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Chemical Reactivity of Enolate Ions: The Local Hard and Soft Acids and Bases Principle Viewpoint

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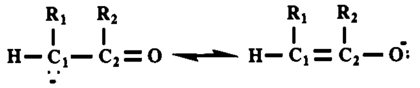
Abstract: Density functional theory and molecular orbital theory are used to calculate the fukui function and the condensed fukui function for several enolate ions in order to carry out an analysis of the different effects that have an influence on the chemical reactivity at the carbon and oxygen atoms. It is shown that substituent, substrate, and solvent effects may be explained in a unified way in terms of the values of the condensed fukui function when these are analyzed through a local version of the hard and soft acids and bases principle. The results suggest that it could be interesting to carry out experimental work that may confirm the importance of the hardness and softness parameters to get a better understanding of enolate ion chemistry.

I. Introduction

Enolate ions are very important ambident nucleophiles. They have been proposed as stable intermediates in nucleophilic addition and substitution reactions on carbonylic carbon and in nucleophilic substitution reactions on saturated carbon, silicon, and phosphorus compounds.[1-3]

Their stability is usually attributed to resonance effects, due to their great capacity to delocalize the negative charge between the carbon and the oxygen atoms,



$$\mathrm{H}-\overset{\mathrm{R_1}}{\underset{\ddot{}}{\mathrm{C_1}}}-\overset{\mathrm{R_2}}{\mathrm{C_2}}=\mathrm{O} \longleftrightarrow \mathrm{H}-\overset{\mathrm{R_1}}{\mathrm{C_1}}=\overset{\mathrm{R_2}}{\mathrm{C_2}}-\dot{\mathrm{O}}\colon$$

It has been found that the enolate ions may react with some electrophiles at carbon (C_1) and with others at oxygen. This behavior depends on several factors like substituent,[4,5] substrate,[6] and solvent effects.[2,7] That is, depending on the substituent, for a same solvent and a same reagent, the reaction with the enolate ion may take place at the carbon or at the oxygen atom; for a same enolate ion, depending on the substrate, the reaction may take place at the carbon or at the oxygen atom; also, for a same enolate ion and a same substrate, the amount of product that results from the reaction taking place at the carbon or at the oxygen atom may vary drastically depending on the nature of the solvent.

This behavior of the enolate ions under different circumstances has been explained, in general, in terms of the hard and soft acids and bases (HSAB) principle.[8,9] The combination of a qualitative scale for the hardness and softness of the carbon and oxygen atoms in an enolate ion and the statement "hard likes hard and soft likes soft" at the local level has led to a qualitative explanation of the behavior of these species with respect to different electrophiles. However, recently, the concept of softness[10] has been found to be intimately related to fundamental variables of density functional theory.[11] This situation has provided a more solid theoretical basis to the HSAB principle.[12-15] and has led to operational formulas that allow one to quatify the hardness or the softness of a chemical species.[16-29]

Since enolate ions play a fundamental role in many organic reactions, we believe that it is important to make use of density functional theory and molecular orbital theory to calculate the local softness and the condensed local softness for several enolate ions in order to carry out a more detailed analysis of the different effects that have an influence on the chemical reactivity at the carbon atom and at the oxygen atom in terms of a local version of the HSAB principle. This is precisely the objective of the present work.

II. The Local HSAB Principle

Density functional theory has provided the framework for a coherent quantitative language of hardness and softness functions: nonlocal, local, and global.[30] In particular, the local softness

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is given by[10]

$$s(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial \mu}\right)_v = \left(\frac{\partial N}{\partial \mu}\right)_v \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v = sf(\mathbf{r}) \qquad (1)$$

where $f(\mathbf{r})$ is the fukui function,[31]

$$f(\mathbf{r}) = \left(\frac{\delta \mu}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v \qquad (2)$$

μ is the chemical potential, N is the total number of electrons, s is the global softness, $\rho(\mathbf{r})$ is the electronic density, and $v(\mathbf{r})$ is the external potential generated by the nuclei.

