J. Phys. Chem. A **2000,** *104,* 11993−11998

A Semiquantitative Description of Electrostatics and Polarization Substituent Effects: Gas-Phase Acid−Base Equilibria as Test Cases

Patricia Pérez,*,† Alejandro Toro-Labbé,† and Renato Contreras‡

Departamento de Química Física, Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Correo 22, Santiago, Chile, and Departamento de Química, Facultad de Ciencias, Casilla 653-Santiago, Chile

Received: July 19, 2000; In Final Form: September 15, 2000

A semilocal (regional) model to describe the effects of chemical substitution on gas-phase acid−base reactivity is developed and tested. A simple relationship connecting regional changes in electron density and global changes in electronic chemical potential is used to describe inductive (electrostatic) substituent effects. Electronic (polarization) substituent effects are described in terms of regional changes in local softness at the active site, that are responses to changes in electronic chemical potential induced by chemical substitution. The model correctly explains the variations of the gas-phase acidity of alkyl alcohols and some thio derivatives within a local hard and soft acid and bases (HSAB) rule. Increase in local softness is correlated with a decrease in proton affinity of the conjugated base and therefore with an enhancement of the gas-phase acidity. It is shown that this is basically a HSAB result. The local analysis based on second-order variations in electron density (i.e., regional changes in the Fukui function) is consistent with the classical analysis based on first-order variations in electron population at the active site: a decrease in the electronic chemical potential induced by substitution results in a decrease in the electron population at the site (inductive effect, −I), thereby stabilizing the conjugated base and therefore increasing the acidity of the neutral parent molecule.

1. Introduction

The replacement of an atom or group may change the global and local reactivity pattern of a molecule. These changes are usually referred to as substituent effects (SE).[1−3] Substituent effects have been treated in classical organic physical chemistry in the form of empirical linear free energy relationships. The Hammett equation is a good example of this treatment.[4,5] Substituent effects may also be described on a more quantitative basis in terms of global and local reactivity indexes. For instance, Geerlings et al. have proposed a theoretical scheme to deal with SE using group molecular properties, such as group hardness and group electronegativity.[6,7] Other attempts to rationalize SE by means of reactivity indexes have been proposed by Nalewajski[8] and Komorowski.[9]

In the Organic Chemistry literature, SE are arbitrarily separated into electrostatic (inductive) SE and polarization SE. The first group involves the fluctuation of the electron population at the active site induced by chemical substitution.[3] Specifically, the inductive substituent effect (ISE) measures the intramolecular charge transfer from or to the active site. If the electron population decreases at the active site, the substituent group is classified as electron withdrawing, and the net effect is defined by ISE = − I. Conversely, if the electron population is enhanced at the active site by chemical substitution, the substituent group is classified as electron donating, and the net effect is defined as ISE = + I. Polarization (electronic) substituent effects (ESE) mainly encompass resonance effects. An excellent source about this topic has been recently addressed by Rablen.[10] The discussion was illustrated for the case of the acetate anion. For instance, the classical explanation given to describe the gas-phase acidity of acetic acid refers to the extra stabilization of the acetate anion by resonance.[11,12] This explanation, however, has been challenged in the last years and an alternative electrostatic explanation has been offered.[13,14]

Substituent effects may be described with the aid of global and local reactivity indexes, used in connection with the empirical hard and soft acid and bases (HSAB) principle.[15] Substituent effects were discussed therein in the form of empirical energy−density relationships, similar to that suggested by Hammett.[4] Chemical substitution was represented as responses (global and local) induced by an external stimulus that changes the number of electrons from N to $N + dN$. The global responses were assessed by studying the variations in electronic chemical potential. Local responses at the active site are monitored by looking at the changes in the Fukui function and local softness at this site.

In this work, we present a more quantitative model of SE that describes the ISE in terms of the electronic chemical potential, and the ESE in terms of fluctuations in local softness at the active site. The gas-phase acidity of alcohols and thioderivatives is used to illustrate the reliability of the proposed model.

2. Model Equations

2.1. Inductive (Electrostatic) Substituent Effects. Local softness is a local descriptor of reactivity. It has been given the following definition in the context of the density functional theory formulation of Parr, Pearson and Yang:[16,17]

$$s(\mathbf{r}) = \left[\frac{\partial \rho(\mathbf{r})}{\partial \mu}\right]_{v(\mathbf{r})} \qquad (1)$$

In eq 1, $\rho(\mathbf{r})$ is the electron density of the N-electron system under the influence of the external potential $v(\mathbf{r})$ due to the

---

* Corresponding author.

