The Basicity of *p*-Substituted Phenolates and the Elimination−Substitution Ratio in *p*-Nitrophenethyl Bromide: A HSAB Theoretical Study

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The influence of basicity in a set of para-substituted phenolates on the elimination−substitution ratio obtained upon reaction with *p*-nitrophenethyl bromide has been studied. A correlation between experimental equilibrium data (pK_a) and reactivity indices obtained from density functional theory (DFT) was looked for in order to show that the hard and soft acids and bases principle (HSAB) is well suited to describe the basicity properties of the para-substituted phenolates. When the basicity of para-substituted phenolates increases, their global hardness and their condensed softness at the oxygen atom increase; the negative net charge, condensed nucleophilic fukui function, and condensed nucleophilic softness of the oxygen atom increase. The proposal that the alkyl halide substrate possesses a hard β-hydrogen atom and a soft α-carbon was studied for *p*-nitrophenethyl bromide; it turns out that the β-hydrogen atom is soft, even softer than the carbon atom. The experimental results for the elimination−substitution ratio for *p*-nitrophenethyl bromide can be explained from a local−local HSAB viewpoint for the para-substituted phenolates and *p*-nitrophenethyl bromide and not from a global−local level viewpoint as suggested before. The results suggest that para-substituted phenolates with higher basicity (harder), less delocalized negative charge into the fragment R−C_6H_4, and a more polarizable oxygen atom (softer) do have a lower (relative) attraction toward an alkyl carbon atom (soft) than toward a hydrogen atom (softer) from *p*-nitrophenethyl bromide. The β-hydrogen and α-carbon atoms can be considered to act as a Lewis acid toward the para-substituted phenolate nucleophile considered as a base.

Introduction

The vast collection of information concerning the interconversion of organic compounds can be classified into a small number of elementary reaction types.[1] Two of them are elimination (E) and substitution (S_N). In the alkyl halide elimination, a base is almost always required to remove a proton; usually, this process cannot be completely isolated, for under these conditions the base will also act as nucleophile toward the carbon atom and nucleophilic substitution will result. It has been known for a long time that strong bases not only favor bimolecular elimination (E2) over unimolecular elimination (E1) but also favor elimination over substitution (E > S_N1, S_N2). With a high concentration of strong base in a nonionizing solvent, the bimolecular mechanism is favored and bimolecular elimination predominates over bimolecular nucleophilic substitution.[2]

The influence of the base on the elimination−substitution competition has been explained in terms of basicity (related to proton affinity) and nucleophilicity (related to carbon affinity). In the context of the hard and soft

acids and bases principle (HSAB),[3] Klopman et al. suggested[4] that basicity bears a direct relationship to the hardness of a base. Considering basicity in the Brønsted sense (proton affinity) and taking into account that the proton is hard (local level), the base will show increasing proton affinity as its hardness increases (global level). They also suggested that nucleophilicity is related to the softness of the nucleophile. In a Lewis sense, the nucleophile shows affinity toward an electrophilic carbon atom. If the carbon atom attached to the leaving group is soft (local level), then the nucleophile will increase its carbon affinity when its softness increases (global level). This idea is expressed by March as follows: "The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer, ... We may then expect the alkyl group to prefer softer nucleophiles than the proton does. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton."[5]

Although there are several examples in the literature concerning the interaction between a base and a substrate where this rule is observed,[1,6,7] the role of the HSAB principle has not been explored in detail. In this

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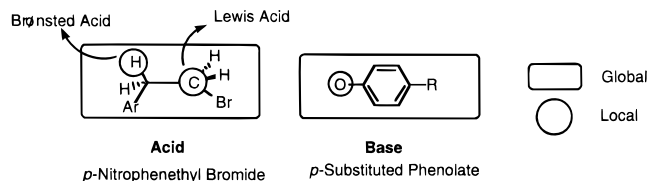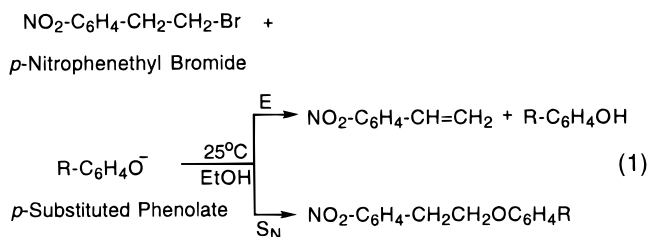(7) Parke, A. J. *Adv. Phys. Org. Chem.* **1967,** *5,* 173.