In a finite differences approximation, the fukui function becomes

$$f^+(\mathbf{r}) \approx \rho_{N+1}(\mathbf{r}) - \rho_N(\mathbf{r}) \qquad \text{for nucleophilic attack} \quad (3)$$

$$f^-(\mathbf{r}) \approx \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r}) \qquad \text{for electrophilic attack} \quad (4)$$

$$f^0(\mathbf{r}) \approx {}^1/_2(\rho_{N+1}(\mathbf{r}) - \rho_{N-1}(\mathbf{r})) \qquad \text{for radical attack} \quad (5)$$

where $\rho_{N+1}(\mathbf{r})$, $\rho_N(\mathbf{r})$, and $\rho_{N-1}(\mathbf{r})$ are the electronic densities of the system with $N + 1$, N, and $N - 1$ electrons, respectively, all with the ground state geometry of the N electron system.

An alternative and more simple procedure to obtain information about $f(\mathbf{r})$ is to condense its values around each atomic site into a single value that characterizes the atom in the molecule. In the case of the fukui function, this can be done by condensing first the electronic density to the charge of each atom in the molecule and differentiating afterwards with respect to the total number of electrons in the system.[20] Thus, in a finite differences approximation,

$$f^+_{Ak} = q_{Ak}(N_A + 1) - q_{Ak}(N_A) \qquad \text{for nucleophilic attack} \quad (6)$$

$$f^-_{AK} = q_{Ak}(N_A) - q_{Ak}(N_A - 1) \qquad \text{for electrophilic attack} \quad (7)$$

$$f^0_{Ak} = {}^1/_2(q_{Ak}(N_A + 1) - q_{Ak}(N_A - 1)) \qquad \text{for radical attack} \quad (8)$$

while the condensed local softness becomes

$$S^+_{Ak} = S_A f^+_{Ak} \qquad \text{for nucleophilic attack} \quad (9)$$

$$S^-_{Ak} = S_A f^-_{Ak} \qquad \text{for electrophilic attack} \quad (10)$$

$$S^0_{Ak} = S_A f^0_{Ak} \qquad \text{for radical attack} \quad (11)$$

where q_{Ak} is the charge of the kth atom in the molecule A, which may be determined by several procedures.[32] The simplest one is to make use of a Mulliken gross population analysis.[20]

It should be noted from eq 1 and eqs 9–11 that within a molecule the relative values of the fukui function provide the same information as the local softness. Thus, for simplicity, one can calculate the fukui function, but it may be used to rationalize the inherent reactivity of a given molecule as if it were the local softness.[21–27] This implies that the regions of a molecule where the fukui function is large are chemically softer than the regions where the fukui function is small, and by invoking the HSAB principle in a local sense, one may establish the behavior of the different sites with respect to hard or soft reagents.

A more detailed analysis of such a situation may be done in terms of the interaction energy between two chemical species, A and B, when one makes the assumption that such interaction may be divided into two steps which can be taken as happening in succession,[14,15,33] that is,

$$\Delta E_{\text{int}} = \Delta E_v + \Delta E_\mu \qquad (12)$$

where

$$\Delta E_v \approx -{}^1/_2 \frac{(\mu_A - \mu_B)^2}{S_A + S_B} S_A S_B \qquad (13)$$

$$\Delta E_\mu \approx -{}^1/_2 \frac{\lambda}{S_A + S_B} \qquad (14)$$

and λ is a constant[33] related to an "effective number of valence electrons" that participate in the interaction between A and B.

The first step, ΔE_v, corresponds to the charge transfer process between A and B arising from the chemical potential equalization principle at constant external potential $v(\mathbf{r})$. The second step, ΔE_μ, corresponds to a reshuffling of the charge distribution, and it is basically a manifestation of the maximum hardness principle and takes place at constant chemical potential μ.

Now, in a general analysis of the inherent chemical reactivity of the sites of a given species A with respect to different reagents, one should invoke a local viewpoint for A and a global viewpoint for B. From a local viewpoint, the interaction between the two chemical systems A and B occurs through the kth atom of A. In this context, it seems reasonable to assume that the interaction energy will be dominated by the local properties of the kth atom when it is placed in the chemical environment provided by the molecule A rather than by the global properties of A. This is equivalent to the assumption that only the kth atom of A participates in the charge transfer and in the reshuffling steps and that the changes in all the other atoms can be neglected, which means that one should replace the global softness s_A by s_{Ak} in the expressions for ΔE_v and ΔE_μ, because this value characterizes better than the global value the behavior of the site at which the interaction takes place. Thus, since μ_A is the same for all the atoms in A, one can express the interaction energy at the kth atom in the form[34]

$$(\Delta E_{\text{int}})_{Ak} \approx -{}^1/_2 \frac{(\mu_A - \mu_B)^2}{S_A f_{Ak} + S_B} S_B S_A f_{Ak} - {}^1/_2 \frac{\lambda}{S_A f_{Ak} + S_B} \qquad (15)$$

According to eq 15, among two sites in A, each one characterized by its own value of f_{Ak}, when s_B is large, there is a greater stabilization when the interaction occurs at the site with the greater value of f_{Ak}. However, when s_B is small, there is a greater stabilization when the interaction occurs at the site with the smallest value of f_{Ak}. These results seem to imply that the statement "soft likes soft and hard likes hard" may be extended to a local level since, as we have already seen, within a molecule the relative values of the fukui function provide the same information as the local softness.