† Pontificia Universidad Católica de Chile.

‡ Universidad de Chile.

10.1021/jp0025734 CCC: $19.00

compensating (nuclear) charges in the system. The quantity μ is the electronic chemical potential; that is, the first derivative of the electronic energy E with respect to N.[16] The electronic chemical potential is the negative of the molecular electronegativity and it may be understood as a descriptor for the escaping tendency of electrons from the system in its ground state.[16,17] If eq 1 is condensed to atoms or groups in a molecule, by performing for instance a regional integration over an arbitrary domain Ω_k, then the following approximate relationship for the first-order variation in the condensed electron population ρ_k may be written:[18]

$$\Delta\rho_k = s_k\Delta\mu \tag{2}$$

Equation 2 gives a simple yet useful criterion to analyze the changes in electron population at any atomic center in a molecule, in terms of the variation of the electronic chemical potential induced by changes in the number of electrons. As proposed by Berkowitz and Parr,[18] eq 2 shows the meaning of regional softness as a capacitance of a group in the molecule to acquire additional charge. The higher the value of s_k, the softer (i.e., more polarizable) is the group. Other useful relationships between charge capacity and hardness as well as relationships between softness and polarizability have been discussed by Politzer,[19] Simón-Manso and Fuentealba,[20] and Chattaraj and Sengupta.[21]

On the other hand, the variations of electron density may be also expressed in terms of the Fukui function, which is defined as:[16,17]

$$f(\mathbf{r}) = \left[\frac{\partial\rho(\mathbf{r})}{\partial \mathrm{N}}\right]_{\upsilon(\mathbf{r})} = \frac{s(\mathbf{r})}{S} \tag{3}$$

where S is the global softness, the inverse of the chemical hardness η. Equation 3 may also be given a regional form by performing a regional integration similar to that leading to eq 2, which results in eq 4:

$$\Delta\rho_k = f_k\,\Delta N \tag{4}$$

Equations 2 and 4 may be used to define the (electrostatic) ISE. In classical organic physical chemistry, the ISE is associated with the variations in electron density at the active site of reaction $\Delta\rho_k$ as follows: for example, if there is an increase in the electron density at the (active) site ***k*** (i.e. $\Delta\rho_k = \rho_k$ (substituted molecule) $- \rho_k$ (reference) > 0), then ISE = + I; and conversely, if $\Delta\rho_k < 0$, then ISE = − I. From eqs 2 and 4 we then have eq 5:

$$\mathrm{sign}(\Delta\rho_k) = \mathrm{sign}(\Delta N) = \mathrm{sign}(\Delta\mu) \tag{5}$$

that is, the sign of $\Delta\rho_k$ defining the ISE may be either associated with the charge transfer from or to the substituent at the active site (ΔN) or by the sign of the change in electronic chemical potential $\Delta\mu = \mu$(substituted molecule) $- \mu$ (reference). Relationship 5 holds because, in general, the regional Fukui function is a positive definite quantity (which is not necessarily the case for the local counterpart $f(\mathbf{r})$[22]); and because S is also a positive definite quantity. The criterion to assign the ISE within a family of related molecules based on ΔN usually demands suitable population analysis methods that may be, in some cases, strongly dependent on the basis set and Hamiltonian used to obtain the approximate wave function of an N electron system. Other methods to analyze ESE based on the electronegativity equalization principle (EEP) and group properties have been presented.[9]

We propose here to analyze the ISE based on the variations of electronic chemical potential on chemical substitution using eq 2. Note that this method has the potential advantage of giving a more transparent analysis of ISE in terms of local reactivity indexes instead of a population analysis. This may be shown by rewriting eq 2 with the aid of relationship 3 as follows:

$$\Delta\rho_k = s_k\Delta\mu = f_k(S\Delta\mu) \tag{6}$$

Although the term $S\Delta\mu$ uniformly affects the electron population at any atomic center in the molecule, the quantity f_k helps to discriminate the ISE: eq 6 tell us that the major changes in ρ_k will manifest themselves at the site where f_k displays its maximum value, which is the active site in the molecule. Therefore, we propose the following definition for ISE:

$$\begin{aligned} \mathrm{ISE} &= +\,\mathrm{I} \text{ if } \Delta\mu > 0 \\ \mathrm{ISE} &= -\,\mathrm{I} \text{ if } \Delta\mu < 0 \end{aligned} \tag{7}$$

where the changes in electronic chemical potential $\Delta\mu$ are to be evaluated with reference to the unsubstituted molecule.

