

# Intermolecular Reactivity Trends Using the Concept of Group Softness

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Density functional theory (DFT) descriptors have been used in the present work to explain “intermolecular” reactivity. Very few parameters have been successful in explaining the concept of intermolecular reactivity sequences until now. It has been shown recently (Roy et al., *J. Phys. Chem.* **1998**, *102*, 3746) for the case of carbonyl compounds that local hardness works better than other parameters for predicting intermolecular reactivity trends. In this paper, we show that “group softness” can predict the intermolecular reactivity trends in carbonyl compounds and organic acids correctly. A group is a set of atoms in the molecule that influences the behavior of the most reactive atom in the molecule. Once the group is correctly defined for a series of molecules, group softness is an effective parameter for predicting the most reactive molecule among the given series. The concept of group softness is seen to work efficiently for both types of charge partitioning used and all of the basis sets used for the studies.

## 1. Introduction

The understanding and prediction of molecular reactivity has been a challenging area of work in the field of quantum chemistry. The past few decades have seen several attempts at describing and predicting trends of molecular reactivity and mechanisms using quantum chemical methods as well as density-functional-based descriptors. Of particular interest are studies for understanding chemical reactivity using the response functions of the system commonly called atomic or molecular reactivity descriptors. Within the context of density functional theory (DFT), several response functions such as electronegativity, chemical potential, hardness, softness, and molecular electrostatic potential have become increasingly more important for the prediction of molecular reactivity. Several working definitions of these descriptors have been proposed, enabling the calculation of these quantities from first principles. Of these, the most commonly and widely used concept for studying molecular reactivity is the hardness of the molecule, which is defined as the second derivative of the energy with respect to the variation in the number of electrons. Pearson<sup>1</sup> defined two categories of acids and bases, ranked according to the hardness (or its inverse, softness) of the molecule, namely, hard acid/base and soft acid/base, and proposed a principle called the hard–soft acid–base (HSAB) principle. According to this principle, a hard acid prefers to react with a hard base, whereas a soft acid forms stronger bonds with a soft base. These hard–hard and soft–soft interactions were later explained by Klopman<sup>2</sup> to be charge-controlled and frontier-controlled, respectively. Parr and Chattaraj gave a proof for this global HSAB principle,<sup>3</sup> along with a proof for principle of maximum hardness (PMH)<sup>4</sup>, which relates the stability of molecule with its hardness. This global HSAB principle was used effectively to explain the reactions between acids and bases.<sup>5–7</sup> Along with studies on the HSAB principle, PMH was also tested and studied rigorously by many groups,<sup>8–11</sup> and the conditions under which PMH is valid have been the subject of extensive investigations.<sup>12</sup>

In addition to global properties, local concepts varying from point to point in the molecule were proposed. Concepts of Fukui function, local hardness, and local softness have emerged to describe the atoms-in-molecules viewpoint and the role of a specific atom within a molecule during the reactivity of the molecule.<sup>13</sup> Local softness has been shown to be proportional to the Fukui function and is well-defined.<sup>14,15</sup> On the other hand, the definition of local hardness is ambiguous.<sup>14,15,16</sup> Local softness describes the reactivity of an individual atom in a molecule. The reactivity of any center toward an electrophilic or nucleophilic attack is defined through the electrophilic local softness and nucleophilic local softness, respectively. According to Parr and Yang, the atom with the highest electrophilic/nucleophilic Fukui function, and hence highest electrophilic/nucleophilic local softness, is the most reactive center within a molecule.<sup>17</sup>

However, Gàzquez and Mendez later showed that the interaction between two molecules does not necessarily take place through the softest atoms in the molecules but rather take place through atoms of equal softness.<sup>18</sup> This principle was later called the local hard–soft acid–base principle, and it has been studied by many groups to understand the validity of both of the concepts described above,<sup>19</sup> as well as to predict the reacting atoms within pairs of molecules.<sup>20,21,22</sup>

Thus, the global HSAB principle explains the interactions between two molecules (one acid and one base) on the basis of the global softness or hardness of the molecules, whereas the local HSAB principle predicts the atoms in the two molecules through which the interaction between two molecules takes place. These principles have been able to explain a large number of chemical interactions. However, the interaction of a molecule with another molecule is predetermined by its own structure, and hence, intramolecular and intermolecular reactivity sequences have gained significant importance. Intramolecular reactivity sequences predict the most reactive site within a molecule, whereas intermolecular reactivity sequences predict the most reactive molecule among a group of molecules with the same functional group. Both of these reactivity trends have been studied recently by Roy et al.,<sup>23</sup> and it was found that the