An important consequence of the local HSAB principle is that although the softest atom in a molecule A is, in general, the most reactive site, there may be other sites, not as soft, that may become the most reactive sites, depending on the softness of the reacting molecule B.

Thus, even though eq 15 may be used only at a qualitative level, because the constant λ is not well known, it allows one to analyze the behavior of the reactive sites of a molecule with respect to a family of reagents characterized by different values of s_B.

It should be mentioned that λ, being a constant[33] related to an "effective number of valence electrons" that participate in the

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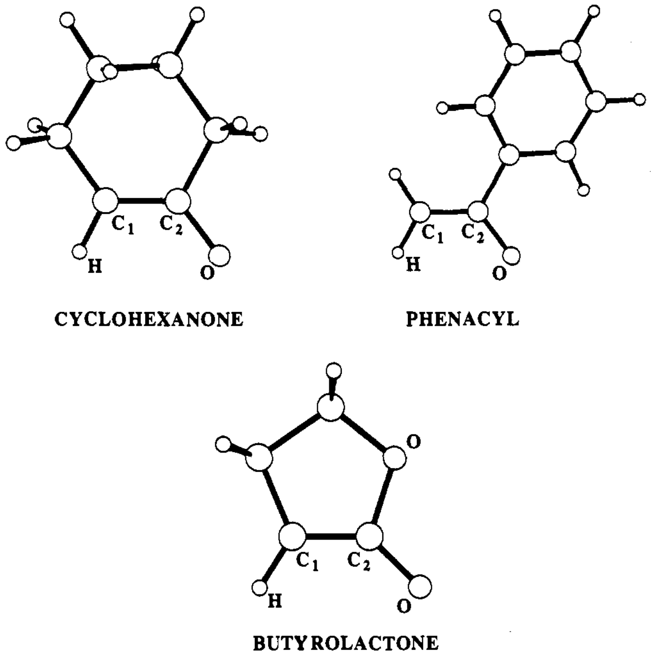

CYCLOHEXANONE

PHENACYL

BUTYROLACTONE

Figure 1. Enolate ions studied in this work. Large circles represent carbon atoms, except where indicated. Small circles represent hydrogen atoms.

interaction between A and B, could, in principle, be related to other parameters of the reacting species. Unfortunately, although this would be very important to be able to use eq 15 at a quantitative level, it is not clear to us, for the moment, how to obtain such a relationship.

III. Carbon and Oxygen Reactivity in Enolate Ions

The local HSAB principle and the relations for the fukui function and the softness described in the previous section will be used now together with molecular orbital calculations to analyze the chemical behavior of the carbon and oxygen atoms in an enolate ion. In this work we present results for the electrophilic attack on three enolate ions: cyclohexanone, phenacyl, and butyrolactone (see Figure 1).

According to eqs 3–5 and 6–8, one needs to calculate the electronic density of the molecule and the charges of the atoms in the molecule in order to determine the fukui function $f(\mathbf{r})$ and the condensed fukui function f_{Ak}. A convenient way to do this is to perform molecular orbital calculations within the Hartree–Fock LCAO approximation to determine first $\rho(\mathbf{r})$ and to carry out, afterwards, a Mulliken gross population analysis to determine q_{Ak}.

For the case of electrophilic attack, eqs 4 and 7, one needs to obtain the electronic density and the charges for the reference molecule and its corresponding cation at the minimum of the potential energy surface of the reference molecule (the enolate ion). Thus, we have done these calculations[35] with a 6-31G** basis set. The equilibrium geometry of the reference molecule was determined by the gradient technique.[36]

The surface diagram of the fukui function for each case is presented in Figures 2–4. One can see that, in all three cases, the largest values of $f(\mathbf{r})$ lie around the oxygen atom and that the values around the carbon atom (C_1), although smaller, are positive. Since large and positive values of the fukui function are associated with soft regions of the molecule and a large softness signals high reactivity,[18] one can see that $f(\mathbf{r})$ provides a measure of the most reactive sites of the molecule. In these cases, the oxygen and the carbon atoms are indeed reactive sites, in agreement with the experimental evidence. One can also see that $f(\mathbf{r})$ around the carbonyl carbon (C_2) is very small or negative, a result that implies that this site is very hard.