2.2 Polarization (Electronic) Substituent Effects. Polarization (electronic) substituent effects (ESE) may be described in terms of the variation of local (regional) softness at the active site ***k***. We introduce then the following definition for ESE:

$$\begin{aligned} \mathrm{ESE} &= +\mathrm{S} \text{ if } \Delta s_k > 0 \\ \mathrm{ESE} &= -\mathrm{S} \text{ if } \Delta s_k < 0 \end{aligned} \tag{8}$$

The relationship ESE = +S means that the substituent renders the active site softer than in the reference (unsubstituted) molecule; and conversely, ESE = − S means that the substituent makes the active site ***k*** less soft (i.e., harder) than in the reference molecule. Working expressions for Δs_k, may be obtained from higher (third)-order derivatives of electronic energy as proposed by Fuentealba and Parr.[23] For instance, the following relationship for the variations in the regional Fukui function is obtained:

$$\Delta f_k = t_k\Delta\mu \tag{9}$$

where t_k is a regional index obtained by a regional integration procedure similar to that leading to eq 2 of the function $t(\mathbf{r})$ defined by Fuentealba and Parr:[23]

$$t(\mathbf{r}) = \left[\frac{\partial f(\mathbf{r})}{\partial\mu}\right]_{\upsilon(\mathbf{r})} \tag{10}$$

The corresponding change in local (regional) softness is given by (see Appendix):

$$\Delta s_k = t_kS\Delta\mu + f_k\Delta S = S\Delta f_k + f_k\Delta S \tag{11}$$

It is interesting to note that whereas the first-order variation in electron density is related to changes in the electronic chemical potential in eq 2, the variations in the Fukui function (i.e., second-order variation in the electron density) are related to $\Delta\mu$ through the quantity $t(\mathbf{r})$, which contains the variations of local an global softness with respect to the variations in the number of electrons, at constant external potential (see *Appendix*).

3. Applications: The Gas-Phase Acidity of Alkyl Alcohols and Thio Derivatives

Consider the following proton transfer (PT) equilibrium of species RXH and RX′⁻ (R = alkyl group, X = O, S) in the gas phase:

$$\mathrm{RXH} + \mathrm{RX'^-} \Rightarrow \mathrm{RX^-} + \mathrm{RX'H} \qquad \Delta E = \Delta E_{\mathrm{pt}} \quad (12)$$

If we consider, on the other hand, that the gas-phase equilibria are governed by proton affinity (PA), defined as the enthalpy change for the bond cleavage reaction:

$$\mathrm{RXH} \Rightarrow \mathrm{RX^-} + \mathrm{H^+} \qquad \mathrm{PA} = \Delta E \quad (13)$$

then we can immediately get a relationship between the energy associated to the PT process in the gas phase, and the variations in PA of the charged species RX^- and RX'^- (the last one taken as reference), namely:

$$\Delta E_{\mathrm{pt}} = \delta\mathrm{PA} = \mathrm{PA(RX^-)} - \mathrm{PA(RX'^-)} \quad (14)$$

On the other hand, to better understand the charge rearrangements induced by chemical substitution, it is also interesting to analyze the changes in electronic chemical potential associated to the gas-phase PT process described in eq 12. Using the fact that the electronic chemical potential is an extensive property of the system, the variations of this quantity associated to the PT process 12 may be written as:

$$\Delta\mu_{\mathrm{pt}} = [\mu(\mathrm{RX^-}) - \mu(\mathrm{RX'^-})] + [\mu(\mathrm{RX'H}) - \mu(\mathrm{RXH})] = \Delta\mu^- + \Delta\mu^N \quad (15)$$

If we keep our HSAB reasoning about gas-phase acidity around the electronic properties of the conjugated bases RX^- and RX'^-, then the pertinent quantity to be considered is $\Delta\mu^-$, which is defined as:

$$\Delta\mu^- = [\mu(\mathrm{RX^-}) - \mu(\mathrm{RX'^-})] \quad (16)$$

Therefore, for the electrophilic interaction between the proton and the alkoxyde or thio-alkoxyde the corresponding t_k^- quantity to be considered is obtained by replacing in eq 9 Δf_k by Δf_k^-, the difference in electrophilic Fukui function in the substituted anion and in the reference.