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ratio of electrophilic/nucleophilic softness or nucleophilic/electrophilic softness is an extremely reliable descriptor for the prediction of intramolecular reactivity trends. However, it was shown by this group, as well as by the work done by previous groups, that the prediction of intermolecular reactivity using local softness is extremely difficult, and hence, parameters such as local hardness, electrostatic potential, and ratio of softness have been used to explain intermolecular reactivity trends.<sup>23–27</sup> Geerlings and co-workers have pointed out the significance of these intermolecular reactivity sequences and the difficulty in predicting the correct acidity trends in substituted benzenes, acids, alcohols amines, and few other molecules.<sup>25–32</sup> The ratio of the local softness was, however, seen to work better for the prediction of intermolecular reactivity trends within zeolites,<sup>24</sup> whereas derivatives of local hardness seemed to work better for some other molecules.<sup>23,26–32</sup> However, the definition of local hardness is not very clear,<sup>33–35</sup> and the ratio of the softness is not a very consistent parameter for the prediction of the most reactive molecule within a group.

This paper deals with this problem of predicting the correct intermolecular reactivity trends using the summation of the local softness of a group of atoms around the most reactive site in a molecule. This sum is called as the “group softness”. The molecule with the maximum group softness is the most reactive molecule within a series. However, this is also dependent to some extent on the other interacting molecule, as we will mention later in the context of the local HSAB principle. The concept of the summation of a reactivity parameter, viz., electronegativity of a few atoms, was used earlier by Nalewajski and co-worker<sup>36</sup> and few other groups<sup>37–40</sup>, whereas Geerlings and co-workers<sup>26–27</sup> used the summation of softness to obtain a concept such as group softness. In one of the most recent applications of group properties, Alejandro Toro-Labbe and co-workers have used group chemical potential and hardness for studies of the local HSAB principle.<sup>41,42,43</sup> While the group electronegativity was computed for the case in which the group of atoms was a part of molecule, the group softness was calculated for the group of atoms individually and not when these atoms were a part of a molecule. These properties will undergo a change when computed for the same atoms within a molecule. Moreover, the group softness was used by Geerlings and co-workers<sup>26–27</sup> in conjunction with local hardness to predict correct acidity trends for a few organic acids, and hence, separately, its use has not been exploited. The group for each series of molecules can vary in itself and requires chemical intuition and the concept of group softness, as discussed in more detail in the next section. In the present work, the concept of group softness has been studied for an effective prediction of the correct acidity trends in the case of carbonyl compounds and acetic acids.

Section 2a deals with the theoretical details and the definitions of various reactivity parameters used in the present work. Section 2b describes in more detail the concept of group softness and the significance and uniqueness of it for each series of molecules. Section 3 presents the methodology and computational details. Section 4 presents the results and discussion of the work, and section 5 summarizes the main points of this work.

## 2a. Density-Functional-Based Reactivity Descriptors

Parr and Pearson defined global hardness as the second derivative of the energy with respect to the change in the number of particles  $N$ .<sup>44</sup>

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right)_{\nu(r)} = \left( \frac{\partial \mu}{\partial N} \right)_{\nu(r)} \quad (1)$$

where  $E$  is the energy of the system,  $N$  is the number of electrons in the system,  $\nu(r)$  is the external potential, and  $\mu$  is called the chemical potential of the system. The inverse of the hardness is called the total softness of the system.

$$S = \frac{1}{2\eta} \quad (2)$$

Using the finite difference approximation to the above expression, the expression for the global softness is obtained as

$$S = \frac{1}{\text{IP} - \text{EA}} \quad (3)$$

where IP and EA are the first ionization potential and electron affinity of the chemical species, respectively. The mixed second derivative of the energy of the system with respect to  $N$  and the potential  $\nu(r)$  is a local property. It represents the response of the electron density at each point in space to the variation in the number of electrons and was called as Fukui function by Parr and Yang.<sup>17</sup> The Fukui function describes the sensitivity of the chemical potential of a system to a local external perturbation.<sup>45</sup> This function has been widely used as a reactivity parameter to describe the most reactive point in a molecule.

$$\left( \frac{\partial^2 E}{\partial N \partial \nu(r)} \right) = \left( \frac{\partial \rho(r)}{\partial N} \right)_{\nu(r)} = f(r) \quad (4)$$