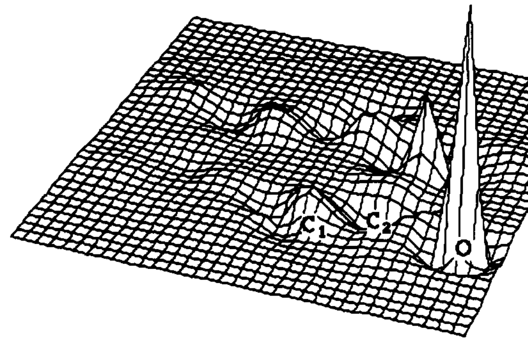

Figure 2. Surface diagram of the fukui function, $f_{Ak}(\mathbf{r}) = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r})$, of cyclohexanone (see Figure 1) on a plane located 0.4 au above the molecular plane. This is the plane where the maximum value of the fukui function is located.

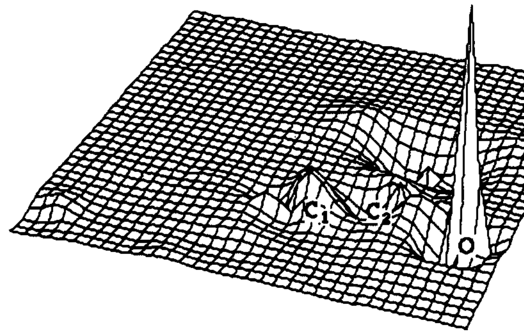

Figure 3. Surface diagram of the fukui function, $f_{Ak}(\mathbf{r}) = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r})$, of phenacyl (see Figure 1) on a plane located 0.4 au above the molecular plane. This is the plane where the maximum value of the fukui function is located.

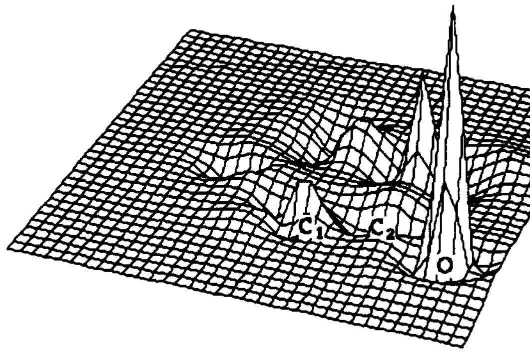

Figure 4. Surface diagram of the fukui function, $f_{Ak}(\mathbf{r}) = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r})$, of butyrolactone (see Figure 1) on a plane located 0.4 au above the molecular plane. This is the plane where the maximum value of the fukui function is located.

In order to study the substituent, substrate, and solvent effects, it is more convenient to make use of the condensed fukui function that implicitly is taking into account a finite region around the atomic site. Therefore, it includes the positive and the negative values of $f(\mathbf{r})$. The values of f_{Ak} for $k = C_1$ and $k = O$ for the three molecules are given in Table 1. The analysis of these values should be done taking into account the local HSAB principle, which, as we have seen, implies that the statement "hard likes hard and soft likes soft" may be extended to the local level.

Thus, if we consider first the substituent effect, one can see from Table 1 that the values of f_{Ak} depend on the substituents R_1 and R_2, and that one may have cases like cyclohexanone and phenacyl where oxygen is softer than carbon, and cases like butyrolactone where carbon is slightly softer than oxygen. The general situation is presented in Figure 5, where we report two

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Table 1. Values of the Condensed Fukui Function at the Carbon (C_1) and Oxygen Atoms for the Enolate Ions Calculated through Eq 7 with a Mulliken Gross Population Analysis

molecule	carbon (C_1)	oxygen
cyclohexanone	0.25	0.36
phenacyl	0.25	0.35
butyrolactone	0.28	0.27