3.1 Computational Details. Total energies needed to evaluate PAs and δPAs from eqs 13 and 14 as well as the global and local electronic reactivity indexes were performed at the HF/6-311G(d)//HF/6-311G(d) level of theory, using the GAUSSIAN94 package of programs.[24] The electronic chemical potential is approached as:[16,17]

$$\mu \approx \frac{\epsilon_{\mathrm{H}} + \epsilon_{\mathrm{L}}}{2} \quad (17)$$

in terms of the one-electron energies of the frontier molecular orbitals HOMO (ϵ_H) and LUMO (ϵ_L). Global softness is obtained as the inverse of hardness; namely,

$$S = \frac{1}{\eta} \approx \frac{2}{\epsilon_{\mathrm{L}} - \epsilon_{\mathrm{H}}} \quad (18)$$

The regional Fukui function f_k is obtained from a single-point calculation at the optimized geometry, using a method described elsewhere.[25] With the f_k and S values already at hand, the regional softness s_k is obtained via eq 3 as $s_k = f_k S$.

4. Results and Discussion

4.1 First-Order Global Changes. The proposed model of chemical substitution will be illustrated in the study of the gas-phase acidity for a series of alkyl alcohols and alkyl thioalcohols RXH (X = O, S). The gas-phase acidity of these systems has been experimentally determined by ion cyclotron resonance experiments by Bartmess et al.[26] In a series of related molecules, the acidity scale may be assigned in terms of the difference in proton affinity $\delta\mathrm{PA} = \mathrm{PA}(\mathrm{RX^-}) - \mathrm{PA(RX'^-)}$, where RX'^- is the reference molecule (CH_3O^- for alcohols and CH_3S^- for thioalcohols in the present case). Values of δPA obtained at the HF/6-311G(d)//HF-6311G(d) level of theory compare reasonably well with the experimental data, as shown in Table 1, second and third columns, for both subseries of alcohols.

TABLE 1: Global Analysis of the Gas-Phase Acidity of Alkyl Alcohols and Thio Derivatives[a]

RX^-	δPA(exp)	δPA(theo)	S	ΔS
CH_3O^-	0.0	0.0	4.5592	0.0
$CH_3CH_2O^-$	−3.1	−4.1	4.6744	0.1152
$(CH_3)_2CHO^-$	−5.1	−6.6	4.7272	0.1680
$(CH_3)_3CCH_2O^-$	−7.4	−10.1	5.0058	0.4466
CH_3S^-	0.0	0.0	4.9633	0.0
$CH_3CH_2S^-$	−1.6	−0.8	5.1327	0.1694
$(CH_3)_2CHS^-$	−3.4	−1.8	5.1847	0.2214
$(CH_3)_3CCH_2S^-$	−	−3.2	5.5128	0.5495

[a] $\delta\mathrm{PA} = \mathrm{PA(RX^-)} - \mathrm{PA(reference)}$. δPA values in kcal/mol. In the series of alkyl alcohols, the reference anion is CH_3O^-; in the series of thio derivatives, the reference anion is CH_3S^-. Global softness values in atomic units. All quantities evaluated at HF/6-311G(d)//HF/6-311G(d) level of theory.

Up to first order, the energy changes are directly related to the δPA scale as defined in eq 14. Furthermore, the acidity of RXH species in the gas phase obeys the following empirical rule: *within a family of related molecules, the greater the PA value of the conjugated base* RX^-, *the lower is the acidity of the corresponding RXH species*. It is interesting to note from Table 1 that there is an inverse relationship between δPA and global softness (see Table 1, columns 2, 3 and 4): increasing acidity entails a decrease in PA and an increase in the global softness of the conjugated bases (RX^-). This result may be easily interpreted within a global HSAB principle.[27] If we consider the opposite reaction to that shown in eq 13, we immediately realize that increasing PA will be correlated with an increasing global hardness of the RX^- species because the proton is absolutely hard. Using the empirical acidity rule just stated, we may conclude that an increasing acidity pattern within a family of related molecules will always be associated with a decrease in the chemical hardness of the anion. Using the inverse relationship between global hardness and global softness given in eq 18, the following HSAB rule for gas-phase acidity may be proposed: *within a family of related molecules, the greater the global softness value of the conjugated base* RX^-, *the higher is the acidity of the corresponding RXH species*. This result is an HSAB one in the sense that an increase in the global softness of the RX^- species will result in an unfavorable interaction with the proton to yield the RXH species (hard−soft interactions are associated with unfavorable enthalpy changes, with respect to hard−hard interactions[27]), thereby stabilizing the RX^- species.[15] The positive variations of ΔS quantity confirm the rule in this case (see fifth column of Table 1).

