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Acetalization and Thioacetalization of Cabonyl Compounds: A Case Study Based on Global and Local Electrophilicity Descriptors

RAM KINKAR ROY,[1] V. USHA,[1] BHISMA K. PATEL,[2] KIMIHIKO HIRAO[3]

[1]*Department of Chemistry, Birla Institute of Technology and Science (BITS), Pilani, 333 031 Rajasthan, India*
[2]*Department of Chemistry, Indian Institute of Technology, Guwahati-781 039, India*
[3]*Department of Applied Chemistry, School of Engineering, The University of Tokyo, Tokyo 113-8656, Japan*

Abstract: Acetalization of benzaldehyde and substituted benzaldehydes (containing both electron-donating and electron-withdrawing groups) is explained qualitatively on the basis of global electrophilicity descriptor, *w*, as proposed by Parr and coworkers (J Am Chem Soc 1999, 121, 1922). The generated values of *w* can explain qualitatively the preferential electrophilic addition, and hence, the yield of acetalization obtained in an earlier experimental study carried by Patel and coworkers (J Org Chem 2002, 67, 5842). The present study also reveals that although both steric and electronic factors affect the yield, only later can be taken care of by *w*. In the case of a competitive formation of cyclic acetals and cyclic thioacetals from a reaction mixture containing *p*-hydroxybenzaldehyde, *p*-nitrobenzaldehyde, 1,2-ethanediol (i.e., glycol), and 1,2-ethanedithiol, the relative experimental yields (Org Biomol Chem 2004, 2, 1670) could be explained from the difference of the global electrophilicity values between aldehydes and acetalizing agents in the same line of arguments of Maynard et al. (Proc Natl Acad Sci USA 1998, 95, 11578).

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Introduction

In the last 2 decades several global and local reactivity descriptors were proposed,[1–8] the foundation of which is conceptual density functional theory (DFT).[9,10] Recently, a new addition to this is the global electrophilicity proposed by Parr et al.[11] as:

$$w = \frac{\mu^2}{2\eta} \tag{1}$$

Here, *w* is considered to be the electrophilic power of the concerned chemical species, and bears the conceptual similarity to power of classical electricity (i.e.,

$$\text{Power} = \frac{V^2}{R}$$

of classical electricity, where *V* and *R* represent the potential difference and resistance, respectively). In eq. (1), μ is the "chem-ical potential" and η is "global chemical hardness" of the concerned chemical species. It should be mentioned here that the above definition of *w* originated from a qualitative suggestion of Maynard et al.[12] There are subsequent efforts to extend the global electrophilicity indices to its local counterpart, so that these new descriptors can be used to explain both intra- and intermolecular reactivity trends.[13,14] However, recently, Roy and his collaborators have shown in two consecutive articles that in the case of intramolecular reactivity trends these new descriptors will not provide any extra information than what is obtained from Fukui function indi-

ces.[15] Also, in the case of intermolecular reactivity these descriptors will be useful only in specific cases.[16]

The present study is a theoretical investigation of the relative yields of acetals formed from benzaldehyde and substituted benzaldehydes. The substituted groups are of both types, that is, electron donating and electron withdrawing. Recently, one of the present authors (B.K.P.) and his coworkers have shown that when PhCHO (i.e., benzaldehyde) and different substituted benzaldehydes (with substituted groups as —OMe, —NO$_2$, —OH, and —Cl in different positions of the Ph-ring) undergo acetalization, yields vary depending upon the types and positions of substitutions.[17] The reactions were carried out at room temperature using tetrabutylammonium tribromide (TBATB) as a promoter in the presence of triethyl (and also trimethyl) orthoformate in absolute alcohol. After analyzing the factors, which affect the yields, the authors concluded that between electronic and steric, it is the former that plays the dominant role.