Figure 1. Global–local and local–local interactions between *p*-nitrophenethyl bromide and para-substituted phenolates.

context, we have analyzed results from Klopman et al. on the influence of basicity in a set of para-substituted phenolates on the elimination/substitution (E/S_N) ratio obtained upon reaction with *p*-nitrophenethyl bromide.[8]

A correlation between kinetic (E/S_N ratio) and equilibrium (pK_a) parameters shows that basicity is related to the E/S_N ratio. With density functional theory (DFT)-based electronic properties,[9] we try to understand basicity from both a global and a local point of view. The global softness for *p*-nitrophenethyl bromide and the local softness for its β-hydrogen and α-carbon atoms were calculated to study the reaction between *p*-nitrophenethyl bromide and para-substituted phenolates in order to see (a) if the HSAB principle is at work at a global–local or local–local level and (b) if the β-hydrogen can be considered to act as a Brønsted acid (high local hardness) and the α-carbon as a Lewis acid (high local softness) toward the nucleophile considered as a base (Figure 1).

Results and Discussion

The reaction between *p*-nitrophenethyl bromide and a set of para-substituted phenolates was shown to yield elimination (E) and substitution (S_N) products:[8]

NO₂-C₆H₄-CH₂-CH₂-Br +

p-Nitrophenethyl Bromide

$$
\text{R-C}_6\text{H}_4\text{O}^- \xrightarrow[\text{EtOH}]{25^\circ\text{C}}
\begin{array}{l}
\xrightarrow{\text{E}} \text{NO}_2\text{-C}_6\text{H}_4\text{-CH=CH}_2 + \text{R-C}_6\text{H}_4\text{OH} \\
\\
\xrightarrow{\text{S}_N} \text{NO}_2\text{-C}_6\text{H}_4\text{-CH}_2\text{CH}_2\text{OC}_6\text{H}_4\text{R}
\end{array}
\quad (1)
$$

p-Substituted Phenolate

Substitution products were obtained in higher yield than elimination products. However the results of the ratio of the rates E/S_N and the pK_a values for six para-substituted phenols in 45.9% aqueous alcohol[10] show that the percentage of elimination increases steadily with the basicity of the para-substituted phenolate used as a nucleophile[8] (Table 1 and Figure 2).

DFT-Based Electronic Properties. It has been shown that a two-parameter linear model gives a satisfactory correlation between the observed acidities and basicities and those calculated using DFT-based electronic properties.[11–19] For the reaction $RC_6H_4OH \rightleftharpoons$

Table 1. Reaction between *p*-Nitrophenethyl Bromide and Para-Substituted Phenolates: Correlation of the E/S_N Ratio and pK_a Values

R	$pK_a{}^a$	$E/S_{N\ obsd}{}^b$	$E/S_{N\ calcd}{}^c$
NO₂	7.63	0.2	0.10
COCH₃	9.21	0.3	0.41
Br	10.5	0.52	0.66
H	11.28	0.86	0.82
CH₃	11.67	0.93	0.89
OCH₃	11.52	0.94	0.87

^{a} pK_a determined in 45.9% alcohol (ref 10). ^{b} Data from ref 8. ^{c} Calculated with the correlation equation $E/S_{N\ calcd} = -1.406 + 0.197\ pK_a$; $r = 0.951$.

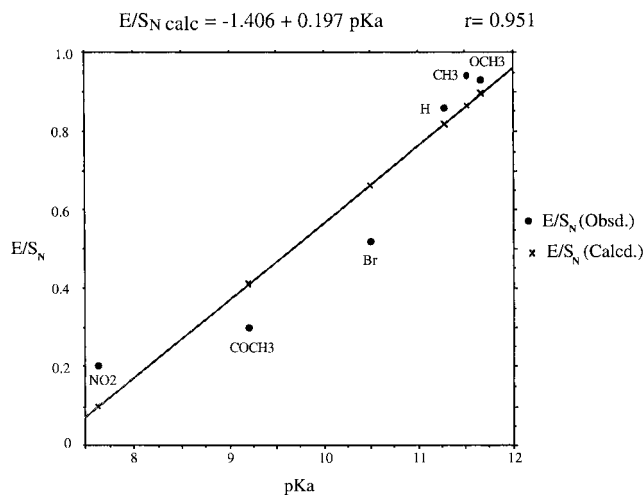**Figure 2.** Correlation of the E/S_N ratio and pK_a for the reaction between *p*-nitrophenethyl bromide and para-substituted phenolates.