4.2 Electrostatic versus Polarization Substituent Effects. According to the proposed model, the inductive (electrostatic) effect of the alkyl substituent may be monitored either by the variations in the electronic population at the basic site (oxygen atom of the alkoxyde ion or sulfur atom of thioalkoxyde ion) or by the variations in the electronic chemical potential $\Delta\mu^-$. In Table 2, the Mulliken population analysis (MPA) is used to assess the changes in the electron density at the X = O, S sites in the family of alkoxyde an thioalkoxyde ions (Table 2, fifth

TABLE 2: Local Electronic Properties and (Electrostatic) Inductive Substituent Effect (ISE) Analysis on the RX⁻ Species (X = O,S)[a]

RX^-	q_X(MPA)	s_X^-	$\Delta\mu^-$	$\Delta\rho_X$(calc.)[b]	$\Delta\rho_X$(pred.)[c]	ISE
CH_3O^-	−0.8273	3.3854	0.0	0.0	0.0	−
$CH_3CH_2O^-$	−0.8111	3.3809	−0.0162	−0.0163	−0.0548	−I (−I)
$(CH_3)_2CHO^-$	−0.8052	3.3879	−0.0280	−0.0221	−0.0949	−I (−I)
$(CH_3)_3CCH_2O^-$	−0.7985	3.9970	−0.0469	−0.0288	−0.1875	−I (−I)
CH_3S^-	−0.7920	4.7546	0.0	0.0	0.0	−
$CH_3CH_2S^-$	−0.7804	4.8813	−0.0105	−0.0116	−0.0513	−I (−I)
$(CH_3)_2CHS^-$	−0.7654	4.9048	−0.0169	−0.0266	−0.0829	−I (−I)
$(CH_3)_3CCH_2S^-$	−0.7616	5.2197	−0.0298	−0.0304	−0.1556	−I (−I)

[a] All quantities (in atomic units) evaluated at HF/6-311G(d)//HF/6-311G(d) level of theory. Atomic charges (q_X) from Mulliken population analysis (MPA). [b] Calculated $\Delta\rho_X$ values obtained as $\Delta\rho_X = -\Delta q_X$ from MPA. [c] Predicted $\Delta\rho_X$ values obtained from eq 2 (see the text for further details).

column). It may be seen that in all cases, $\Delta\rho_X < 0$, indicating that the alkyl group develop an electrostatic effect ISE $= -$ I. This result means that in both subsets of alcohols, the alkyl substituents behave as electron-withdrawing groups. This result is consistent with those reported by Geerlings et al.[28] from a different analysis based on group electronegativity and hardness. Although alkyl groups have been currently classified as electron-donating groups on an absolute basis, these results show that in the discussion of the electrostatic inductive substituent effect of groups, it is necessary to consider the relative charge capacity (measured in the present model by local softness) together with the electronegativity of the substrate. In this sense, a group cannot be considered as electron donor or acceptor in absolute terms, and their ability as good Lewis acids or bases will depend on the substrate intrinsic electronegativity.[29] Table 2 also include the variations in the electronic chemical potential $\Delta\mu^-$ obtained from eq 16, and the regional softness obtained as $s_k^- = f_k^- S$.[15,25] These quantities are necessary to alternatively predict the ISE from eq 2 on the basis of electronic chemical potential variations. The predicted $\Delta\rho_X$ values obtained from eq 2 are also included in Table 2 (sixth column). It is interesting to note that both eqs 2 and 4 consistently predict an electrostatic inductive effect ISE $= -$ I for both series of alkoxyde ions. This result validates the use of the electronic chemical potential as a useful quantity to describe electrostatic substituent effects.[30] This result is important because population analysis is in general strongly dependent on the methods and basis set used to derive the electron distribution of atoms in molecules.

TABLE 3: Fukui Functions for RX⁻ Species (X = O,S)[a]

RX^-	f_X^-	Δf_X^-
CH_3O^-	0.7426	0.0
$CH_3CH_2O^-$	0.7233	−0.0193
$(CH_3)_2CHO^-$	0.7167	−0.0259
$(CH_3)_3CCH_2O^-$	0.7249	−0.0177
CH_3S^-	0.9580	0.0
$CH_3CH_2S^-$	0.9510	−0.0070
$(CH_3)_2CHS^-$	0.9460	−0.0120
$(CH_3)_3CCH_2S^-$	0.9468	−0.0111

[a] All quantities (in atomic units) evaluated at HF/6-311G(d)//HF/6-311G(d) level of theory.