Also, a local property, called local softness, is defined as

$$s(r) = \left( \frac{\partial \rho(r)}{\partial \mu} \right)_{\nu(r)} \quad (5)$$

so that we obtain

$$\int s(r) dr = S \quad (6)$$

From eqs 4 and 6, it is seen that

$$s(r) = f(r)S \quad (7)$$

The above expression also indicates that  $s(r)$  distributes the total softness among different regions in the space.  $s(r)$  carries the same information as  $f(r)$  and has been widely used to understand the reactivity of an atom in a molecule. Because of the discontinuity of the derivative in eq 4 at  $N$ , it was proposed to associate different reactivity indices to eq 4. Using left and right derivatives with respect to the number of particles, electrophilic and nucleophilic Fukui functions and local softness can be defined. The nucleophilic Fukui function  $f^+(r)$  is defined as

$$f^+(r) = \rho_{N+1}(r) - \rho_N(r) \quad (8)$$

$\rho_N$  in the above expression represents the electron density on atom  $k$  for the  $N$ -electron system.  $\rho_{N+1}$  is the electron density of the  $(N+1)$ -electron system calculated at the geometry of the  $N$ -electron system. The nucleophilic local softness is written as

$$s^+(r) = f^+(r)S \quad (9)$$

Similarly, the electrophilic Fukui function and electrophilic local softness can be written as

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r) \quad (10)$$

where  $\rho_{N-1}$  is the electron density of the  $(N-1)$ -electron system calculated at the geometry of the  $N$ -electron system. The electrophilic local softness is given as

$$s^-(r) = f^-(r)S \quad (11)$$

To describe the reactivity of an atom, Yang and Mortier<sup>46</sup> defined the condensed quantities, which represent the integrated electron density over an atom. For example, the condensed nucleophilic Fukui function and local softness can be written as

$$f_k^+ = q_k(N+1) - q_k(N) \quad (12)$$

$$s_k^+ = f_k^+S \quad (13)$$

where  $q_k(N+1)$  and  $q_k(N)$  are the charges on atom  $k$  for the  $(N+1)$ -electron and  $N$ -electron systems, respectively. Similarly, the condensed electrophilic Fukui function and local softness can be written as

$$f_k^- = q_k(N) - q_k(N-1) \quad (14)$$

$$s_k^- = f_k^-S \quad (15)$$

The quantities  $q_k(N)$  and  $q_k(N-1)$  are the charges on atom  $k$  for the  $N$ - and  $(N-1)$ -electron systems, respectively. These condensed quantities have been used extensively for the study of site selectivity of atoms in a molecule.<sup>19-23</sup> In this paper, the condensed local softness will be computed and used for predicting the intermolecular reactivity trends.

## 2b. Group Softness

The differences in the strength of acidity among a group of molecules arise mainly from variations in the geometry, additions of another group at a specific site in the molecules, substitutions of one atom by another atom, etc. These variations have a pronounced effect on the acidity of the reactive site. Because local softness is a measure of the acidity of the site, we should be able to predict the qualitative trends of acidity using the local softness of the reactive atom in the series of molecules with specific acidity trends. However, these acidity trends are not reproduced clearly in the values of local softness. This may be due to the following factors: (i) Variations in the electron density around the reactive atom as a result of the changes in the geometry of the molecular structure are not effectively reproduced by population analysis, which is required to compute the condensed reactive quantities. (ii) The reactivity of an atom is also significantly influenced by the variations in the electron density of the atoms surrounding it. The error due to the first factor and the contribution of the second factor can be handled by adding the local softness of the first circle of neighboring atoms to the local softness of the reactive atom. This summed softness over a group of relevant atoms has been defined as the "group softness". The group softness can be written as

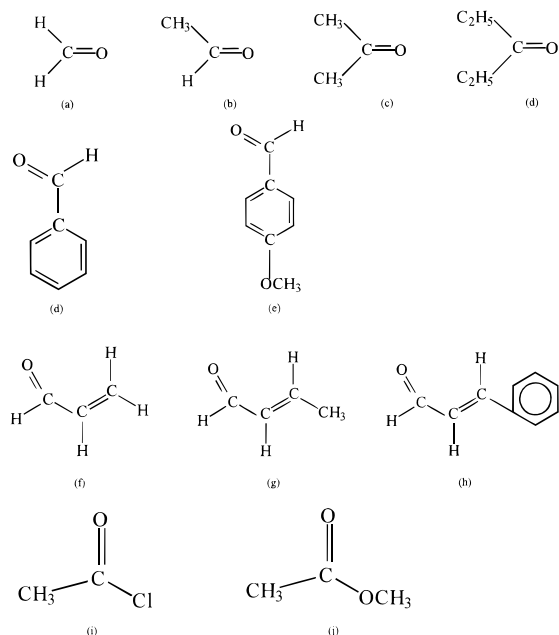
$$s_g = \sum_{k=1}^n s_k \quad (16)$$

where  $n$  is the number of atoms bonded to the reactive atom,  $s_k$  is the local softness of the atom  $k$ , and  $s_g$  is the group softness obtained after summing over the local softness of all of the neighboring atoms. However, in some cases, as will be seen in the case of organic acids in this work, the group must be