To verify whether the electronic factors really play the major role in determining the yield of acetalization we have used global electrophilicity descriptor w as well as local softness s_k^+ (which indicates the electrophilic power of atom k in the molecule) of C$_{CHO}$ (i.e., C-atom of the —CHO group). This is because we are comparing the intermolecular trend of acetalization, which is obtained by the attack of Nu$^-$ (i.e., of the alcohol R′OH; see ref. 17 for probable reaction mechanism) on C$_{CHO}$. In a previous study Roy et al.[16] have shown that, for systems having more than one reactive sites of comparable strength, local reactivity descriptors cannot be used as reliable indicators of global reactivity trends. The systems chosen in the present study have more than one comparatively strong reactive sites (different Ph-ring carbon atoms). Thus, the electron-withdrawing or -releasing effects (by the substituted groups) are somewhat stabilized by the intervening Ph-ring carbon atoms, before these effects are felt by the C$_{CHO}$. Under such circumstances it looks to be more physical to compare values of w rather than the s_k^+-values of C$_{CHO}$ to explain the yield of acetalization.

The second part of the present study deals with the competitive formation of cyclic acetals and thioacetals. Very recently, in a separate article, Patel and coworkers[18] have shown that *p*-hydroxybenzaldehyde undergoes cyclic thioacetalization, whereas *p*-nitrobenzaldehyde to cyclic acetalization almost exclusively in a reaction mixture containing 1,2-ethanediol (i.e., glycol), 1,2-ethanedithiol and the above two substituted benzaldehydes. Here, it is obvious that the reaction occurs in a competitive environment, where the type of product and also its quantity apparently vary because of the variation of local electrophilicity of C$_{CHO}$ of the substrates (i.e., the aldehydes) and of the local nucleophilicity of the O$_{OH}$ and S$_{SH}$ of the reactants (i.e., 1,2-ethanediol and 1,2-ethanedithiol). But as both *p*-nitrobenzaldehyde and *p*-hydroxybenzaldehyde have more than one electrophilic center of comparative strength apart from C$_{CHO}$ (i.e., different Ph-ring C-atoms, because of the reason discussed in the previous paragraph), the global electrophilicity values (i.e., w) of these compounds will be more reliable than s_k^+- values of C$_{CHO}$ in explaining competitive cyclic acetalization and thioacetalization products. Also because of the analytical relation $s(\bar{r}) = Sf(\bar{r})$ [where S is the global softness and $f(\bar{r})$ is the Fukui function indices), it is obvious that $s(\bar{r})$ decreases for systems having large size (owing to the fact that

Fukui function normalizes to unity) even though the systems have a comparable band gap (i.e., equal global softness when evaluated using the working equation

$$S = \frac{1}{2\eta} = \frac{1}{\text{LUMO} - \text{HOMO}}.$$

From the condensed form definition of local softness (i.e., s_k^α, see next section) it means that if two systems have comparable *S*-values the system in which number of atoms are more s^α will, in general, have lower values because f_k^α-values will be summed over to unity. Thus, we will compare the w values of the above two substituted aldehydes along with the w values of 1,2-ethanediol and 1,2-ethanedithiol for the said purpose.

The article is organized as follows: a brief theoretical background of DFT-based global and local reactivity indices are described in the next section. The chosen chemical systems, and based on these systems the adopted computational techniques, are then discussed. Then the results and their critical analysis are shown. The variation of the yield of acetalization with the types and positions of substitution is discussed in details in a subsection of Results and Discussion. In another subsection we have done a critical analysis on higher value of w for *p*-(NO$_2$)C$_6$H$_4$CHO than that for *o*-(NO$_2$)C$_6$H$_4$CHO. The competitive acetalization and thioacetalization is analyzed in another subsection. Finally, in the concluding section the overall study is summarized and probable ways of improving the present investigation are pointed out.