Electronic (polarization) substituent effects ESE are described within the present approach in terms of the fluctuation in local (regional) softness at the active X site. We will show that such substituent effects may be also rationalized in terms of a local HSAB rule. The local HSAB principle has been recently generalized by Li and Evans,[31] using the regional Fukui function as the basic quantity. The Li−Evans HSAB rule states that in a hard−hard interaction, which is actually the case for the gas-phase acid−base equilibria studied here, the protonation site in a molecule is the one presenting the minimum value of the Fukui function condensed to atoms. In the present case, there is a single site per molecule available for protonation, namely the X = O, S sites. In such a case, the molecule presenting the minimum value of f_x^- in the conjugated base is expected to show the maximum value of PA, and therefore the corresponding alcohol is the less acidic within the series. Values of regional Fukui function at the basic center are displayed in Table 3, second column, for the series of alkyl alcohols and the thio derivatives. Applying this criterion and taking into account the inverse relationship between gas-phase acidity and PA discussed in Section 4.1, the following gas-phase acidity order for the alkyl alcohol is predicted: $(CH_3)_2CHOH < CH_3CH_2OH < (CH_3)_3CCH_2OH < CH_3OH$, which is at variance with the experimental order relationship.[26] For the series of alkyl thioalcohols, the following order is predicted from the minimum Fukui function criterion: $(CH_3)_2CHSH < (CH_3)_3CCH_2SH < CH_3CH_2SH < CH_3SH$, which is again at variance with the experimental order relationship.[26] The apparent failure of the Fukui function to account for the experimental gas-phase acidity scale may be traced to the fact that for the Li−Evans[30] selectivity rule to be satisfied, there is an additional prerequisite to be fulfilled. This additional condition requires that the whole series of molecules has to be characterized by a global reactivity pattern not differing too much from each other. The natural descriptor of the gas-phase acidity within the present approach is global softness, as shown in Section 4.1. Global softness values, depicted in Table 1, that within both subseries of molecules, the *S* values (in atomic units) present significant variations, especially in the $(CH_3)_3CCH_2O(S)^-$ molecule. The remaining three molecules of each subset fulfill the condition that their *S* values are quite close to each other. We observe that their predicted acidity order of the neutral parent molecule is in agreement with the experimental data.

The effect of a varying global softness may be taken into account by looking at the changes in local (regional) softness instead of the regional Fukui function, using eq 11. Values of local softness condensed at the basic X center are shown in Table 2. It may be seen that, in general, the regional softness displays an increasing pattern similar to that displayed by their global counterpart. This result means that the gas-phase acidity order results from both a local and global HSAB rule. The values of regional softness are also useful to describe the polarization substituent effect ESE using eqs 8 and 11. The predicted Δs_x^- values obtained from eq 11, including the Δf_x^- and ΔS contributions, are listed in Table 4 (third column). For the alkyl alcohol series, with the only exception of $(CH_3)_2CHO^-$ (for which both the calculated and predicted Δs_O^- values are marginal), they all agree with the calculated values, showing that, in general, the net ESE manifests itself by rendering the basic site O softer than in the reference molecule. For the thioalcohol series, however, where a better resolution is

TABLE 4: Variations of Local Softness and Electronic Substituent Effect (ESE) Analysis for the RX⁻ Species (X = O,S)[a]

RX^-	Δs_X^- (calc.)[b]	Δs_X^- (pred.)[c]	=	$\Delta f_X^- S$	+	$f_X^- \Delta S$	ESE[d]
CH_3O^-	0.0	0.0		0.0		0.0	−
$CH_3CH_2O^-$	−0.0045	−0.0069		−0.0902		0.0833	−S (−S)
$(CH_3)_2CHO^-$	0.0025	−0.0020		−0.1224		0.1204	+S (−S)
$(CH_3)_3CCH_2O^-$	0.6116	0.2351		−0.0886		0.3237	+S (+S)
CH_3S^-	0.0	0.0		0.0		0.0	−
$CH_3CH_2S^-$	0.1267	0.1252		−0.0359		0.1611	+S (+S)
$(CH_3)_2CHS^-$	0.1502	0.1472		−0.0622		0.2094	+S (+S)
$(CH_3)_3CCH_2S^-$	0.4651	0.4586		−0.0617		0.5203	+S (+S)

