# Local Softness and Hardness Based Reactivity Descriptors for Predicting Intra- and Intermolecular Reactivity Sequences: Carbonyl Compounds

**R. K. Roy,[†,‡] S. Krishnamurti,[†] P. Geerlings,[§] and S. Pal*,[†]**

*Physical Chemistry Division, National Chemical Laboratory, Pune-411008, India, and*
*Eenheid Algemene Chemie (ALGC), Vrije Universiteit Brussel, Belgium*

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The DFT-based reactivity descriptors "local softness" and "local hardness" are used as reactivity indices to predict the reactivity sequences (both intramolecular and intermolecular) of carbonyl compounds toward nucleophilic attack on them. The finite difference approximation is used to calculate local softness, whereas local hardness is approximated by $-V_{el}/2N$, where $V_{el}$ is the electronic part of the molecular electrostatic potential. Both aldehydes and ketones, aliphatic and aromatic, have been selected as systems. Critical cases, e.g., $C_6H_5CH{=}CHCHO$, $CH_3CH{=}CHCHO$, and $CH_2{=}CHCHO$, where a C═C double bond is in conjugation with the C═O group, are also considered. Two new reactivity descriptors are proposed, "relative electrophilicity" ($s_k^+/s_k^-$) and "relative nucleophilicity" ($s_k^-/s_k^+$), which will help to locate the preferable reactive sites. Our results show that local hardness can be used as a guiding parameter when constructing intermolecular reactivity sequences.

## 1. Introduction

Ever since the concept of hard and soft acids and bases (HSAB) was introduced by Pearson,[1] it was exploited by the chemist community to explain the wide-ranging phenomena in organic,[2a−c] inorganic,[2a−c] and biological chemistry.[2c,d] The concept got renewed impetus after Parr and Pearson gave precision to chemical hardness, affording its calculation via approximate working equations.[3] The proposition of the principle of maximum hardness (PMH)[4] added a new dimension in understanding the driving forces of chemical processes.

Whereas hardness and softness are global properties of acids and bases, there are parallel developments on the local front. The motivation behind these studies is to predict the site selectivity or site specificity in a chemical reaction. The most important local reactivity parameter, defined as the Fukui function, was introduced by Parr and Yang.[5] Later on, other local reactivity parameters based on the hard and soft acids and bases, e.g, local hardness[6a,b] and local softness,[6b] were introduced. Recently Krishnamurti et al.[7] have shown that in case of gases interacting with zeolite surfaces the reaction follows the local HSAB principle, which was originally proposed by Parr and Yang[8] and analytically proved by Gazquez and Mendez.[9] One of the present authors and co-workers also exploited the Fukui functions and local softness parameters to explain a variety of features of chemical species, e.g., intrinsic group properties,[10a] influence of isomorphous substitution on the catalytic activity of zeolites,[10b] acidity of substituted acetic acids,[10c] acidity of first- and second-row hydrides,[10d] acidity of alkyl-substituted alcohols,[10e] basicity of primary amines,[10f] etc.

Whereas Fukui functions and local softness are well-defined, the definition of local hardness is ambiguous.[11a,b] Recently Langenaeker et al.[12] have proposed several approximate working equations of local hardness and also defined a new local reactivity parameter as "hardness density". They have shown that in the case of electrophilic aromatic substitution, where the intramolecular reactivity sequences (i.e., site selectivity) can be predicted correctly by condensed local softness values of the atoms, the intermolecular reactivity sequences are explained better by local hardness values.

In this article we want to address the reactivity aspects of some carbonyl compounds through local softness and hardness based reactivity descriptors. We will consider both aldehydes and ketones, aliphatic and aromatic. The nucleophilicity and electrophilicity of the atoms are compared to find out the preferable site selectivities of different sites. The critical cases (e.g., $CH_2{=}CHCHO$, $CH_3CH{=}CHCHO$, and $C_6H_5CH{=}CHCHO$), where an α,$\beta$ unsaturated double bond is present in conjugation with $C_{carb}$ (carbonyl carbon), are also discussed. We propose a new scheme, based on the local softness parameters, which successfully explains the preferred sites of attack in almost all cases we have studied. Our study also reveals that for prediction of intermolecular reactivity sequences of the $C_{carb}$, the local hardness parameter $\eta_D^{TFD}(\bar{r})$ provides the best result.

The article is organized as follows: In section 2 a brief description of the background theory is given. Section 3 contains the computational part. The detailed methodology for calculating local hardness on $C_{carb}$ is given. The results are critically analyzed and compared with other available theoretical and experimental results in section 4. This section is subdivided into three subsections. In subsection 4.A we have tested the validity of the local softness parameters $s_k^+$ and $s_k^-$ to locate the preferable electrophilic and nucleophilic sites respectively in the compounds studied. The superiority of the newly proposed local reactivity descriptors $s_k^+/s_k^-$ and $s_k^-/s_k^+$ in predicting preferable reactive sites is discussed in subsection 4.B. The importance of local hardness parameters to evaluate intermolecular reactivity sequences is shown in subsection 4.C.

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[*] Author for correspondence.
[†] National Chemical Laboratory.
[‡] Presently Visiting Postdoctoral Fellow (FWO) at ALGC, VUB, Belgium.
[§] Vrije Universiteit Brussel.

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## 2. Theoretical Background

**(i) Global Hardness and Softness.** Parr and Pearson[3] first provided the analytical definition of global hardness of any chemical species as

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

where $E$ is the total energy, $N$ is the number of electrons of the chemical species, and $\mu$ is the chemical potential, which is identified as the negative of the electronegativity[13] ($\chi$) as defined by Iczkowski and Margrave.[14]

The corresponding global softness is expressed as

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

By applying the finite difference approximation to eq 1, we get the operational definition of $\eta$ and $S$ as[3]

$$\eta = \frac{\mathrm{IP} - \mathrm{EA}}{2} \tag{3}$$

$$S = \frac{1}{\mathrm{IP} - \mathrm{EA}} \tag{4}$$

where IP and EA are the ionization potential and electron affinity of the chemical species.

**(ii) Local Softness and Fukui Functions.** The local softness $s(\bar{r})$ can be defined as

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

so that

$$\int s(\bar{r})\, \mathrm{d}\bar{r} = S$$

Combining eqs 5 and 2, we can write

$$s(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{\nu(\bar{r})} \left(\frac{\partial N}{\partial \mu}\right)_{\nu(\bar{r})} = f(\bar{r}) S = \left(\frac{\partial \mu}{\partial \nu(\bar{r})}\right)_N S \tag{6}$$

where $f(\bar{r})$ is defined as the Fukui function by Parr and Yang.[5] From eq 6 it is obvious that local softness contains the same information as Fukui functions (i.e., sensitivity of the chemical potential of a system to a local external perturbation[15]) plus additional information about the total molecular softness. Therefore either the Fukui function or local softness can be used in studies of intramolecular reactivity sequences (i.e., relative site reactivity in a molecule). But only $s(\bar{r})$ (and not $f(\bar{r})$) should be a better descriptor of the global reactivity with respect to a reaction partner with a given hardness (or softness), as stated in the HSAB principle.

As $\rho(\bar{r})$ is a discontinuous function of $N$, three types of $f(\bar{r})$ can be defined which, when multiplied by $S$, result in three different local softness. Within a finite difference approximation the condensed form of these three local softness for any particular atom ($k$) can be written as[16]

$$s_k^{\,+} = [\rho_k(N_0 + 1) - \rho_k(N_0)]S \tag{7a}$$

(suited for studies of nucleophilic attack)

$$s_k^{\,-} = [\rho_k(N_0) - \rho_k(N_0 - 1)]S \tag{7b}$$

(suited for studies of electrophilic attack)

$$s_k^{\,0} = \frac{1}{2}[\rho_k(N_0 + 1) - \rho_k(N_0 - 1)]S \tag{7c}$$

(suited for studies of radical attack)

Here $\rho_k(N_0)$ represents the electronic population (Mulliken) on atom $k$ for the $N_0$ electron system.