extended beyond just the first-neighbor atoms. A similar trend was observed in preliminary studies on alcohols. In both of these cases, the OH functional group behaves as the nucleophile. However, this is a much less powerful nucleophilic group, and in such cases, the intermolecular trends are not clearly reproduced by considering the OH group (oxygen atom being the first neighbor of the acidic hydrogen) alone. The local softness of the carbon atoms adjacent to the OH group (especially in the case when the second neighbors are the carboxylic carbons) must be considered to obtain correct reactivity trends, as they exert a considerable influence on the acidic hydroxyl. In other words, the local softnesses of the atoms forming the second-neighbor circle to the reactive atom also must be added to predict the correct trends for weak nucleophiles. In this case,  $n$  stands for all of the atoms connected to the reactive atom and also the atoms connected to the atoms bonded to the reactive atom. However, extending beyond the second circle of neighboring atoms is not necessary for all of the molecules studied in this work, and adding the second group should be sufficient for predicting reactivity trends for most of the molecules. The concept of additivity of the local softness is, itself, not very new and was previously used by several groups.<sup>25-32</sup> This summation of local softness (group softness) was used in conjunction with local hardness for the prediction of the reactivity trends. The group softness computed in this paper must not be confused with the group softness proposed by the earlier groups, as we consider the summation of the local softness of the atoms around the reactive center as the group softness whereas the earlier works were based on the summation of the local softness of the substituent atoms. In the present work, group softness is used independently for the first time to obtain the correct acidity trends for carbonyl compounds and acetic acids. The concept of group softness could also be significant in the context of the local HSAB principle in which two molecules can interact through groups with similar group softness values. The formulas for interaction energy according to the local HSAB principle can be generalized using group softness. Thus, soft-soft interactions between two molecules can occur when the interacting groups of both the molecules have higher group softness, and hard-hard interactions are likely occur when the interacting groups of both the molecules have lower group softness. However, these aspects are not tested in the present paper, and more detailed studies must be undertaken in future.

## 3. Methodology and Computational Details.

**a. Aldehydes and Ketones.** In this class of molecules, we have studied intermolecular reactivity trends for nucleophilic attack on the carbonyl carbon. Both aliphatic and aromatic aldehydes and ketones were used for this study. The systems studied for the prediction of intermolecular reactivity trends are: (i) HCHO, CH<sub>3</sub>CHO, CH<sub>3</sub>COCH<sub>3</sub>, and C<sub>2</sub>H<sub>5</sub>COC<sub>2</sub>H<sub>5</sub>; (ii) C<sub>6</sub>H<sub>5</sub>CHO and *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO; (iii) CH<sub>2</sub>=CHCHO, CH<sub>3</sub>CH=CHCHO, and C<sub>6</sub>H<sub>5</sub>CH=CHCHO, a case including both  $\alpha$ - and  $\beta$ -unsaturated compounds; and (iv) CH<sub>3</sub>COCl and CH<sub>3</sub>-COOCH<sub>3</sub>. In all of these compounds (Figure 1), the carbonyl carbon can undergo a nucleophilic addition reaction.<sup>47,48</sup> A few of the systems above were also studied by Roy et al.,<sup>24</sup> who found that intermolecular reactivity trends could not be predicted using local softness. These systems were studied at the Hartree-Fock level using four different basis sets, 3-21G, 6-31G, 3-21G\*\*, and 6-31G\*\*. The optimized geometry for these systems was computed using all of the above basis sets. All of these systems are closed-shell systems, and hence, the geometry

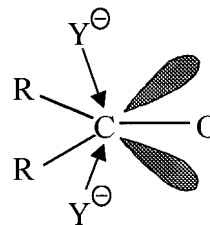


**Figure 1.** Carbonyl compounds studied for intermolecular reactivity trends.

optimization of these systems was carried out using the restricted Hartree–Fock (RHF) procedure. The GAMESS<sup>49</sup> system of programs was used for this purpose. The ionization potential and electron affinity were studied using the  $\Delta$ SCF procedure. For the computation of the vertical ionization potential and electron affinity, corresponding cations and anions of these systems were taken, and the energy was computed at the same geometry as that of the neutral system using the restricted open-shell Hartree–Fock (ROHF) procedure. The charges on the atoms for these neutral, anionic and cation systems were obtained from two types of population analysis, viz., (i) Mülliken population analysis and (ii) Löwdin population analysis. The local softness was computed from these charges, and the reactivity trends among the molecules were studied.