[a] All quantities evaluated at HF/6-311G(d)//HF/6-311G(d) level of theory. [b] Calculated values of Δs_X^- (in atomic units) obtained as $\Delta s_X^- = s_X^-(RX^-) - s_X^-(\text{reference})$, with $s_X^- = f_X^- S$. [c] Predicted variations of local softness (in eV) at the active site from eq 11. [d] Electronic substituent effect ESE = +S means that the active site becomes softer and ESE = −S means the active site becomes less soft (i.e., harder) than in the reference molecule. The ESE value in parentheses refers to that predicted from eq 8.

obtained, the ESE effect consistently predicts an increase of local softness at the sulfur site induced by chemical substitution. In summary, the electrostatic ISE and electronic ESE of the alkyl groups in both subseries is to withdraw electron density from the basic site X, rendering this site in RX⁻ softer than in the reference molecule.

5. Concluding Remarks

Electrostatic and (electronic) polarization effects induced by substituent groups at the active site of molecule may be approximately described in terms of global and local reactivity indexes. Inductive (electrostatic) substituent effects (ISE) may be qualitatively described in terms of the electronic chemical potential variations. Electronic (polarization) substituent effects (ESE) may be assessed as responses at the active site, in the form of variations in local (regional) softness induced by chemical substitution. In the case of the gas-phase acidity of alcohols and thioalcohols, the ISE analysis based on the variations of electronic chemical potential consistently predict an inductive effect ISE = − I, in agreement with the results obtained from the population analysis based on eq 4. The ESE analysis on the other hand, shows that chemical substitution in both subseries renders the active site in the conjugated bases softer than in the reference molecule, and the observed relative acidity of the parent alcohol may be explained within a local HSAB framework.

Acknowledgment. This work received partial financial support from Fondecyt, under contracts 3990033, 1990543 and 1000816, and Cátedra Presidencial en Ciencias 1998 awarded to A.T.L.

Appendix. Derivation of Equation 11 Defining the Changes in Regional Softness

The function $t(\mathbf{r})$ has been defined as:[23]

$$t(\mathbf{r}) = \left[\frac{\partial f(\mathbf{r})}{\partial \mu}\right]_{v(\mathbf{r})} = \left[\frac{\partial f(\mathbf{r})}{\partial N}\right]_{v(\mathbf{r})}\left[\frac{\partial N}{\partial \mu}\right]_{v(\mathbf{r})} = h(\mathbf{r})S \quad \text{(A1)}$$

where

$$h(\mathbf{r}) = \left[\frac{\partial f(\mathbf{r})}{\partial N}\right]_{v(\mathbf{r})} \quad \text{(A2)}$$

Changes in local softness may be obtained from eq A1 by evaluating the function $h(\mathbf{r})$ using eq 3:

$$t(\mathbf{r}) = \left[\frac{\partial s(\mathbf{r})}{\partial N}\right]_{v(\mathbf{r})} - f(\mathbf{r})\left[\frac{\partial S}{\partial N}\right]_{v(\mathbf{r})} \quad \text{(A3)}$$

Now, write

$$\mathrm{d}s(\mathbf{r}) = \left[\frac{\partial s(\mathbf{r})}{\partial N}\right]_{v(\mathbf{r})} \mathrm{d}N \quad \text{(A4)}$$

and

$$\mathrm{d}S = \left[\frac{\partial S}{\partial N}\right]_{v(\mathbf{r})} \mathrm{d}N \quad \text{(A5)}$$

to obtain

$$\mathrm{d}s(\mathbf{r}) = t(\mathbf{r})\,\mathrm{d}N + f(\mathbf{r})\,\mathrm{d}S \quad \text{(A6)}$$

Equation A6 may be conveniently transformed to leave the first contribution in terms of changes in μ instead of changes in N. Consider the total differential for μ in the $\{N, v(\mathbf{r})\}$ ensemble:

$$\mathrm{d}\mu = \eta\,\mathrm{d}N + \int \mathrm{d}\mathbf{r}\, f(\mathbf{r})\,\delta v(\mathbf{r}) \quad \text{(A7)}$$

where

$$\eta = \left[\frac{\partial \mu}{\partial N}\right]_{v(\mathbf{r})} = \frac{1}{S} \quad \text{(A8)}$$

is the chemical hardness, the inverse of global softness S.[16] At constant external potential:

$$\mathrm{d}\mu = \eta\,\mathrm{d}N = \frac{\mathrm{d}N}{S} \quad \text{(A9)}$$

Substitution of eq A9 into eq A6 yields the desired result, namely:

$$\mathrm{d}s(\mathbf{r}) = t(\mathbf{r})\,S\,\mathrm{d}\mu + f(\mathbf{r})\,\mathrm{d}S = S\,\mathrm{d}f(\mathbf{r}) + f(\mathbf{r})\,\mathrm{d}S \quad \text{(A10)}$$

A regional integration of eq A10 leads to eq 11 of the text.