**(iii) Local Hardness.** The analytical definition of local hardness was first proposed by Ghosh and Berkowitz[6a] as

$$\tilde{\eta}(\bar{r}) = \left(\frac{\delta \mu}{\delta \rho(\bar{r})}\right)_{\nu(\bar{r})} \tag{8}$$

An explicit form of the local hardness $\tilde{\eta}(\bar{r})$ can be obtained starting from the Euler equation resulting from the application of the variation principle to the energy functional[8]:

$$\nu(\bar{r}) + \frac{\delta F_{\mathrm{E}}[\rho(\bar{r})]}{\delta \rho(\bar{r})} = \mu \tag{9}$$

with $F_{\mathrm{E}}[\rho(\bar{r})]$ containing the kinetic energy and electron−electron interaction energy. Now multiplying eq 9 by a composite function $\lambda(\rho(\bar{r}))$,[11] which integrates to N,

$$\int \lambda(\rho(\bar{r}))\, \mathrm{d}\bar{r} = N \tag{10}$$

we get after integrating both sides

$$N\mu = \int \nu(\bar{r})\, \lambda(\rho(\bar{r}))\, \mathrm{d}\bar{r} + \int \frac{\delta F_{\mathrm{E}}}{\delta \rho(\bar{r})} \lambda(\rho(\bar{r}))\, \mathrm{d}\bar{r} \tag{11}$$

Taking the functional derivative with respect to $\rho$, at constant external potential $\nu$, we obtain the following expression:

$$\left(\frac{\delta \mu}{\delta \rho}\right) N + \mu = \nu(\bar{r}) \left(\frac{\delta \lambda(\rho)}{\delta \rho}\right)_\nu + \frac{\delta F_{\mathrm{E}}}{\delta \rho} \left(\frac{\delta \lambda(\rho)}{\delta \rho}\right)_\nu + \left(\int \frac{\delta^2 F_{\mathrm{E}}}{\delta \rho(\bar{r})\, \delta \rho(\bar{r}')} \lambda(\rho(\bar{r}'))\, \mathrm{d}\bar{r}'\right)_\nu \tag{12}$$

which can be written as

$$\left(\frac{\delta \mu}{\delta \rho}\right)_\nu N = \left(\nu(\bar{r}) + \frac{\delta F_{\mathrm{E}}}{\delta \rho}\right) \left(\frac{\delta \lambda(\rho)}{\delta \rho}\right) - \mu + \left(\int \frac{\delta^2 F_{\mathrm{E}}}{\delta \rho(\bar{r})\, \delta \rho(\bar{r}')} \lambda(\rho(\bar{r}'))\, \mathrm{d}\bar{r}'\right)_\nu \tag{13}$$

Using eq 9, we get

$$\left(\frac{\delta \mu}{\delta \rho}\right)_\nu N = \left(\left(\frac{\delta \lambda(\rho(\bar{r}))}{\delta \rho(\bar{r})}\right)_\nu - 1\right)\mu + \left(\int \frac{\delta^2 F_{\mathrm{E}}}{\delta \rho(\bar{r})\, \delta \rho(\bar{r}')} \lambda(\rho(\bar{r}'))\, \mathrm{d}\bar{r}'\right)_\nu \tag{14}$$

Now if local hardness is forced to have an expression of the type (eq 3.25 in ref 11b)

$$\left(\frac{\delta\mu}{\delta\rho(\bar{r})}\right)_\nu = \frac{1}{N}\int \frac{\delta^2 F_E}{\delta\rho(\bar{r}')\,\delta\rho(r)}\lambda(\rho(\bar{r}'))\,d\bar{r}' \qquad (15)$$

the composite function $\lambda(\rho)$ should have an additional constraint (in addition to that of eq 10),

$$\left(\frac{\delta\lambda(\rho)}{\delta\rho}\right)_\nu = 1 \qquad (16)$$

Defining the hardness kernel, $\eta(\bar{r},\bar{r}')$,[6a] as

$$\eta(\bar{r},\bar{r}') = \frac{\delta^2 F_E}{\delta\rho(\bar{r}')\,\delta\rho(\bar{r})} \qquad (17)$$

the final expression for the local hardness is as follows:

$$\eta_\lambda(\bar{r}) = \left(\frac{1}{N}\right)\int \eta(\bar{r},\bar{r}')\,\lambda(\rho(\bar{r}'))\,d\bar{r}' \qquad (18)$$

As pointed out by Ghosh[11a] as well as Harbola et al.,[11b] the definition of local hardness is ambiguous if we imply only the condition of eq 10 on the composite function. This is because, in principle, any function which fulfills the condition of eq 10 can be accepted as a composite function. However if the conditions of both eqs 10 and 16 are imposed, then the series of composite functions is restricted. A first function that was originally used by Ghosh and Berkowitz[6a] is the electron density $\rho$. The other obvious choice is $Nf(\bar{r})$. However, in our present study we will use the expression of local hardness derived from $\rho$ (denoted by $\eta_D$), which can be expressed as

$$\eta_D(\bar{r}) = \left(\frac{1}{N}\right)\int \eta(\bar{r},\bar{r}')\,\rho(\bar{r}')\,d\bar{r}' \qquad (19)$$

As it is difficult to provide any routine calculational scheme for $\eta_D(\bar{r})$, Langenaeker et al.[12] have proposed approximate working equations for it. These approximations are based on the Thomas−Fermi−Dirac (TFD) approach to DFT. If we keep in mind that the nucleus−electron attraction is not contained in $F_E[\rho(\bar{r})]$, the following equation is obtained from the general form of the energy functional $E^{TFD}[\rho(\bar{r})]$,[8] without further approximations:

$$F_E^{TFD}[\rho(\bar{r})] = C_F\int \rho(\bar{r})^{5/3}\,d\bar{r} + \left(\frac{1}{2}\right)\int\int \frac{\rho(\bar{r})\,\rho(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}\,d\bar{r}' + C_X\int \rho(\bar{r})^{4/3}\,d\bar{r} \qquad (20)$$

Inserting eq 20 in eq 15 and taking $\lambda = \rho$, the local hardness can be written as

$$\eta_D^{TFD}(\bar{r}) = \left(\frac{10}{9N}\right)C_F\rho(\bar{r})^{2/3} - \left(\frac{1}{2N}\right)V_{el}(\bar{r}) + \left(\frac{4}{9N}\right)C_X\rho(\bar{r})^{1/3}\,d\bar{r} \qquad (21)$$

with $V_{el}(\bar{r})$ being the electronic contribution to the molecular electrostatic potential,[17] corresponding to the proposal made before by Berkowitz and Parr.[6b]

Considering the exponential falloff of the electron density in the outer regions of the system considered, eq 21 can be approximated as

$$\eta_D^{TFD}(\bar{r}) = -\frac{V_{el}(\bar{r})}{2N} \qquad (22)$$

It was shown that this approximated form of local hardness, (i.e., $-V_{el}(\bar{r})/2N$) can be used as a reliable parameter for comparison of intermolecular reactivity sequences of any particular site in a series of molecules.[12]

## 3. Methodology and Computational Details

For our present study we have considered 12 carbonyl compounds: $CH_3CHO$, $CH_3COCH_3$, $C_2H_5COC_2H_5$, $CH_2ClCHO$, $CH_2FCHO$, $CH_3CF_2CHO$, $CH_2{=}CHCHO$, $CH_3CH{=}CHCHO$, $C_6H_5CH{=}CHCHO$, $C_6H_5COCH_3$, $C_6H_5COC_2H_5$, $C_6H_5COC_6H_5$. The geometries have been generated by using the Unichem program system.[18] Subsequently these geometries are optimized with three different basis sets, STO-3G, DZ, and DZP,[19] using the Gaussian-94 program[20] on the CRAY computer of the Universities of Brussels. The last two basis sets are named as D95 and D95* in the Gaussian-94 program system. For neutral systems (closed-shell) RHF and for the corresponding cations and anions (open-shell) ROHF[21] methods are used.

Local softness values (both $s_k^+$ and $s_k^-$) are in a straightforward way calculated for all the atoms by using eqs 8a and 8b. However for calculation of local hardness $\eta_D^{TFD}(\bar{r})$, we require $V_{el}(\bar{r})$. This quantity has been evaluated only for the $C_{carb}$ center (as the intramolecular reactivity study will reveal that $C_{carb}$ normally is the most reactive center, i.e., the center to be attacked by a nucleophile $Nu^-$, and so is to be considered when comparing intermolecular electrophilicity order of different carbonyl compounds).