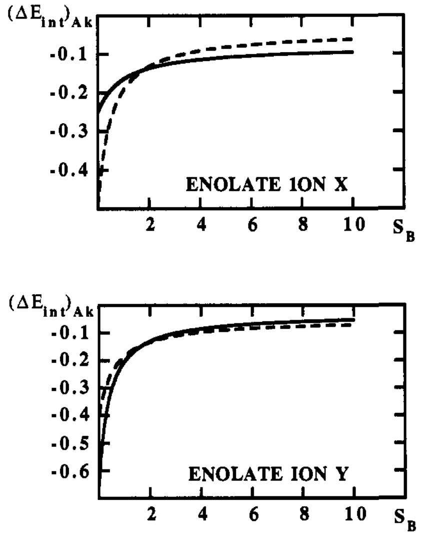

Figure 5. Behavior of interaction energy at oxygen (continuous line) and at carbon (broken line) as a function of the global softness of the reacting molecule B (eq 15) with the following typical values: $(\mu_A - \mu_B) = -0.4$, $s_A = 2.5$, and $\lambda = 0.5$. The enolate ion X corresponds to $f_{Xk} = 0.40$ for oxygen and $f_{Xk} = 0.20$ for carbon. The enolate ion Y corresponds to $f_{Yk} = 0.15$ for oxygen and $f_{Yk} = 0.25$ for carbon (all quantities in atomic units).

typical plots of the interaction energy, eq 15, as a function of s_B. In the upper plot it has been assumed that the set R_1,R_2 leads to an enolate ion in which f_{Ak} for oxygen is greater than f_{Ak} for carbon, while in the lower plot it has been assumed that another set R_1',R_2' leads to a different enolate ion in which f_{Ak} for oxygen is lower than f_{Ak} for carbon. One can see that for a same value of s_B, which represents a same reagent and a same solvent, the electrophilic attack may be energetically favored at C_1 in one enolate ion and at O in the other one. That is, the effect of the substituent is such that it may change the relative values of the condensed fukui functions at the carbon and at the oxygen atoms from one enolate ion to another, leading to a change in the reaction site, even though the substrate and the solvent are the same. These results are in agreement with experimental evidence. For example, it has been established experimentally that triphenylphosphine reacts with cyclohexanone at the oxygen atom, and it reacts with butyrolactone at the carbon atom.[4,5]

In order to analyze the substrate effect, one can see that (Table 1), in general, within the enolate ion, the values of f_{Ak} for carbon and oxygen are different. Thus, either one of the two plots in Figure 5 indicates that for a same enolate ion and a same solvent, the reaction site for a hard substrate is energetically favored at the hard atom, and the reaction site for a soft substrate is energetically favored at the soft atom. These results are also in agreement with experimental evidence. Carbon compounds show a tendency to attack at the carbon atom, while silicon compounds show a tendency to attack at the oxygen atom. The carbon atom in the carbon compounds is, in general, harder than the silicon atom in silicon compounds.[6]

Solvent effects are more difficult to analyze by the present approach because, in principle, one should carry out the molecular orbital calculations taking into account the reaction field potential due to the medium polarization to establish a relationship between the condensed fukui function and the dielectric constant of the solvent. However, because of the dependence of f_{Ak} on the charges of the atoms in the molecule, it seems reasonable to assume that such a relationship exists and that the effect of the solvent will be different for each one of the atoms in the molecule. If this occurs, the solvent effects could be analyzed through Figure 5 by assuming that both plots correspond to the same enolate ion and that in the upper plot for a given solvent f_{Ak} for oxygen is greater than f_{Ak} for carbon, while in the lower plot, for a different solvent, f_{Ak} for oxygen is lower than f_{Ak} for carbon. This way one can see that for a given enolate ion and a same value of s_B, which represents a same reagent, the electrophilic attack may be energetically favored at C_1 in one enolate ion and at O in the other one. That is, the effect of the solvent is such that it may change the relative values of the condensed fukui functions at the carbon and at the oxygen atoms for a same enolate ion, leading to a change in the reaction site, even though the substrate is the same. These results are in agreement with experimental evidence.[2,7] However, a more complete analysis of solvent effects should also consider the nature of the counterions.

In summary, the results presented in this work seem to indicate that the different effects that have an influence on the chemical reactivity at the carbon atom and at the oxygen atom in a given enolate ion may be explained in terms of the values of the condensed fukui function when these are analyzed through a local version of the HSAB principle. The overall situation suggests that it could be interesting to carry out experimental work that may confirm the importance of the hardness and softness parameters to get a better understanding of enolate ion chemistry.