$RC_6H_4O^- + H^+$, the change of the Gibbs free energy, $\Delta G°$, can be represented by

$$\Delta G° = a_0 + \sum_{i=1}^{n} a_i x_i \quad i = 1, 2, ..., n \quad (2)$$

where a_0 and a_i are fitted constants and the x_i are local and global DFT-based electronic properties of the para-substituted phenols and para-substituted phenolates. In a DFT context and for a system with N electrons subject to an external potential $v(\mathbf{r})$ (i.e., due to the nuclei),[9] a series of global and local properties x_i appear in a natural way as response functions to changes of the number of electrons and the external potential, respectively.

Global properties represent the properties of the system as a whole and have the same value everywhere. Examples are the electronic chemical potential[20] μ: the change of the energy (E) with the number of electrons and identified as the negative of the electronegativity, χ

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$$\mu = \left(\frac{\partial E}{\partial N}\right)_v = -\chi \tag{3}$$

The hardness,[21] η, is the change of the chemical potential with respect the number of electrons and is of direct importance when applying the HSAB principle at a global level.

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_v \tag{4}$$

The global softness,[22] S, is the inverse of the global hardness:

$$S = \frac{1}{\eta} \tag{5}$$

In a finite difference approximation to the derivatives (eqs 3 and 4) using Koopman's approximation, these quantities were obtained as[23]

$$\mu \approx \frac{\epsilon_L + \epsilon_H}{2} \tag{6}$$

$$\eta \approx \frac{\epsilon_L - \epsilon_H}{2} \tag{7}$$

where ϵ_H and ϵ_L are the HOMO and LUMO eigenvalues, respectively.

Local properties reflect the properties of different sites within a molecule. Well-known examples are the fukui function:[24] $f(\mathbf{r})$

$$f(\mathbf{r}) = \left(\frac{\delta\mu}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\partial\rho(\mathbf{r})}{\partial N}\right)_v \tag{8}$$

is the change of the electron density ρ at a given point with respect the number of electrons, and the local softness,[22] $s(\mathbf{r})$, is the change of the electron density with respect to the electronic chemical potential:

$$s(\mathbf{r}) = \left(\frac{\partial\rho(\mathbf{r})}{\partial\mu}\right)_v = Sf(\mathbf{r}) \tag{9}$$

Because of the discontinuity of the derivative in eq 8, three different fukui functions can be written for a system: $f^+(\mathbf{r})$ for nucleophilic attack, $f^-(\mathbf{r})$ for electrophilic attack, and $f°(\mathbf{r})$ for radical attack. In a condensed version,[14] using the charge of atom k in the molecule instead of the molecular electronic density, the fukui function and the local softness for atom k can be written in the case of a nucleophilic attack as

$$f_k^+ = q_k(N+1) - q_k(N) \tag{10}$$

$$s_k^+ = Sf_k^+ \tag{11}$$

and for an electrophilic attack as

$$f_k^- = q_k(N) - q_k(N-1) \tag{12}$$

$$s_k^- = Sf_k^- \tag{13}$$

DFT-Based Electronic Properties and the Basicity of Para-Substituted Phenolates. To apply the correlation analysis (eq 2), we studied the electronic structure of the para-substituted phenols and their para-substituted phenolates. Calculations were performed at the Hartree−Fock-LCAO level with a 3-21G* basis set using GAUSSIAN 92.[25] The geometry of the para-substituted phenols and phenolates was optimized at the RHF level.

The chemical potential and the global hardness were calculated using eqs 6 and 7 using Koopman's approximation for the electron affinity and the ionization energy.

Tables 2 and 3 show the chemical potential (μ) and the hardness (η) values for the para-substituted phenols and their conjugated bases, respectively. To obtain the local properties for the para-substituted phenolates, we calculated in a ΔSCF approximation, using UHF theory, the electronic structure of their neutral species at the same geometry (cf. demand for constant external potential, $v(\mathbf{r})$ in eqs 4 and 8). The condensed fukui functions and condensed softnesses (f^-_O) and (s^-_O) (cf. the nucleophilic attack by the oxygen atoms) were calculated using Mulliken charges via eqs 12 and 13. Table 4 shows the condensed fukui function (f^-_O), the condensed softness (s^-_O), and the oxygen net charge (q_O) for the para-substituted phenolates and the hydrogen net charge (q_H) for the para-substituted phenols.