We have used the Felkin−Anh model[22a−d] for addition of the nucleophile to the C=O group. It is to be noted that the Felkin−Anh model was proposed to predict or rationalize the stereochemical outcome from kinetically controlled additions to the carbonyl group of chiral aldehydes and ketones in which a stereogenic center is adjacent to the carbonyl group. According to this model, the bulkiest of the α groups (i.e., the groups attached to the stereogenic carbon) take up a perpendicular relationship to the plane of the carbonyl group anti to the incoming nucleophile, and the sterically next most demanding α substituent (medium size groups) is placed gauche to the carbonyl function. It was argued that for such a mode of attack the torsional strain involving the partially formed bonds in the transition state will be minimized.[22a−c] Later on Bürgi et al.[23a−c] argued that it is not necessary that the medium sized group should be gauche to the oxygen atom in the preferred transition state. Instead they suggested that the angle of approach of the attacking nucleophile should be about 109° with respect to the plane of the carbonyl group (known as the Bürgi−Dunitz trajectory).

However, none of the carbonyl compounds we have studied contain any stereogenic center adjacent to the carbonyl carbon. Stricto sensu the Felkin−Anh model (or its modified form by Bürgi et al.) cannot be applied. So, we have considered the optimized geometry at different basis sets and then invoked the Bürgi−Dunitz trajectory to choose the angle $\angle Nu^- - C_1 - O = 109°$ (see Figure 1). The dihedral angle $\angle Nu^- - C_1 - O - C_2$ is taken as 90°. The distance $Nu^- - C_1$ is 4 au, as Langenaeker et al.[12] have shown that at a distance of 4 au the approximation $\eta_D^{TFD}(\bar{r}) = -V_{el}(\bar{r})/2N$ is justified.

## 4.A. Local Softness: A Measure for Intramolecular Reactivity (Site Selectivity)

The numbering of the atoms in the molecules considered is given in Figure 2. The local softness values (both $s_k^+$ and $s_k^-$) of individual atoms (only the atoms that are of interest, i.e.,

**TABLE 1: $s_k^+$ and $s_k^-$ Values of the Relevant Atomic Positions of All 12 Compounds Studied**

| carbonyl compound | atomic center | STO-3G $s_k^+$ | STO-3G $s_k^-$ | DZ $s_k^+$ | DZ $s_k^-$ | DZP $s_k^+$ | DZP $s_k^-$ |
|---|---|---|---|---|---|---|---|
| $CH_3CHO$ | 1 | 0.6088 | 0.3029 | 0.9793 | 0.1911 | 0.9832 | 0.1468 |
| | 2 | 0.5372 | 0.7191 | 0.5711 | 1.0823 | 0.5284 | 1.0739 |
| $CH_3COCH_3$ | 1 | 0.6112 | 0.2832 | 0.7263 | 0.1086 | 0.7505 | 0.0882 |
| | 2 | 0.5077 | 0.7169 | 0.5610 | 1.0614 | 0.5167 | 1.0573 |
| $C_2H_5COC_2H_5$ | 1 | 0.6149 | 0.2707 | 0.6480 | 0.1154 | 0.6792 | 0.0925 |
| | 2 | 0.5034 | 0.7168 | 0.5697 | 1.0772 | 0.5209 | 1.0719 |
| $CH_2FCHO$ | 1 | 0.6092 | 0.2989 | 0.9559 | 0.2761 | 0.9557 | 0.2254 |
| | 2 | 0.5365 | 0.7150 | 0.6012 | 1.0810 | 0.5546 | 1.0765 |
| $CH_2ClCHO$ | 1 | 0.5852 | 0.3017 | 0.9042 | 0.2240 | 0.9473 | 0.1857 |
| | 2 | 0.5156 | 0.7203 | 0.5580 | 1.0895 | 0.5355 | 1.0760 |
| | 4 | 0.3748 | 0.3583 | 0.4790 | 0.4945 | 0.3369 | 0.3851 |
| $CH2{=}CHCHO$ | 1 | 0.3388 | 0.2632 | 0.8027 | 0.5030 | 0.7699 | 0.4427 |
| | 3 | 0.5220 | 0.3047 | 0.5757 | 0.1936 | 0.4194 | 0.1647 |
| | 4 | 0.4880 | 0.7541 | 0.5596 | 1.1663 | 0.4793 | 1.1759 |
| $CH_3CH{=}CHCHO$ | 2 | 0.3469 | 0.2653 | 0.6240 | 0.4267 | 0.5871 | 0.3806 |
| | 4 | 0.5216 | 0.2899 | 0.5694 | 0.1466 | 0.4405 | 0.1260 |
| | 5 | 0.4806 | 0.7552 | 0.5535 | 1.1673 | 0.4718 | 1.1758 |
| $C_6H_5CH{=}CHCHO$ | 1 | 0.2756 | 0.2796 | 0.4992 | 0.5243 | 0.4207 | 0.4823 |
| | 2 | 0.2061 | −0.0053 | 0.3057 | −0.1166 | 0.3782 | −0.1390 |
| | 3 | 0.1512 | 0.2773 | 0.2524 | 0.0696 | 0.2132 | 0.0605 |
| | 4 | 0.3998 | 0.7915 | 0.4748 | 1.2610 | 0.3810 | 1.2871 |
| | 6 | 0.1231 | 0.0818 | 0.2465 | 0.1708 | 0.2167 | 0.1510 |
| | 8 | 0.1801 | 0.1046 | 0.3331 | 0.1859 | 0.3421 | 0.1680 |
| | 10 | 0.1264 | 0.0736 | 0.3159 | 0.1397 | 0.3004 | 0.1150 |
| $C_6H_5COCH_3$ | 2 | 0.1562 | 0.1143 | 0.3602 | 0.1624 | 0.3188 | 0.1554 |
| | 4 | 0.2032 | 0.1362 | 0.4266 | 0.1847 | 0.4594 | 0.1695 |
| | 6 | 0.1393 | 0.0913 | 0.3764 | 0.1944 | 0.3353 | 0.1666 |
| | 7 | 0.5017 | 0.2802 | 0.4235 | 0.1023 | 0.3315 | 0.1009 |
| | 8 | 0.4118 | 0.7655 | 0.4632 | 1.1790 | 0.3835 | 1.2010 |
| $C_6H_5COC_2H_5$ | 2 | 0.1568 | 0.1120 | 0.3720 | 0.1642 | 0.3318 | 0.1566 |
| | 4 | 0.2044 | 0.1347 | 0.4202 | 0.1799 | 0.4544 | 0.1651 |
| | 6 | 0.1396 | 0.0902 | 0.3750 | 0.1928 | 0.3343 | 0.1638 |
| | 7 | 0.4963 | 0.2767 | 0.4174 | 0.0993 | 0.3324 | 0.0976 |
| | 8 | 0.4103 | 0.7681 | 0.4659 | 1.1882 | 0.3867 | 1.2119 |
| $C_6H_5COC_6H_5$ | 2 | 0.1095 | 0.1005 | 0.2291 | 0.1245 | 0.1956 | 0.1226 |
| | 4 | 0.1519 | 0.1224 | 0.2706 | 0.1628 | 0.2657 | 0.1523 |
| | 6 | 0.1120 | 0.0748 | 0.2764 | 0.1524 | 0.2351 | 0.1248 |
| | 7 | 0.5788 | 0.2833 | 0.5946 | 0.1647 | 0.5508 | 0.1544 |
| | 8 | 0.3780 | 0.7840 | 0.4740 | 1.1981 | 0.4383 | 1.2200 |
| | 10 | 0.1095 | 0.1005 | 0.2291 | 0.1245 | 0.1956 | 0.1226 |
| | 12 | 0.1519 | 0.1224 | 0.2706 | 0.1628 | 0.2657 | 0.1523 |
| | 14 | 0.1120 | 0.0748 | 0.2764 | 0.1524 | 0.2351 | 0.1248 |
| $CH_3CF_2CHO$ | 1 | 0.6118 | 0.3009 | 0.8909 | 0.2673 | 0.9168 | 0.2307 |
| | 2 | 0.5329 | 0.7113 | 0.5994 | 1.0676 | 0.5575 | 1.0608 |