Mülliken<sup>50</sup> and Löwdin<sup>51</sup> population analyses are based on the partition of the electrons into net atomic populations in the atomic basis functions. In Mülliken population analysis, the population on an atom is defined to be sum over the diagonal elements centered on that atom of the  $\mathbf{PS}$  matrix, where  $\mathbf{P}$  is the density matrix and  $\mathbf{S}$  is the overlap matrix of the atomic basis. However, for the Löwdin population analysis, diagonal elements are more symmetrized ( $\mathbf{S}^{1/2}\mathbf{PS}^{1/2}$ ). Thus, in the Löwdin population analysis, the total number of electrons is the trace of the density matrix in terms of a symmetrically orthogonal basis. These two types of population analysis are dependent on the basis sets and are functions of molecular properties. Hence, these population analyses are not always quantitatively significant for electronic structure. However, the local softness computed from the difference of the population analysis is much more significant and more independent of the basis sets.

**b. Carboxylic Acids.** The alkyl acids have dual acidity trends in the gas phase and solvent phase.<sup>47,48</sup> It has been difficult to predict the gas-phase acidity trend of the carboxylic acids from the local softness of the acidic hydrogen. In this work, we try to study the gas-phase acidity trends of alkyl acids. The alkyl acid groups whose trends are studied in the present paper are  $\text{CH}_3\text{COOH}$  and  $\text{C}_2\text{H}_5\text{COOH}$ . The geometry optimization was carried out at the Hartree–Fock level using the 3-21G, 6-31G, and 3-21G\*\* bases. As in the case of carbonyl compounds, the neutral systems of the alkyl acids studied are closed-shell



**Figure 2.** Possible modes of nucleophilic attack toward the carbonyl carbon.

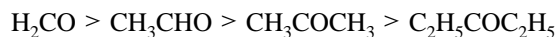
systems and were optimized using the RHF method. As in case a, the calculations for the ionization potential and electron affinity of the charged systems were carried out at the optimized geometry of the neutral systems using the ROHF method. The local softness were computed using both Mülliken and Löwdin population analyses.

## 4. Results and Discussion

**a. Carbonyl Compounds.** (1)  $\text{HCHO}$ ,  $\text{CH}_3\text{CHO}$ ,  $\text{CH}_3\text{COCH}_3$ , and  $\text{C}_2\text{H}_5\text{COC}_2\text{H}_5$ . The  $\text{C}=\text{O}$  linkage in a carbonyl compound produces a dipole moment because the oxygen atom of the  $\text{C}=\text{O}$  group is more electronegative than the carbon.  $\text{C}=\text{O}$ , because of its bipolar nature, can be initiated either by an electrophilic attack of  $\text{X}^+$  or  $\text{X}$  on oxygen or by a nucleophilic attack of  $\text{Y}^-$  or  $\text{Y}$  on carbon. In practice, the electrophilic attack on oxygen is of little importance except when the nucleophilic addition on carbon is acid-catalyzed.<sup>47,48</sup> The least energy-demanding direction of approach by a nucleophile to the carbonyl compound is from above or below the carbonyl carbon. An equally probable direction of approach is slightly from the rear of the carbon, as shown in Figure 2, because of coulomb repulsion between the approaching nucleophile and the high electron density at the carbonyl oxygen atom. In simple nucleophilic additions where the rate-limiting step is attack by  $\text{Y}^-$ , the positive character of the carbonyl carbon atom is reduced from the starting material to a transition state during the course of reaction.<sup>47</sup> Therefore, it is expected that the rate of addition on the carbonyl compound is reduced by electron-donating alkyl groups and enhanced by electron-withdrawing ones. The expected sequences for the possible nucleophilic addition reaction on the carbon is of the following order:<sup>47,48,52</sup>



where  $\text{R}$  is an alkyl group and  $\text{R}^1$  is another alkyl group. In the first series of our studies on the carbonyl compounds, we study this particular reactivity trend using local softness. It is expected that, for the four compounds in our study, the order of reactivity is the following:



The local softness of these four molecules is given in the Table 1. It can be observed that simple local softness  $s_c^+$  on the carbonyl carbon does not provide the expected trend. This carbonyl carbon ( $\text{C}_{\text{carb}}$ ) is surrounded by three neighboring atoms, viz.,  $\text{C}$ ,  $\text{H}$ , and  $\text{O}$ . In the next step, we add the local softness of all three atoms to the local softness of the carbonyl atom so as to obtain the group softness values for the molecules. It is seen in the Table 1 that the group softness gives the correct reactivity trends for all four molecules, indicating that the effect of the neighboring atoms is significant for the prediction of the intermolecular reactivity trends. It must be noted that the group softness of  $\text{HCHO}$  is equal to its global softness, as it involves