Examination of Table 2 reveals that when the acidity of a para-substituted phenol decreases, its chemical potential (μ) increases (decreasing electronegativity) and its global hardness (η) increases but not in a regular way. Table 3 shows that when the basicity of the para-substituted phenolate increases, its global hardness increases. Interesting results of the para-substituted phenolates and para-substituted phenols are shown in Table 4 for the local properties. When the acidity of a para-substituted phenol decreases, the positive net charge of the hydrogen atom (q_H) decreases. In contrast, for the para-substituted phenolate, the condensed fukui function (f^-_O), the condensed softness (s^-_O), and the negative net charge (q_O) for the oxygen atom increase upon increasing basicity.

Table 5 shows the results of a linear correlation analysis between the pK_a values and one local or global DFT-based electronic property (x_i) of the para-substituted phenols and para-substituted phenolates (using eq 2 and pK_a values instead $\Delta G°$). In general, local properties ((q_H), (f^-_O), (s^-_O), and (q_O)) yield a correlation coefficient higher than 0.97. From global properties only, the chemical potential (μ) of the para-substituted phenols and the global hardness (η) of the para-substituted phenolates give correlation coefficients about 0.98 and 0.94, respectively. The global hardness (η) of the para-substituted phenols shows a correlation coefficient that is appreciably smaller (0.86).

The high correlation between the pK_a values of para-substituted phenols and the hydrogen net charge (q_H) and

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Table 2. HOMO and LUMO Eigenvalues (ϵ_H and ϵ_L), Global Hardness (η), and Chemical Potential (μ) Values for Para-Substituted Phenols (Values in au)

R	ϵ_H	ϵ_L	μ^a	η^b
NO$_2$	−0.359	0.048	−0.156	0.204
COCH$_3$	−0.328	0.099	−0.115	0.214
Br	−0.330	0.129	−0.101	0.230
H	−0.333	0.145	−0.094	0.239
CH$_3$	−0.307	0.146	−0.081	0.227
OCH$_3$	−0.309	0.140	−0.085	0.225

[a] Calculated with eq 6. [b] Calculated with eq 7.

Table 3. HOMO and LUMO Eigenvalues (ϵ_H and ϵ_L), Global Hardness (η), and Global Softness (S) Values for Para-Substituted Phenolates (Values in au)

R	ϵ_H	ϵ_L	η^a	S^b
NO$_2$	−0.120	0.213	0.167	5.988
COCH$_3$	−0.091	0.272	0.182	5.495
Br	−0.078	0.317	0.198	5.051
H	−0.058	0.340	0.199	5.025
CH$_3$	−0.056	0.336	0.196	5.102
OCH$_3$	−0.061	0.328	0.195	5.128

[a] Calculated with eq 7. [b] Values in au^{-1} calculated with eq 5.

Table 4. Nucleophilic Condensed Fukui Function (f_O^-), Nucleophilic Condensed Softness (s_O^-), and Oxygen Net Charge (q_O) for Para-Substituted Phenolates and the Hydrogen Net Charge (q_H) for Para-Substituted Phenols

R	$f_O^{-\,a}$	$s_O^{-\,b}$	q_O	q_H
NO$_2$	0.136	0.814	−0.732	0.406
COCH$_3$	0.159	0.874	−0.766	0.399
Br	0.186	0.939	−0.794	0.393
H	0.199	1.000	−0.811	0.389
CH$_3$	0.197	1.005	−0.812	0.391
OCH$_3$	0.201	1.031	−0.812	0.392

[a] Calculated with eq 12. [b] Values in au^{-1} calculated with eq 13.