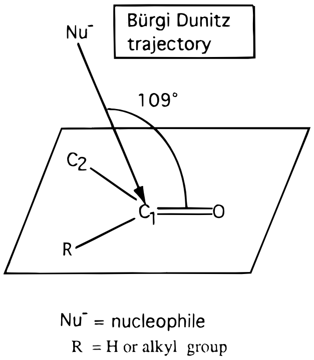


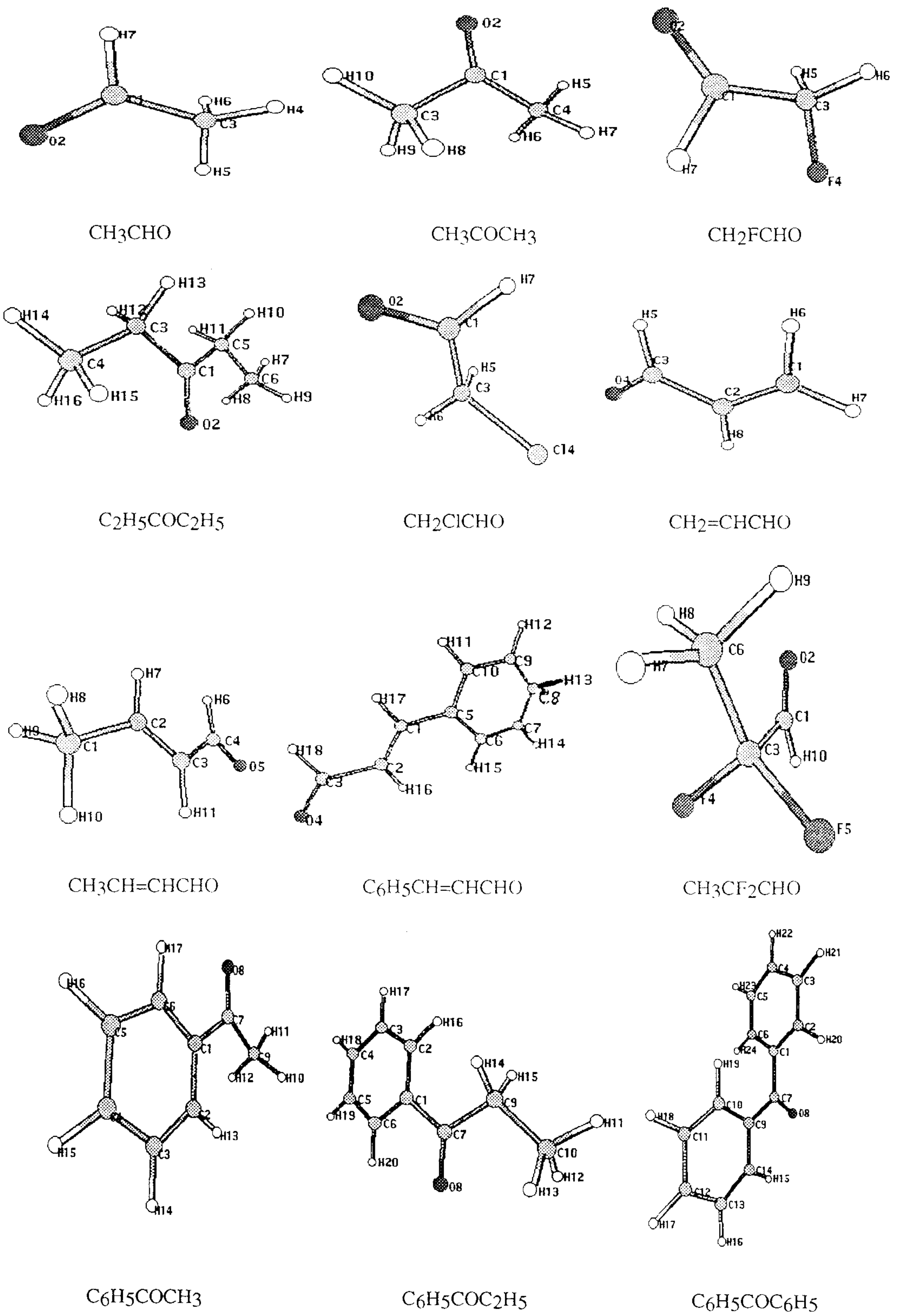
**Figure 1.** Felkin−Anh model for addition of nucleophiles to the carbonyl group.

having higher $s_k^+$ and $s_k^-$ values) are tabulated in Table 1. These will help us to estimate the relative tendency of an atomic center to behave as an eletrophile or a nucleophile.

It is obvious from Table 1 that for simple systems, e.g. $CH_3CHO$, $CH_3COCH_3$, $C_2H_5COC_2H_5$, $CH_2ClCHO$, $CH_2FCHO$, and $CH_3CF_2CHO$, the highest $s_k^+$ value is found for $C_{carb}$, which is the most reactive (electrophilic) site. Similarly the highest $s_k^-$ is found for the carbonyl−oxygen atom. This clearly shows that $C_{carb}$ is the most reactive center toward a nucleophile ($Nu^-$), whereas the carbonyl−oxygen atom displays the highest reactivity toward an electrophile ($El^+$).

However, observation of other complex systems, e.g., having a C═C bond in conjugation with a C═O group (case 1) or having a Ph group that can participate in extended delocalization with the C═O group (case 2) reveals some interesting features. Let us consider these two cases one by one.

**Case 1.** We have studied three systems of this type. These are $C^1H_2 = C^2HC^3HO^4$, $CH_3C^1H = C^2HC^3HO^4$, and $C_6H_5C^1H = C^2HC^3HO^4$. These types of systems have received special attention by both theoretical[24a] and experimental chemists[24b] because they have two reactive centers to be attacked by a nucleophile. The first one is center 1, the reaction usually described as a "nucleophilic attack on an activated C═C bond". Here the C═C bond is activated because of the electron pulling effect of the adjacent C═O group. The second type of attack, which demonstrates the common type of reaction of aldehydes and ketones, is on center 3. Which center will be preferred by a nucleophile is both system and condition dependent. If we look into the hybridization aspect, then both $C_1$ and $C_3$ are $sp^2$



$CH_3CHO$ $CH_3COCH_3$ $CH_2FCHO$

$C_2H_5COC_2H_5$ $CH_2ClCHO$ $CH_2{=}CHCHO$

$CH_3CH{=}CHCHO$ $C_6H_5CH{=}CHCHO$ $CH_3CF_2CHO$

$C_6H_5COCH_3$ $C_6H_5COC_2H_5$ $C_6H_5COC_6H_5$

**Figure 2.** Numbering of atoms of the cabonyl compounds.

hybridized. But $C_3$ is attached to the more electronegative O atom (i.e., C═O bond is more polarized than C═C bond). So, neglecting resonance effects, $C_3$ should behave as the strongest electrophilic center. However, center 1 becomes important toward nucleophilic attack as the resultant negative charge is distributed by delocalization.

Anyway, experimental observations suggest the presence of both types of addition products[24b] (known as 1,2 and 1,4 addition). For α,*β* unsaturated aldehydes (which we are studying here) exclusively 1,2 addition products are obtained when treated with Grignard reagents.[24b] But with other reactants the product ratio may vary.

We analyze the results of these three systems one by one: *(i)* $C^1H_2 = C^2HC^3HO^4$. In this molecule the preferable sites for electrophilic attack by a nucleophile ($Nu^-$) should be the centers 1 and 3. The results from the STO-3G basis set show that the $s_k^+$ value of center 3 is higher than that of center 1. However, these values at the DZ and DZP basis set levels are higher for center 1 than for center 3. Even the O atom also shows high $s_k^+$ values (may be because of its high electronegativity), although its $s_k^-$ value is higher than the $s_k^+$ value and also the highest of all the centers.

Thus according to the results at the STO-3G basis set, center 3 seems to be a stronger electrophilic ($El^+$) one than center 1. However, at the DZ and DZP basis set levels this trend changes, and center 1 seems to be more electrophilic than center 3. The highest $s_k^-$ value of the O atom shows it to be the strongest nucleophilic center in all three basis sets.

*(ii)* $CH_3C^1H = C^2HC^3HO^4$. From experiment it is known that center 1 and center 3 are the two reactive sites susceptible to be attacked by a nucleophile.[24b] In this case also our observed results show that the $s_k^+$ value of center 3 is higher than that of center 1 at the STO-3G level, although it is reversed at the DZ and DZP level. Thus at the STO-3G level although center 3 is shown to be a stronger electrophile ($El^+$) than center 1, it is reversed at the DZ and DZP levels. The high $s_k^+$ values of the O atom show it to be also an electrophilic center. But as its $s_k^-$ values are higher than its $s_k^+$ values, we can argue that its nucleophilicity is stronger than its electrophilicity.