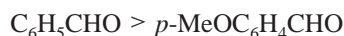
**TABLE 1: Local Softness on the Carbonyl Carbon ( $s_c^+$ ) and Group Softness for the First Series of Carbonyl Compounds at Various Basis Sets**

carbonyl compound	Mülliken population analysis		Löwdin population analysis	
	$s_c^+$	group softness <sup>a</sup>	$s_c^+$	group softness <sup>a</sup>
3-21G Basis				
HCHO	0.635	2.175	0.982	2.175
CH <sub>3</sub> CHO	0.529	1.401	0.904	1.707
CH <sub>3</sub> COCH <sub>3</sub>	0.507	0.713	0.820	1.293
C <sub>2</sub> H <sub>5</sub> COC <sub>2</sub> H <sub>5</sub>	0.530	0.640	0.839	1.268
3-21G** Basis				
HCHO	0.650	2.170	0.993	2.170
CH <sub>3</sub> CHO	0.608	1.397	0.913	1.735
CH <sub>3</sub> COCH <sub>3</sub>	0.526	0.708	0.830	1.307
C <sub>2</sub> H <sub>5</sub> COC <sub>2</sub> H <sub>5</sub>	0.540	0.638	0.847	1.135
6-31G Basis				
HCHO	0.649	2.263	1.002	2.263
CH <sub>3</sub> CHO	0.608	1.465	0.907	1.796
CH <sub>3</sub> COCH <sub>3</sub>	0.498	0.748	0.806	1.377
C <sub>2</sub> H <sub>5</sub> COC <sub>2</sub> H <sub>5</sub>	0.520	0.644	0.821	1.336
6-31G** Basis				
HCHO	0.656	2.212	1.013	2.212
CH <sub>3</sub> CHO	0.633	1.426	0.881	1.775
CH <sub>3</sub> COCH <sub>3</sub>	0.557	0.765	0.775	1.433
C <sub>2</sub> H <sub>5</sub> COC <sub>2</sub> H <sub>5</sub>	0.574	0.698	0.793	1.377

<sup>a</sup> The group consists of the carbonyl carbon, adjacent oxygen, adjacent hydrogen, and adjacent carbon (CHCO).

all of the atoms of the molecule. Thus, in this particular case, the group consists of the entire molecule, and the group softness is identical for both of the population analyses, as global softness is only dependent on the energy values of the neutral and charged species in the system. Table 1 gives the trends for just four basis sets. However, we can remark here that we have verified that these trends are predicted correctly by other basis sets such as STO-3G and 6-31G\* as well. It is very encouraging to note that group softness predicts the correct intermolecular reactivity trends for all of the basis sets shown in the table and for both Mülliken and Löwdin population analyses.

2. *C<sub>6</sub>H<sub>5</sub>CHO* and *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO. Alkyl groups in which the C=O group is conjugated with C=C or with a benzene ring exhibit slower addition reactions than their saturated analogues. This is because the stabilization in the initial carbonyl compounds, through the process of delocalization, is lost on proceeding to the transition states during the course of reaction. The addition reactions are also slowed by steric as well as electronic effects. The influence of the electronic effects alone can be seen to result in the following acidity trend:



However, the local softness shown in Table 2 for the above molecules does not necessarily show the expected acidity trend. However, again the group softness, which is the addition of local softness of the carbonyl carbon and the three atoms surrounding it ( $C_{\text{carb}}$ , C, H, and O), is able to predict the correct acidity trend for the three molecules. The values of the group softness are presented in Table 2. It is again very gratifying to note that group softness works well for all of the basis sets and both population analyses, indicating that this is a very consistent parameter for predicting intermolecular reactivity trends.

3. *CH<sub>2</sub>=CHCHO*, *CH<sub>3</sub>CH=CHCHO*, and *C<sub>6</sub>H<sub>5</sub>CH=CHCHO*. This is one of the critical cases studied by Roy et al.<sup>23</sup> for understanding the prediction of intra- and intermolecular reactivity sequences. This is a typical case in which we have