References and Notes

(1) Carey, F.; Sundberg, R. J. *Advanced Organic Chemistry*, Third Edition, Plenum Press: New York, London, Part A, 1990.
(2) Siggel, M. R.; Thomas, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 4360.
(3) Wiberg, K. B. *Acc. Chem. Res.* **1999**, *32*, 922.
(4) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.
(5) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(6) De Proft, F.; Langenaeker, W.; Geerlings, P. *J. Phys. Chem.* **1993**, *97*, 1826.
(7) De Proft, F.; Amira, S.; Choho, K.; Geerlings, P. *J. Phys. Chem.* **1994**, *98*, 5227.
(8) Nalewajski, R. F. In *Structure and Bonding 80, Chemical Hardness*; Sen, K. D., Ed.; Springer-Verlag: Berlin, New York, London, 1993; p 115.
(9) Komorowski, L.; Lipinski, J.; Pyka, M. J. *J. Phys. Chem.* **1993**, *97*, 3166.
(10) Rablen, P. R. *J. Am. Chem. Soc.* **2000**, *122*, 357.

(11) Neto, J. D. d. M.; Nascimiento, M. A. C. *J. Phys. Chem*. **1996**, *100*, 15105.

(12) Wheland, G. W. *Resonance in Organic Chemistry*; Wiley: New York, 1955; p 345.

(13) Ji, D.; Thomas, T. D. *J. Phys. Chem*. **1994**, *98*, 4301.

(14) Siggel, M. R. F.; Streitwieser, A., Jr.; Thomas, T. D. *J. Am. Chem. Soc*. **1988**, *110*, 8022.

(15) Pérez, P.; Simón-Manso, Y.; Aizman, A.; Fuentealba, P.; Contreras, R. *J. Am. Chem. Soc*. **2000**, *122*, 4756

(16) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*, Oxford Science Publications: Oxford, New York, 1989.

(17) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc*. **1983**, *105*, 7512.

(18) Berkowitz, M.; Parr, R. G. *J. Chem. Phys*. **1988**, *88*, 2554.

(19) Politzer, P. *J. Chem. Phys*. **1987**, *86*, 1072.

(20) Simón-Manso, Y.; Fuentealba, P. *J. Phys. Chem. A*. **1998**, *102*, 2029.

(21) Chattaraj, P. K.; Sengupta, S. *J. Phys. Chem*. **1996**, *100*, 16126.

(22) Fuentealba, P.; Pérez, P.; Contreras, R. *J. Chem. Phys*. **2000**, *113*, 2544.

(23) Fuentealba, P.; Parr, R. G. *J. Chem. Phys*. **1991**, *94*, 5559.

(24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M.; Johnson, B. G.; Robb, M. A.; Cheesman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. V.; Ciolowski, J.; Stephanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, T. Y.; Chen, W.; Wong, M. W.; Andres, J.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, V. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian Inc.: Pittsburgh, PA, 1995.

(25) Contreras, R.; Fuentealba, P.; Galván, M.; Pérez, P. *Chem. Phys. Lett*. **1999**, *304*, 405.

(26) Bartmess, J. E.; Scott, J. A.; McIver, R. T., Jr. *J. Am. Chem. Soc*. **1979**, *101*, 6046.

(27) Pearson, R. G. *Hard and Soft Acids and Bases*; Dowden, Hutchinson and Ross: Stroudsberg, PA, 1973.

(28) De Proft, F.; Langenaeker, W.; Geerlings, P. *Tetrahedron* **1995**, *51*, 4021.

(29) Huheey, J. E. *J. Org. Chem*. **1971**, *36*, 204.

(30) Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Phys. Chem. A*. **1999**, *103*, 11246.

(31) Li, Y.; Evans, N. S. *J. Am. Chem. Soc*. **1995**, *117*, 7756.