*(iii)* $C_6H_5C^1H = C^2HC^3HO^4$. This case is somewhat more complicated. Normally in this case centers 1 and 3 should behave as the most reactive electrophilic centers. However, some of the positions on the Ph ring (particularly ortho and para) could also behave as electrophilic centers because the $-C^1H = C^2HC^3HO^4$ side group should act, in principle, as ortho, para directing toward nucleophilic attack on the Ph ring. Interestingly our calculation also shows high $s_k^+$ values for the ortho and para positions, thus exhibiting a highly electrophilic nature of these sites. However, having the highest $s_k^+$ values, center 1 emerges as the most electrophilic center at the DZ and DZP level. The calculated values reflect that STO-3G is really a bad choice for this case, as the O atom has the highest $s_k^+$ value, showing it to be the most electrophilic center in this basis set. Also for center 3 $s_k^- > s_k^+$, which indicates that its nucleophilicity is higher than its electrophilicity for this basis set. These irregularities disappeared with improvement of basis set.

**Case 2.** The systems that are studied in this category are $C_6H_5COCH_3$, $C_6H_5COC_2H_5$, and $C_6H_5COC_6H_5$. We focus on these individual systems one by one.

*(i)* $C_6H_5COCH_3$. The $s_k^+$ value at the STO-3G basis is highest for position 7 (i.e., $C_{carb}$) (see Figure 2), claiming it to be the most electrophilic one. Similarly, the highest $s_k^-$ value for position 8 (i.e., O atom) points to its most nucleophilic nature. Interestingly, at higher basis sets the importance of the ortho and para position of the Ph ring becomes obvious, and at the DZP level the $s_k^+$ value of position 4 (i.e., the para carbon atom) is the highest, suggesting its stongest electrophilic nature. However, the O atom remains the strongest nucleophilic one in all three basis sets.

*(ii)* $C_6H_5COC_2H_5$. In this case also at the STO-3G level the $s_k^+$ and $s_k^-$ values are the highest for $C_{carb}$ (i.e., position 7) and the O atom (i.e., position 8), indicating the most electrophilic and most nucleophilic nature of these two centers, respectively. However, with improvement of the basis set the electrophilicity of the ortho and para positions is enhanced, and at the DZP level the highest $s_k^+$ value of position 4 (i.e., the para carbon atom) reveals it to be the strongest electrophilic center. Comparison of $s_k^+$ and $s_k^-$ values indicates that the O atom is the strongest nucleophilic center (i.e., having the highest $s_k^-$ values) in all three basis sets.

*(iii)* $C_6H_5COC_6H_5$. For this system the observation is similar in all three basis sets. The $s_k^+$ and $s_k^-$ values are the highest for $C_{carb}$ and the O atom, indicating their strongest electrophilic and strongest nucleophilic nature, respectively. However, the ortho and para positions of the two Ph rings also exhibit some electrophilic character. This is quite expected as the C=O group is, in principle, ortho, para directing toward a nucleophilic attack on the Ph ring.

## 4.B. Summary of the Previous Observations and Propositions of New Reactivity Descriptors

From our previous analysis we saw that for simple systems the $s_k^+$ and $s_k^-$ values are the highest for the $C_{carb}$ and the O atom, respectively, indicating their strongest electrophilic and strongest nucleophilic nature, respectively. However, when complexity arises either because of the presence of $\alpha,\beta$ unsaturation (i.e., presence of C=C bond at the $\alpha$ position of the $C_{carb}$) or because a Ph ring can participate in the extended delocalization with the C=O group, some irregularities are observed. In the case of $\alpha,\beta$ unsaturation the $\beta$ position (i.e., position 1) becomes competitive with $C_{carb}$. If we look only at $s_k^+$ values, this feature is observed at the DZ and DZP level in the case of $CH_2{=}CHCHO$, $CH_3CH{=}CHCHO$, and $C_6H_5CH{=}CHCHO$. While it is still accepted with some reservation (as the nature of the attacking nucleophile also influences the 1,2 or 1,4 character of the reaction), serious discrepancies become evident in other cases. The $s_k^+$ values of the O atom are highest at the STO-3G level of $C_6H_5CH{=}CHCHO$ and the DZ level of $C_6H_5COCH_3$ and $C_6H_5COC_2H_5$, revealing it to be the most reactive electrophilic center. Following the same argument para positions of $C_6H_5COCH_3$ and $C_6H_5COC_2H_5$ at the DZP level become the strongest electrophilic center, which might call for some bias when selecting most reactive sites.

However, a careful analysis reveals that the centers that show anomalous high electrophilicity (i.e., have high $s_k^+$ values) in some cases also show high nucleophilicity (having high $s_k^-$ values). This indirectly suggests that for a reliable trend of site reactivity we have to consider both of these two features and have to take some sort of "relative electrophilicity" or "relative nucleophilicity". By "relative electrophilicity" we want to describe the "electrophilicity of any site as compared to its own nucleophilicity". Similarly "relative nucleophilicity" is understood as "the nucleophilicity of any site as compared to its own electrophilicity". This argument seems to be physically realistic, as in most of the addition reactions to carbonyl compounds the attack by a nucleophile ($Nu^-$) is always accompanied by an electrophilic ($El^+$) attack (for a discussion in depth on this subject see ref 24b). So with the simultaneous presence of both $Nu^-$ and $El^+$, the $Nu^-$ fragment of the reactant will prefer to attack that position of the substrate that has the highest "relative electrophilicity". Similarly $El^+$ will attack that position of the substrate having the highest "relative nucleophilicity".

The next question that automatically arises is how to measure this "relative nucleophilicity" or "relative electrophilicity" of a particular site. The first rational choice, which automatically comes to mind, is to take the ratios $s_k^+/s_k^-$ and $s_k^-/s_k^+$ for "relative electrophilicity" and "relative nucleophilicity", respectively. Indeed individual $s_k^+$ (or $s_k^-$) values are strongly influenced by basis set or correlation effects. So far the influence of these two effects on the redistribution of electron densities with the change in number of electrons (i.e., passing from $N_0$ to $N_0 + 1$ and from $N_0$ to $N_0 - 1$, where $N_0$ is the number of electrons of the neutral system) is not clearly known. As an alternative, it may be expected that the ratio of $s_k^+$ and $s_k^-$, involving two differences of electron densities of systems differing by one in their number of electrons at constant nuclear framework, is less sensitive to the basis set and correlation