**TABLE 2: Local Softness on the Carbonyl Carbon ( $s_c^+$ ) and Group Softness for the Second Series of Carbonyl Compounds at Various Basis Sets**

carbonyl compound	Mülliken population analysis		Löwdin population analysis	
	$s_c^+$	group softness <sup>a</sup>	$s_c^+$	group softness <sup>a</sup>
3-21G Basis				
C <sub>6</sub> H <sub>5</sub> CHO	0.386	1.066	0.542	1.208
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	0.441	1.056	0.622	1.206
3-21G** Basis				
C <sub>6</sub> H <sub>5</sub> CHO	0.386	1.058	0.544	1.202
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	0.439	1.053	0.616	1.197
6-31 G Basis				
C <sub>6</sub> H <sub>5</sub> CHO	0.462	1.104	0.628	1.290
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	0.503	1.091	0.681	1.281
6-31G** Basis				
C <sub>6</sub> H <sub>5</sub> CHO	0.412	1.073	0.551	1.222
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	0.435	1.065	0.611	1.218

<sup>a</sup> The group consists of the carbonyl carbon, adjacent oxygen, adjacent hydrogen, and adjacent carbon (CHCO).

**TABLE 3: Local Softness on the Carbonyl Carbon ( $s_c^+$ ) and Group Softness for the Third Series of Carbonyl Compounds at Various Basis Sets**

carbonyl compound	Mülliken population analysis		Löwdin population analysis	
	$s_c^+$	group softness <sup>a</sup>	$s_c^+$	group softness <sup>a</sup>
3-21G Basis				
CH <sub>2</sub> =CHCHO	0.280	1.169	0.436	1.346
CH <sub>3</sub> CH=CHCHO	0.336	1.144	0.509	1.303
C <sub>6</sub> H <sub>5</sub> CH=CHCHO	0.130	0.991	0.215	1.113
3-21G** Basis				
CH <sub>2</sub> =CHCHO	0.284	1.160	0.447	1.353
CH <sub>3</sub> CH=CHCHO	0.343	1.135	0.521	1.311
C <sub>6</sub> H <sub>5</sub> CH=CHCHO	0.134	0.986	0.229	1.116
6-31G Basis				
CH <sub>2</sub> =CHCHO	0.335	1.204	0.510	1.413
CH <sub>3</sub> CH=CHCHO	0.365	1.171	0.542	1.360
C <sub>6</sub> H <sub>5</sub> CH=CHCHO	0.171	1.046	0.285	1.186
6-31G** Basis				
CH <sub>2</sub> =CHCHO	0.299	1.127	0.463	1.359
CH <sub>3</sub> CH=CHCHO	0.351	1.100	0.511	1.318
C <sub>6</sub> H <sub>5</sub> CH=CHCHO	0.154	0.964	0.269	1.111

<sup>a</sup> The group consists of the carbonyl carbon, adjacent oxygen, adjacent hydrogen, and adjacent carbon (CHCO).

an  $\alpha,\beta$ -unsaturated bond in conjugation with a carbonyl carbon. Each molecule in this series has more than one electrophilic centers, which compete with each other. However, we focus on the possibility of nucleophilic attack on the carbonyl carbon. The acidity trends are expected to be in the following order:



It is once again seen in Table 3 that the local softness on the carbonyl carbon fails to predict the correct acidity trend. However, again the group softness, which is a summation of the local softness of the carbonyl carbon and the three atoms bonded to the carbonyl carbon ( $C_{\text{carb}}$ , H, C, and O), predicts the correct reactivity trend in this series of molecules.

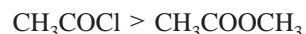
4. *CH<sub>3</sub>COCl* and *CH<sub>3</sub>COOCH<sub>3</sub>*. Finally, in this study on the intermolecular reactivity trends in carbonyl compounds, we consider the case of carboxylic derivatives. Carboxylic derivatives are different from the traditional carbonyl compounds because of the fact that there is a good potential leaving group

**TABLE 4: Local Softness on the Carbonyl Carbon ( $s_c^+$ ) and Group Softness for the Case of Carboxylic Derivatives at Various Basis Sets**

carbonyl compound	Mülliken population analysis		Löwdin population analysis	
	$s_c^+$	group softness <sup>a</sup>	$s_c^+$	group softness <sup>a</sup>
	3-21G Basis			
CH <sub>3</sub> COCl	0.412	1.470	0.743	1.733
CH <sub>3</sub> COOCH <sub>3</sub>	0.585	0.965	0.742	1.302
	3-21G** Basis			
CH <sub>3</sub> COCl	0.544	1.469	0.767	1.764
CH <sub>3</sub> COOCH <sub>3</sub>	0.593	0.967	0.747	1.332
	6-31G Basis			
CH <sub>3</sub> COCl	0.407	1.429	0.675	1.695
CH <sub>3</sub> COOCH <sub>3</sub>	0.570	1.038	0.738	1.397
	6-31G** Basis			
CH <sub>3</sub> COCl	0.527	1.463	0.724	1.778
CH <sub>3</sub> COOCH <sub>3</sub>	0.610	1.001	0.691	1.379