Table 5. Correlation Equation for Para-Substituted Phenols and Para-Substituted Phenolates Involving a Single Local or Global DFT-Based Electronic Property (x_i): $pK_a = b + mx$

x	b	m	r
η^a	−14.592	111.547	0.867
μ^a	16.266	56.626	0.982
η^b	−12.242	118.966	0.943
$f_O^{-\,b}$	−0.422	59.687	0.992
$s_O^{-\,b}$	−7.064	18.399	0.984
q_O^b	−27.992	−48.606	0.997
q_H^a	106.412	−243.31	0.971

[a] Para-substituted phenols. [b] Para-substituted phenolate anions.

chemical potential (η) suggests that the acidity depends on the electronegativity of the para-substituted phenols and the positive hydrogen net charge.[26]

The best correlation was found for the local properties of the oxygen atom of the para-substituted phenolates (($f^-{}_O$), ($s^-{}_O$), and (q_O)). The results suggest that the basicity depends on the way the oxygen charge (q_O) will be delocalized into the fragment RC$_6$H$_4$. When the

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(26) According to the chemical potential equalization principle (see ref 9), the chemical potential μ (negative of the electronegativity, χ) of each atom or group in a molecule must be equal to the chemical potential of the molecule itself. For a molecule A formed by the binding of K atoms or groups, with a total of N_A electrons one therefore has $\mu_k(N_A) = \mu_A(N_A)$ for $k = 1, 2, ..., K$. Thus, for the *para-substituted phenols*, $\mu_{RC_6H_4O}(N_{RC_6H_4OH}) = \mu_{RC_6H_4OH}(N_{RC_6H_4OH})$. Because $N_{RC_6H_4OH} = N_{C_6H_4O} + N_H$ and $N_H > 1$, we expect that trends in $\chi_{RC_6H_4O}$ will be parallel to those in $\chi_{RC_6H_4OH}$.

Table 6. HOMO and LUMO Eigenvalues (ϵ_H and ϵ_L), Chemical Potential (μ), Global Hardness (η), and Global Softness (S) Values for *p*-Nitrophenethyl Bromide (in au)

ϵ_H	ϵ_L	μ^a	η^b	S^c
−0.379	0.037	−0.171	0.208	4.819

[a] Values in au calculated with eq 6. [b] Values in au calculated with eq 7. [c] Values in au^{-1} calculated with eq 5.

Table 7. Electrophilic Condensed Fukui Function (f_k^+), Electrophilic Condensed Softness (s_k^+), and Atomic Net Charge (q) for the Carbon and Hydrogen Atoms of *p*-Nitrophenethyl Bromide

| atom	$f_O^{+\,a}$	$s_O^{+\,b}$	q
C-1	0.013	0.151	−0.411
H-1	0.036	0.172	0.255
H-2	0.036	0.172	0.255

[a] Calculated with eq 10. [b] Values in au^{-1} calculated with eq 11.

basicity increases, the oxygen net charge increases (always negative). If the charge cannot be delocalized well into the fragment, the stability of the base decreases. On the other hand, if the basicity decreases, the oxygen charge decreases because the charge will be delocalized into the fragment and the stability of the base increases. As a consequence of the increasing oxygen charge, its nucleophilic fukui function ($f^-{}_O$) increases (always positive), indicating that the oxygen atom becomes more polarizable and softer (increasing condensed softness) according to Pearson's original softness definition.[3]

The high correlation between the pK_a values and the global hardness (η) of the para-substituted phenolates supports Klopman's original idea that basicity bears a direct relationship to the hardness of a base. When the basicity of a nucleophile increases its global hardness increases.[4]

The HSAB Principle and the E/S$_N$ Ratio. To study the interactions between the para-substituted phenolates and *p*-nitrophenethyl bromide, we calculated the electronic properties of *p*-nitrophenethyl bromide in an analogous way to that used for the para-substituted phenolates and para-substituted phenols.

For the elimination−substitution reactions, the reactive atoms in *p*-nitrophenethyl bromide are the β (benzylic) hydrogen atoms (H$_{-1}$ and H$_{-2}$) and the α-carbon atom bonded to the bromine atom (C$_{-1}$). The possibility for α-elimination via carbene formation exists, but to the best our knowledge there are no reports about α-elimination in this system. α-Elimination can be expected to be difficult because the β-hydrogen atoms are more acidic than the α-hydrogen atoms due to the presence of the nitro group in the benzene ring.