**TABLE 2: $s_k^+/s_k^-$ and $s_k^-/s_k^+$ Values of the Relevant Atomic Positions of All 12 Compounds Studied**

| carbonyl compound | atomic center | basis sets | | | | | |
|---|---|---|---|---|---|---|---|
| | | STO-3G | | DZ | | DZP | |
| | | $s_k^+/s_k^-$ | $s_k^-/s_k^+$ | $s_k^+/s_k^-$ | $s_k^-/s_k^+$ | $s_k^+/s_k^-$ | $s_k^-/s_k^+$ |
| $CH_3CHO$ | 1 | 2.0099 | 0.4976 | 5.1234 | 0.1952 | 6.6968 | 0.1493 |
| | 2 | 0.7470 | 1.3387 | 0.5276 | 1.8953 | 0.4920 | 2.0324 |
| $CH_3COCH_3$ | 1 | 2.1579 | 0.4634 | 6.6907 | 0.1495 | 8.5097 | 0.1175 |
| | 2 | 0.7083 | 1.4118 | 0.5286 | 1.8919 | 0.4887 | 2.0462 |
| $C_2H_5COC_2H_5$ | 1 | 2.2711 | 0.4403 | 5.6139 | 0.1781 | 7.3431 | 0.1362 |
| | 2 | 0.7023 | 1.4238 | 0.5289 | 1.8908 | 0.4860 | 2.0578 |
| $CH_2FCHO$ | 1 | 2.0382 | 0.4906 | 3.4625 | 0.2888 | 4.2393 | 0.2359 |
| | 2 | 0.7503 | 1.3328 | 0.5562 | 1.7980 | 0.5152 | 1.9410 |
| $CH_2ClCHO$ | 1 | 1.9400 | 0.5155 | 4.0361 | 0.2478 | 5.1003 | 0.1961 |
| | 2 | 0.7157 | 1.3972 | 0.5122 | 1.9526 | 0.4977 | 2.0093 |
| | 4 | 1.0459 | 0.9561 | 0.9686 | 1.0325 | 0.8749 | 1.1430 |
| CH2═CHCHO | 1 | 1.2872 | 0.7769 | 1.5959 | 0.6266 | 1.7389 | 0.5751 |
| | 3 | 1.7131 | 0.5837 | 2.9738 | 0.3363 | 2.5460 | 0.3928 |
| | 4 | 0.6472 | 1.5453 | 0.4798 | 2.0840 | 0.4076 | 2.4535 |
| $CH_3CH{=}CHCHO$ | 2 | 1.3076 | 0.7648 | 1.4624 | 0.6838 | 1.5426 | 0.6483 |
| | 4 | 1.7995 | 0.5557 | 3.8839 | 0.2575 | 3.4962 | 0.2860 |
| | 5 | 0.6363 | 1.5715 | 0.4742 | 2.1090 | 0.4013 | 2.4921 |
| $C_6H_5CH{=}CHCHO$ | 1 | 0.9857 | 1.0146 | 0.9521 | 1.0503 | 0.8723 | 1.1464 |
| | 2 | −38.7361 | −0.0258 | −2.6209 | −0.3815 | −2.7217 | −0.3674 |
| | 3 | 0.5454 | 1.8335 | 3.6277 | 0.2757 | 3.5234 | 0.2838 |
| | 4 | 0.5052 | 1.9796 | 0.3765 | 2.6561 | 0.2960 | 3.3783 |
| | 6 | 1.5046 | 0.6646 | 1.4429 | 0.6930 | 1.4346 | 0.6971 |
| | 8 | 1.7214 | 0.5809 | 1.7918 | 0.5581 | 2.0365 | 0.4910 |
| | 10 | 1.7175 | 0.5823 | 2.2616 | 0.4422 | 2.6127 | 0.3827 |
| $C_6H_5COCH_3$ | 2 | 1.3666 | 0.7318 | 2.2184 | 0.4508 | 2.0515 | 0.4875 |
| | 4 | 1.4925 | 0.6700 | 2.3105 | 0.4328 | 2.7100 | 0.3690 |
| | 6 | 1.5266 | 0.6550 | 1.9363 | 0.5165 | 2.0123 | 0.4970 |
| | 7 | 1.7903 | 0.5586 | 4.1403 | 0.2415 | 3.2845 | 0.3045 |
| | 8 | 0.5380 | 1.8588 | 0.3929 | 2.5450 | 0.3193 | 3.1316 |
| $C_6H_5COC_2H_5$ | 2 | 1.4003 | 0.7141 | 2.2658 | 0.4414 | 2.1184 | 0.4721 |
| | 4 | 1.5173 | 0.6591 | 2.3354 | 0.4282 | 2.7524 | 0.3633 |
| | 6 | 1.5473 | 0.6463 | 1.9450 | 0.5142 | 2.0448 | 0.4891 |
| | 7 | 1.7935 | 0.5576 | 4.2051 | 0.2378 | 3.4074 | 0.2935 |
| | 8 | 0.5341 | 1.8722 | 0.3921 | 2.5504 | 0.3191 | 3.1339 |
| $C_6H_5COC_6H_5$ | 2 | 1.0902 | 0.9173 | 1.8410 | 0.5432 | 1.5954 | 0.6268 |
| | 4 | 1.2417 | 0.8054 | 1.6622 | 0.6016 | 1.7442 | 0.5733 |
| | 6 | 1.4965 | 0.6682 | 1.8133 | 0.5515 | 1.8839 | 0.5308 |
| | 7 | 2.0428 | 0.4895 | 3.6104 | 0.2770 | 3.5678 | 0.2803 |
| | 8 | 0.4821 | 2.0742 | 0.3957 | 2.5275 | 0.3593 | 2.7835 |
| | 10 | 1.0902 | 0.9173 | 1.8410 | 0.5432 | 1.5954 | 0.6268 |
| | 12 | 1.2417 | 0.8054 | 1.6622 | 0.6016 | 1.7442 | 0.5733 |
| | 14 | 1.4965 | 0.6682 | 1.8133 | 0.5515 | 1.8839 | 0.5308 |
| $CH_3CF_2CHO$ | 1 | 2.0335 | 0.4918 | 3.3336 | 0.3000 | 3.9745 | 0.2516 |
| | 2 | 0.7492 | 1.3348 | 0.5615 | 1.7811 | 0.5256 | 1.9027 |

effects. The site having the highest $s_k^+/s_k^-$ is the most probable site to be attacked by a nucleophile ($Nu^-$), and the site having the highest $s_k^-/s_k^+$ ratio is the most probable site to be attacked by an electrophile ($El^+$). So the general scheme to predict the site selectivity should be stated as follows:

(i) Choose only those sites having comparable and higher $s_k^+$ and $s_k^-$ values.

(ii) Then compare the $s_k^+/s_k^-$ and $s_k^-/s_k^+$ values to find out the most probable site as prescribed above.

(iii) If for any site $s_k^+/s_k^- > s_k^-/s_k^+$, then it is the preferred electrophilic site and vice versa.

Following the above scheme, we have evaluated the $s_k^+/s_k^-$ and $s_k^-/s_k^+$ values of the important sites of all 12 compounds studied. The results are presented in Table 2. The values show that with this new scheme the trend has become as expected in almost all cases (i.e., $s_k^+/s_k^-$ value is highest for $C_{carb}$). In the case of α,$\beta$ unsaturated aldehydes also the $s_k^+/s_k^-$ values show that $C_{carb}$ is the strongest electrophilic site. But the relative importance of the $\beta$ positions is also evident from the comparable $s_k^+/s_k^-$ values of those sites. Maybe the local HSAB principle[9] would be helpful to locate the most reactive site for any particular case. Only for $C_6H_5CH{=}CHCHO$ at STO-3G is the result not as expected. But we have already mentioned that STO-3G is really a bad choice for $C_6H_5CH{=}CHCHO$. The $s_k^-/s_k^+$ value of the O atom is the highest in all cases, and all basis sets show it to be the nucleophilic center for the systems studied here.

### 4.C. Local Hardness: A Measure For Intermolecular Reactivity Sequences

From the previous discussions we conclude that $C_{carb}$ is the strongest electrophilic center in the compounds we are studying. Now to compare the intermolecular reactivity sequence (electrophilicity orders) of these compounds, we will focus only on the $C_{carb}$. To do this, we have first arranged them in four homologous series. These series are based on the electronic effects (inductive and resonance) exerted on the C═O group by the groups attached to it. The rationality for this procedure is that for nucleophilic substitution of carbonyl compounds the rate-determining step is usually the one involving nucleophilic attack on $C_{carb}$. The inductive (I) and resonance (R) effects exerted by the groups attached to the $C_{carb}$ should obviously influence the speed of nucleophilic attack on it, which also explains the *experimental* observations.[24b,25]

**TABLE 3: $s_k^+$ Values of $C_{carb}$ of All the Compounds Belonging to the Four Homologous Series (See Text)**

| carbonyl compound | basis set | | |
|---|---|---|---|
| | STO-3G | DZ | DZP |
| $CH_3CHO$ | 0.6088 | 0.9794 | 0.9833 |
| $CH_3COCH_3$ | 0.6112 | 0.7263 | 0.7505 |
| $C_2H_5COC_2H_5$ | 0.6149 | 0.6480 | 0.6792 |
| $CH_2FCHO$ | 0.6092 | 0.9559 | 0.9557 |
| $CH_2ClCHO$ | 0.5852 | 0.9042 | 0.9473 |
| $CH_2{=}CHCHO$ | 0.5220 | 0.5757 | 0.4194 |
| $CH_3CH{=}CHCHO$ | 0.5216 | 0.5694 | 0.4405 |
| $C_6H_5CH{=}CHCHO$ | 0.1512 | 0.2524 | 0.2132 |
| $C_6H_5COCH_3$ | 0.5017 | 0.4235 | 0.3315 |
| $C_6H_5COC_2H_5$ | 0.4963 | 0.4174 | 0.3324 |
| $C_6H_5COC_6H_5$ | 0.5788 | 0.5946 | 0.5508 |