<sup>a</sup> The group consists of the carbonyl carbon, adjacent oxygen, adjacent hydrogen, and adjacent carbon (CHCO)

X attached to the carbonyl carbon. In simple carbonyl compounds, the potential leaving group (H<sup>-</sup> or R<sup>-</sup>) is very poor. The relative reactivity of the carbonyl derivatives depends on (i) the relative electron-donating or -withdrawing power of X toward the carbonyl carbon and (ii) The relative ability of X as a leaving group.<sup>47,48</sup> We study two molecules in this series, and their relative reactivity is in the following order:



For the case of carboxylic derivatives too, it is seen that group softness emerges as a successful tool for predicting the intermolecular reactivity trends. (See Table 4.)

**b. Alkyl Acids.** Many attempts have been made in the past to predict the correct gas-phase acidity trend for the organic acids. The trend in acidity of gas-phase CH<sub>3</sub>COOH and C<sub>2</sub>H<sub>5</sub>COOH is exactly opposite to that in the aqueous phase. These systems are the most classic examples of the reversal of acidity trends from the gas phase to the aqueous phase. In aqueous solution, the acidity of CH<sub>3</sub>COOH is greater than that of C<sub>2</sub>H<sub>5</sub>COOH, because of the inductive effect of the alkyl groups, in accordance with the traditional viewpoint. However, in the gas phase, the reactivity trend is reversed because of increased polarizability of C<sub>2</sub>H<sub>5</sub>COOH as compared to CH<sub>3</sub>COOH.<sup>51,52,53</sup> It is observed in the Table 5 that the local softness of the acidic hydrogen atom does not predict the correct gas-phase acidity trend. Hence, as in the case of carbonyl compounds, the local softness of the adjacent oxygen atom was added to the local softness of the hydrogen atom to compute the group softness. In this case, it was seen that the group softness obtained by adding the softness of the reactive atom and its adjacent neighbor failed to provide the correct trend. However, when the group was expanded to consist of also a second-nearest neighbor atom, which is carbon in this case, (Figure 3), it was observed that the softness of this group predicts the acidity trends correctly. Table 3 shows the trends of acidity obtained using three different basis sets, namely, 3-21G, 6-31G, and 3-21G\*\*. This example also shows the importance of defining the group properly from chemical intuition.

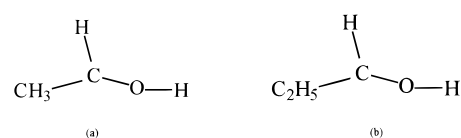
## 5. Conclusions

The group softness computed by adding the sum of the local softness of the reacting atom and the atoms in its neighborhood

**TABLE 5: Local Softness on the Acidic Hydrogen ( $s_H^+$ ) and Group Softness for the Case of Carboxylic Acids at Various Basis Sets**

carbonyl compound	Mülliken population analysis		Löwdin population analysis	
	$s_H^+$	group softness <sup>a</sup>	$s_H^+$	group softness <sup>a</sup>
	3-21G Basis			
CH <sub>3</sub> COOH	0.189	0.907	0.139	1.037
C <sub>2</sub> H <sub>5</sub> COOH	0.184	0.922	0.135	1.041
	3-21G** Basis			
CH <sub>3</sub> COOH	0.186	0.918	0.131	1.043
C <sub>2</sub> H <sub>5</sub> COOH	0.180	0.931	0.128	1.047
	6-31G Basis			
CH <sub>3</sub> COOH	0.175	0.920	0.119	1.055
C <sub>2</sub> H <sub>5</sub> COOH	0.171	0.936	0.117	1.059

<sup>a</sup> The group consists of the acidic hydrogen, first-neighbor oxygen, and second-neighbor adjacent carbon (HOC).



**Figure 3.** Carboxylic acids have a group consisting of the acidic hydrogen, the adjacent oxygen, and the second-nearest neighbor carbon.

was found to work effectively in predicting the intermolecular reactive sequences, as shown from the studies above. For the carbonyl compounds, the group consists of the reacting atom and the atoms chemically bonded (first group of nearest neighbors) to the carbonyl carbon. On the other hand, it is seen for organic acids that it is not sufficient to add the local softness of first group of nearest neighbors to obtain the correct acidity trends. The second group of nearest neighbors must also be included in the group and their local softness considered. In general, it is expected that atoms further than the second circle of neighboring atoms do not influence the acidity of the atom, so this should be the largest possible group that needs to be considered for predicting intermolecular reactivity patterns. It is gratifying to note that the results were stable with respect to different basis sets and population analyses.

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