H$_{-1}$
NO$_2$-C$_6$H$_4$-C-**C**$_{-1}$(H$_2$)Br
H$_{-2}$

p-Nitrophenethyl Bromide
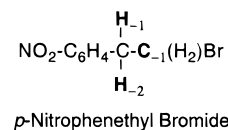
Tables 6 and 7 show the global properties for *p*-nitrophenethyl bromide and the local properties for its H$_{-1}$, H$_{-2}$, and C$_{-1}$ atoms. The original proposal that the β-hydrogen atom is hard and the α-carbon atom is soft[4,5] is not confirmed by the results of Table 7. In fact, the β-hydrogen atom is soft and even a little softer than the α-carbon atom. To explain the results of the E/S$_N$ ratio,

it is necessary to study the interaction from both a local and a global viewpoint.[27–32]

Local–Local Viewpoint. Phenolate 1 (P_1) and phenolate 2 (P_2) are the nucleophiles and their oxygen atom acts as nucleophilic centers. p-Nitrophenethyl bromide (PNPB) acts as the electrophile with its β-hydrogens H_{-1} and H_{-2} and its α-carbon C_{-1} as electrophilic centers. If the relationship between the nucleophilic condensed softnesses is $S_O^-(P_1) > S_O^-(P_2)$ and the electrophilic condensed softnesses obey the sequence $S_H^+ > S_X^+$, then from a local–local HSAB viewpoint[29] we expect that the most favorable interactions should occur between the oxygen atom of P_1 and the β-hydrogen atom of PNPB (elimination mechanism) and between the oxygen atom of phenolate P_2 and the α-carbon atom from PNPB (substitution mechanism). The E/S_N ratio for the reaction between P_1 and PNPB will then be higher, as compared to the ratio for the reaction between P_2 and PNPB. The results of Tables 1, 4, and 7 confirm this prediction. When the basicity of the para-substituted phenolates increases, their oxygen atom becomes more negatively charged, more polarizable, and softer. Its reactivity toward the soft β-hydrogen atom from p-nitrophenethyl bromide thereby increases, resulting in a larger E/S_N ratio.

Global–Local Viewpoint. Phenolate 1 (P_1) and phenolate 2 (P_2) are the nucleophiles, p-nitrophenethyl bromide (PNPB) being the electrophile with its β-hydrogens H_{-1}, H_{-2}, and the α-carbon C_{-1} as electrophilic centers. If the relationship between the global softnesses is $S_{P_1} > S_{P_2}$ and if the electrophilic condensed softnesses show the sequence $S_H^+ > S_X^+$, then from a global–local HSAB viewpoint[27,28] we expect that the best interactions occur between P_1 and the β-hydrogen atom from PNPB (elimination mechanism) and between P_2 and the α-carbon atom from PNPB (substitution mechanism). The E/S_N ratio for the reaction between P_1 and PNPB will be high, whereas for the reaction between P_2 and PNPB it will be low. The results of Tables 1, 3, and 7 show that this is not correct: when the basicity of the para-substituted phenolates increases, its global softness in general decreases and its interaction with the soft

β-hydrogen atom from p-nitrophenethyl bromide will be less favored. The predicted E/S_N ratio thereby decreases, whereas the experimental E/S_N ratio increases.

The results obtained from the local–local viewpoint also show that the β-hydrogen atom from p-nitrophenethyl bromide cannot be considered to act as a Brønsted acid ("locally" hard acid), the β-hydrogen atom being a "locally" soft acid like the α-carbon atom. Both atoms can be considered to act as a Lewis acid toward the para-substituted phenolate nucleophile considered as a base.

Conclusions

The combined use of the HSAB principle and DFT reactivity descriptors has been shown to be an interesting tool to study the reactivity of para-substituted phenolates and p-nitrophenethyl bromide. The influence of the basicity of the para-substituted phenolates on the elimination–substitution competition is very important. The results of a linear correlation analysis suggest that when the basicity of the para-substituted phenolates increases its global hardness and its oxygen condensed softness also increase. For p-nitrophenethyl bromide, its β-hydrogen atom turned out to be soft, even softer than the α-carbon atom, as opposed to previous considerations.[4,5] To explain the results of the E/S_N ratio, it is necessary to study the interaction from a local–local viewpoint and not from a global–local viewpoint as was suggested before.[4,5] Thus, the para-substituted phenolates with larger basicity (harder/global property), lower delocalized negative charge into the fragment RC_6H_4,[33] and a more polarizable oxygen atom (softer/local property) have a lower (relative) attraction toward an alkyl carbon atom (soft/local property) than toward a hydrogen (softer/local property) from p-nitrophenethyl bromide. The β-hydrogen and the α-carbon atoms can be considered to act as a Lewis acid toward the para-substituted phenolate nucleophile and can be considered as a base.

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