*(i) $CH_3CHO$, $CH_3COCH_3$, and $C_2H_5COC_2H_5$.* Here the reactivity order differs because of the difference of the +I effect of the H, $-CH_3$, and $-C_2H_5$ groups. The larger the +I effect the smaller the electrophilicity of the $C_{carb}$. On that basis the electrophilicity order of the $C_{carb}$ should be

$$CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$$

*(ii) $CH_2ClCHO$ and $CH_2FCHO$.* Here normally the electronegativity of Cl and F should play the deciding role. On that basis the order should be

$$CH_2FCHO > CH_2ClCHO$$

But one of the present authors[26] has shown that in the case of gas-phase acidities of halogenated alcohols and silanols both the electronegativity and polarizability of halogen atoms are to be considered. In the case of Cl-substituted alcohols and silanols, these two effects act in parallel as Cl has high polarizability due to its large size. But in the case of F substitution these two effects compete, as F is small and so is less polarizable and also has small charge capacity. The result is that F-substituted alcohols and silanols are less acidic than the Cl-substituted analogues. Following this argument, we can say that the electrophilicity of $C_{carb}$ should be of the following order:

$$CH_2ClCHO > CH_2FCHO$$

*(iii) $CH_2{=}CHCHO$, $CH_3CH{=}CHCHO$, and $C_6H_5CH{=}CHCHO$.* The common moiety in this series is $-CH{=}CHCHO$. The reactivity difference arises due to the difference in electron-donating tendency of the H, $-CH_3$, and $-C_6H_5$ groups. As this trend is H < $-CH_3$ < $-C_6H_5$, the reactivity order should be

$$CH_2{=}CHCHO > CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO$$

*(iv) $C_6H_5COCH_3$, $C_6H_5COC_2H_5$, and $C_6H_5COC_6H_5$.* This series has the $C_6H_5CO-$ moiety in common. So the electrophilicity difference of the $C_{carb}$ arises because of the difference of electron-donating ability between the $-CH_3$, $-C_2H_5$, and Ph groups. As the +I effect of $-C_2H_5$ is higher than that of the $-CH_3$ group and the +R effect is stronger than the +I effect, the electrophilicity order of $C_{carb}$ should be as follows:

$$C_6H_5COCH_3 > C_6H_5COC_2H_5 > C_6H_5COC_6H_5$$

**TABLE 4: $s_k^+/s_k^-$ Values of $C_{carb}$ of All the Compounds Belonging to the Four Homologous Series (See Text)**

| carbonyl compound | basis sets | | |
|---|---|---|---|
| | STO-3G | DZ | DZP |
| $CH_3CHO$ | 2.0099 | 5.1234 | 6.6968 |
| $CH_3COCH_3$ | 2.1579 | 6.6907 | 8.5097 |
| $C_2H_5COC_2H_5$ | 2.2711 | 5.6139 | 7.3431 |
| $CH_2FCHO$ | 2.0382 | 3.4625 | 4.2393 |
| $CH_2ClCHO$ | 1.9490 | 4.0361 | 5.1003 |
| $CH_2{=}CHCHO$ | 1.7131 | 2.9738 | 2.5460 |
| $CH_3CH{=}CHCHO$ | 1.7995 | 3.8839 | 3.4962 |
| $C_6H_5CH{=}CHCHO$ | 0.5454 | 3.6277 | 3.5234 |
| $C_6H_5COCH_3$ | 1.7903 | 4.1403 | 3.2845 |
| $C_6H_5COC_2H_5$ | 1.7935 | 4.2051 | 3.4074 |
| $C_6H_5COC_6H_5$ | 2.0428 | 3.6104 | 3.5678 |

**TABLE 5: $\eta_D^{TFD}(\bar{r})$ ($\approx -V_{el}/2N$) Values of $C_{carb}$ of All the Compounds Belonging to the Four Homologous Series (See Text)**

| carbonyl compound | basis sets | | |
|---|---|---|---|
| | STO-3G | DZ | DZP |
| $CH_3CHO$ | 0.1086 | 0.1086 | 0.1089 |
| $CH_3COCH_3$ | 0.1078 | 0.1078 | 0.1080 |
| $C_2H_5COC_2H_5$ | 0.0971 | 0.0971 | 0.0973 |
| $CH_2FCHO$ | 0.1017 | 0.1055 | 0.1058 |
| $CH_2ClCHO$ | 0.1200 | 0.1163 | 0.1122 |
| $CH_2{=}CHCHO$ | 0.1044 | 0.1045 | 0.1048 |
| $CH_3CH{=}CHCHO$ | 0.0960 | 0.0963 | 0.0965 |
| $C_6H_5CH{=}CHCHO$ | 0.0736 | 0.0739 | 0.0741 |
| $C_6H_5COCH_3$ | 0.0882 | 0.0884 | 0.0885 |
| $C_6H_5COC_2H_5$ | 0.0867 | 0.0869 | 0.0870 |
| $C_6H_5COC_6H_5$ | 0.0828 | 0.0828 | 0.0830 |

As $CH_3CF_2CHO$ does not fall in any of the four homologous series, we will exclude it from our discussion of intermolecular reactivity sequences.

Now we will analyze our results by comparing the $s_k^+$, $s_k^+/s_k^-$, and local hardness ($\approx -V_{el}/2N$) values of the $C_{carb}$ one by one. The comparison of reactivity descriptors will help us to understand the nature of interaction (charge-controlled or orbital-controlled) between the $C_{carb}$ and the nucleophile ($Nu^-$). In Tables 3 (constructed from Table 1), 4 (constructed from Table 2), and 5 we depict these values. The final outcome by comparing the $s_k^+$ values from Table 3 is as follows.

Series 1: $C_2H_5COC_2H_5 > CH_3COCH_3 > CH_3CHO$ (unexpected) STO-3G

$CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$ (expected) DZ

$CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$ (expected) DZP

Series 2: $CH_2FCHO > CH_2ClCHO$ (unexpected) STO-3G

$CH_2FCHO > CH_2ClCHO$ (unexpected) DZ

$CH_2FCHO > CH_2ClCHO$ (unexpected) DZP

Series 3: $CH_2{=}CHCHO > CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO$ (expected) STO-3G

$CH_2{=}CHCHO > CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO$ (expected) DZ

$CH_3CH{=}CHCHO > CH_2{=}CHCHO > C_6H_5CH{=}CHCHO$ (unexpected) DZP

Series 4: $C_6H_5COC_6H_5 > C_6H_5COCH_3 > C_6H_5COC_2H_5$ (unexpected) STO-3G

$C_6H_5COC_6H_5 > C_6H_5COCH_3 > C_6H_5COC_2H_5$ (unexpected) DZ

$C_6H_5COC_6H_5 > C_6H_5COC_2H_5 > C_6H_5COCH_3$ (unexpected) DZP

Similarly summarizing the $s_k^+/s_k^-$ values (from Table 4) we get the following trends:

Series 1: $C_2H_5COC_2H_5 > CH_3COCH_3 > CH_3CHO$ (unexpected) STO-3G

$CH_3COCH_3 > C_2H_5COC_2H_5 > CH_3CHO$ (unexpected) DZ

$CH_3COCH_3 > C_2H_5COC_2H_5 > CH_3CHO$ (unexpected) DZP

Series 2: $CH_2FCHO > CH_2ClCHO$ (unexpected) STO-3G

$CH_2ClCHO > CH_2FCHO$ (expected) DZ

$CH_2ClCHO > CH_2FCHO$ (expected) DZP

Series 3: $CH_3CH{=}CHCHO > CH_2{=}CHCHO > C_6H_5CH{=}CHCHO$ (unexpected) STO-3G

$CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO > CH_2{=}CHCHO$ (unexpected) DZ

$C_6H_5CH{=}CHCHO > CH_3CH{=}CHCHO > CH_2{=}CHCHO$ (unexpected) DZP

Series 4: $C_6H_5COC_6H_5 > C_6H_5COC_2H_5 > C_6H_5COCH_3$ (unexpected) STO-3G

$C_6H_5COC_2H_5 > C_6H_5COCH_3 > C_6H_5COC_6H_5$ (unexpected) DZ

$C_6H_5COC_6H_5 > C_6H_5COC_2H_5 > C_6H_5COCH_3$ (unexpected) DZP

Our general observation is that there is no clear trend of the electrophilicity of $C_{\text{carb}}$. In four cases $s_k^+$ provides the correct trend, but $s_k^+/s_k^-$ provides a correct trend only in two cases. So neither $s_k^+$ nor $s_k^+/s_k^-$ can be considered as a reliable indicator of the intermolecular electrophilicity trend of $C_{\text{carb}}$. This indirectly suggests that the interaction between the $C_{\text{carb}}$ and the nucleophile ($Nu^-$) may not necessarily be an orbital-controlled (i.e., soft−soft) one. Langenaeker et al.[12] have shown that in the case of electrophilic aromatic substitution local hardness values provide a much better trend than local softness values. So it will be interesting to check the reliability of the local hardness ($\eta_D^{TFD}(\bar{r})$) quantity in predicting intermolecular reactivity order of carbonyl compounds. In Table 5 we have tabulated the $\eta_D^{TFD}(\bar{r})$ ($\approx -V_{el}/2N$) values at three different basis sets. Comparing the $\eta_D^{TFD}(\bar{r})$ values, we get the following trend.

