential $\Delta\mu$ induced by changes in the total number of electrons ΔN due to chemical substitution may be written as:

$$\Delta\mu[\Delta N] = \eta \Delta N + \int d\mathbf{r}\, f(\mathbf{r})\, \Delta v(\mathbf{r}) \tag{A.2}$$

Within the present approach, the global chemical hardness η may be written as:

$$\eta = \left[\frac{\partial \mu}{\partial N}\right]_v = \sum \left[\frac{\partial \mu}{\partial N_A}\right]_v \left[\frac{\partial N_A}{\partial N}\right]_v = \sum_A f_A \eta_A \tag{A.3}$$

with

$$\eta_A \equiv \left[\frac{\partial \mu}{\partial N_A}\right]_v \tag{A.4}$$

We may rewrite eq A.2 in a discretized form consistent with our model for the changes in electronic chemical potential as follows:

$$\Delta\mu = \sum_A \eta_A \sum_B \Delta q_B + \sum_A \sum_B \int d\mathbf{r}\, f(\mathbf{r})\, \Delta v_A(\mathbf{r}) \tag{A.5}$$

Next, assume that the changes in external potential may be expressed as a sum of atomic contributions from the different atomic centers in the molecule:

$$\sum_A \Delta v_A(\mathbf{r}) = \sum_A \sum_B \frac{\Delta q_B}{R_{AB}} = \sum_A \Delta v_A \tag{A.6}$$

By approximating the Fukui function as the electron density of the HOMO frontier MO for an electrophilic attack by a proton on the substrate, it may be shown (see refs 18 and 19) that:

$$\sum_B \int d\mathbf{r}\, f_B(\mathbf{r}) = 1 \tag{A.7}$$

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Substitution of eqs A.6 and A.7 into eq A.5 yields:

$$\Delta\mu = \sum_{A}[\eta_A \Delta q_A + \eta_A \sum_{B\neq A} \Delta q_B + \Delta v_A] = \sum_{A} \Delta\mu_A \qquad (A.8)$$

From eq A.8 it follows that:

$$\Delta\mu_A = \eta_A(\Delta q_A + \sum_{B\neq A} \Delta q_B) + \Delta v_A = \eta_A \Delta N + \Delta v_A \qquad (A.9)$$

On the other hand, It has been shown elsewhere,[29,30] that the changes in electron density at center A in a molecule may be expressed in terms of the variation of the external and electronic chemical potentials as:

$$\Delta N_A = -\mathrm{s}_A \Delta v_A + s_A \Delta\mu_A \qquad (A.10)$$

This result follows from the first-order static density response function, and writing the electron density as a function of the number of electrons N and a functional of the external potential. Substitution of eq A.9 into eq A.10 yields the desired result, namely,

$$s_A \eta_A = \frac{\Delta N_A}{\Delta N} \qquad (A.11)$$

which shows that the regional softness and hardness are at least inversely proportional to each other. Equation A.11 is equivalent to the discrete version of the expression proposed by Fuentealba.[31] Note that the relationship in eq A.11 satisfies the correct normalization condition:

$$\sum_{A} s_A \eta_A = 1 \qquad (A.12)$$

Equation A.12 is the discrete expression of the inverse relationship in eq A.1 between local hardness and softness.

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