Series 1: $CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$ (expected) STO-3G

$CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$ (expected) DZ

$CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$ (expected) DZ

Series 2: $CH_2ClCHO > CH_2FCHO$ (expected) STO-3G

$CH_2ClCHO > CH_2FCHO$ (expected) DZ

$CH_2ClCHO > CH_2FCHO$ (expected) DZP

Series 3: $CH_2{=}CHCHO > CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO$ (expected) STO-3G

$CH_2{=}CHCHO > CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO$ (expected) DZ

$CH_2{=}CHCHO > CH_3CH{=}CHCHO > C_6H_5CH{=}CHCHO$ (expected) DZP

Series 4: $C_6H_5COCH_3 > C_6H_5COC_2H_5 > C_6H_5COC_6H_5$ (expected) STO-3G

$C_6H_5COCH_3 > C_6H_5COC_2H_5 > C_6H_5COC_6H_5$ (expected) DZ

$C_6H_5COCH_3 > C_6H_5COC_2H_5 > C_6H_5COC_6H_5$ (expected) DZP

Here we get correct trends in all four series in three different basis sets. Thus the present study gives us confidence to conclude that nucleophilic additions to carbonyl compounds are predominantly charge-controlled, and so the local hardness parameter $\eta_D^{TFD}(\bar{r})$ can be used to investigate such types of intermolecular reactivity sequences.

## 5. Conclusion

In this study we have basically tested the usefulness of “local softness” and “local hardness” parameters in predicting intraand intermolecular reactivity sequences of carbonyl compounds. We have found that "relative electrophilicity" (defined as $s_k^+/s_k^-$) and "relative nucleophilicity" (defined as $s_k^-/s_k^+$) provide the correct intramolecular reactivity trends which are not always attainable by comparing only $s_k^+$ or $s_k^-$ values. This is really interesting, as other known reactivity descriptors, e.g. MEP, show poor predictive power in the case of nucleophilic attack.[27]

It is also evident from our observation that in complicated cases, e.g. systems having α,$\beta$ unsaturation (i.e., C═C bond) or a Ph group, which can participate in extended delocalization of the $+\delta$ charge on $C_{\text{carb}}$, more than one site may have comparable $s_k^+/s_k^-$ values. This suggests that although only one site is dominant in electrophilicity, other sites also become important in favored conditions. This is not surprising, as experimental findings suggest the existence of side products obtained by addition on position 1 and 3 in $C^1H_2{=}C^2HC^3HO$ and $CH_3C^1H{=}C^2HC^3HO^4$. The relevance of a local HSAB principle to find out the most preferable attacking sites, in cases where more than one site of comparable $s_k^+/s_k^-$ values exist, has also been pointed out.

For comparison of intermolecular electrophilicity of $C_{\text{carb}}$, local hardness ($\eta_D^{\text{TFD}}(\bar{r})$) is found to be more reliable, at least in the case of a homologous series.

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## References and Notes

(1) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.

(2) (a) *Chemical Hardness* (Structure and Bonding *80*); Sen, K. D., Ed.; Springer-Verlag: Berlin, Heidelberg, 1993. (b) *Acc. Chem. Res.* **1993**, *26*, contributions by Pearson, R. G.; Parr, R. G.; Zhou, Z. (c) Geerlings, P.; De Proft, F.; Martin, J. M. L. in *Recent Developments and Applications of Modern Density Functional Theory* (Theoretical and Computational Chemistry, Vol. 4, pp 773−809); Seminario, J. M., Ed.; Elsevier: New York, 1996. (d) Baeten, A.; Maes, D.; Geerlings, P. *J. Theor. Biol.*, submitted for publication.

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

(4) Parr, R. G.; Chattaraj, P. K. *J. Am. Chem. Soc.* **1991**, *113*, 1854.

(5) Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049.

(6) (a) Ghosh, S. K.; Berkowitz, M. *J. Chem. Phys.* **1985**, *83*, 2976. (b) Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6723. Berkowitz, M.; Parr, R. G. *J. Chem. Phys.* **1988**, *88*, 2554.

(7) Krishnamurti, S. M.; Roy, R. K.; Vetrivel, R.; Iwata, S.; Pal, S. *J. Phys. Chem.* **1997**, *101*, 7253.

(8) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York; Clarendon Press: Oxford, 1989.

(9) Gázquez, J. L.; Méndez, F. *J. Phys. Chem.* **1994**, *98*, 4591.

(10) (a)De Proft, F.; Langenaeker, W.; Geerlings, P. *J. Phys. Chem.* **1993**, *97*, 1826. (b) Langenaeker, W.; Coussement, N.; De Proft, F.; Geerlings, P. *J. Phys. Chem.* **1994**, *98*, 3010. (c) De Proft, F.; Amira, S.; Choho, K.; Geerlings, P. *J. Phys. Chem.* **1994**, *98*, 5227. (d) De Proft, F.; Langenaeker, W.; Geerlings, P. *Int. J. Quantum Chem.* **1995**, *55*, 459. (e) De Proft, F.; Langenaeker, W.; Geerlings, P. *Tetrahedron* **1995**, *51*, 4021. (f) Baeten, A.; De Proft, F.; Geerlings, P. *Chem. Phys. Lett.* **1995**, *235*, 17.

(11) (a) Ghosh, S. K. *Chem. Phys. Lett.* **1990**, *172*, 77. (b) Harbola, M. K.; Chattaraj, P. K.; Parr, R. G. *Isr. J. Chem.* **1991**, *31*, 395.

(12) Langenaeker, W.; De Proft, F.; Geerlings, P. *J. Phys. Chem.* **1995**, *99*, 6424.

(13) Parr, R. G.; Donnelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys*, **1978**, *68*, 3801.

(14) Iczkowski, R. P.; Margrave, J. L. *J. Am. Chem. Soc.* **1961**, *83*, 3547.

(15) Nalewajski, R. F.; Parr, R. G. *J. Chem. Phys.* **1982**, *77*, 399.

(16) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.

(17) Bonaccorsi, R.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1970**, *52*, 5270.

(18) Unichem, Cray Research Inc., Eagon, MN, 1994.

(19) Huzinaga, S. *J. Chem. Phys*, **1965**, *42*, 1293.; Dunning, T. H. *J. Chem. Phys.* **1970**, *53*, 2823.

(20) Frish, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V..; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision B. 3*; Gaussian Inc.: Pittsburgh, PA, 1995.

(21) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley: New York, 1986.

(22) (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968,** 2199. (c) Cherest, M.; Felkin, H.; Tacheau, P.; Jacques, J.; Varech, D. *J. Chem. Soc., Chem. Commun.* **1977**, 372. (d) Anh, N. T. *Regio- and Stereo-Selectivities in Some Nucleophilic Reactions: Top. Curr. Chem.* **1980**, *88*, 145.

(23) (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563. (b) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (c) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956.

(24) (a) Patai, S.; Rappoport, Z. In *The Chemistry of Alkenes*; Interscience Publishers: London, **1964**, p 469. Wong, S. S.; Paddon-Row: M. N.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 8679. Langenaeker, W.; Demel, K.; Geerlings, P. *J. Mol. Struct. (THEOCHEM)* **1992**, *259*, 317. Dorigo, A. E.; Morokuma, K. *J. Am Chem. Soc.* **1989**, *111*, 6524. (b) Negishi, E. *Organometallics in Organic Synthesis*, Vol. 1; Wiley: New York, 1980, pp 127−133. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, 1992; p 881.

(25) Schaefer, H. F. In Rappoport, Ed. *The Chemistry of the Cyano Group*; Wiley: New York, 1970; pp 239−305.

(26) Damoun, S.; Langenaeker, W.; Van de Woude, G.; Geerlings, P. *J. Phys. Chem.* **1995**, *99*, 12151.

(27) Sjoberg, P.; Politzer, P. *J. Phys. Chem.* **1990**, *94*, 3959.