Global Reactivity Descriptors

In the equation of global electrophilicity the analytical and operational definitions of μ and η are given as follows:[1]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\bar{r})} \cong -\frac{(IP + EA)}{2} \tag{2}$$

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\bar{r})} \cong \frac{(IP - EA)}{2}. \tag{3}$$

The notations *IP*, *EA*, and $v(\bar{r})$, used in eqs.(2) and (3), represent the first vertical ionization potential, first vertical electron affinity, and the external potential (i.e., the potential due to the positions of the nuclei plus applied external field, if any) at position $(\bar{r})$, respectively. Inverse of η is known as global softness "S" and is represented as:

$$S = \frac{1}{2\eta} \cong \frac{1}{(IP - EA)}. \tag{4}$$

Local Reactivity Descriptors

The local (or site) reactivity (selectivity) of a chemical species is represented by local reactivity descriptors. One such descriptor is the Fukui function index and is defined as follows:[4]

$$f(\overline{r}) = \left(\frac{\partial \rho(\overline{r})}{\partial N}\right)_{\nu(\overline{r})} = \left(\frac{\partial \mu}{\partial \nu(\overline{r})}\right)_{N}. \quad (5)$$

Here, N and $\rho(\overline{r})$ represent, respectively, the number of electrons and the electron density at position $(\overline{r})$, of the chemical species. It is thus named because of its conceptual similarity with Fukui's frontier molecular orbital theory.[19] After taking care of the discontinuities in the $f(\overline{r})$ vs. N plot the "condensed to atom" approximations of $f(\overline{r})$, when multiplied by global softness (S), provide three local softness values represented by:[5]

$$s_k^+(\overline{r}) = [p_k(N+1) - p_k(N)]S = f_k^+ S \quad (6a)$$

$$s_k^-(\overline{r}) = [p_k(N) - p_k(N-1)]S = f_k^- S \quad (6b)$$

$$s_k^0(\overline{r}) = \frac{1}{2}[p_k(N+1) - p_k(N-1)]S = f_k^0 S. \quad (6c)$$

Here, in eqs. 6(a)–(c), $p_k(N)$, $p_k(N+1)$, and $p_k(N-1)$, represent the condensed electronic populations on atom k for neutral, anionic, and cationic systems, respectively. So, s_k^+, s_k^-, and s_k^0 represent the condensed local softness values of atom k towards nucleophilic, electrophilic, and radical attack on it, respectively. We could come to eqs. 6(a)–(c) because of following analytical relations:

$$s(\overline{r}) = \left(\frac{\partial \rho(\overline{r})}{\partial \mu}\right)_{\nu(\overline{r})} = \left(\frac{\partial \rho(\overline{r})}{\partial N}\right)_{\nu(\overline{r})}\left(\frac{\partial N}{\partial \mu}\right)_{\nu(\overline{r})} = f(\overline{r})S. \quad (7)$$

Equations 6(a)–(c) can be represented by a generalized expression as follows:

$$S_k^\alpha = f_k^\alpha S. \quad (8)$$

Here, α is $+$, $-$, and 0.

Computational Details

To investigate the effect of the substituted groups on the yield of acetalization we have chosen 10 chemical systems. These are a few of the 17 systems used by Patel and coworkers in their experimental study.[17] The systems are C_6H_5CHO, p-(OMeC$_6$HCHO, o-(NO$_2$)C$_6$H$_4$CHO, p-(NO$_2$)C$_6$H$_4$CHO, p-(Cl)C$_6$H$_4$CHO, o-(OH)C$_6$H$_4$CHOc6h, m-(OH)C$_6$HCHO, p-(OH)C$_6$H$_4$CHO, 4-(OH)-3-(OMe)C$_6$H$_3$CHO, and 2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO. As our purpose in the present study is to explain qualitatively the variation of yield, the 10 systems have been subdivided in different groups. A particular system has been appeared in more than one group (see Results and Discussion) to make the effect of substitution on the yield of acetalization more clear and obvious.

To explain the competitive formation of cyclic acetals and cyclic thioacetals we have chosen four chemical systems as were used by Patel and coworkers.[18] These are p-(NO$_2$)C$_6$H$_4$CHO, p-(OH)C$_6$H$_4$CHO, CH$_2$(OH)—CH$_2$(OH) (1,2-ethanediol, i.e., glycol) and CH$_2$(SH)—CH$_2$(SH) (1,2-ethanedithiol).

The geometries were initially optimized at the semiempirical level using CHEM-3D program system (1986–1999 Cambridge-Soft Corporation) followed by reoptimization at the RHF/6-31G(D,P) level using Gaussian-98.[20] Also, the geometries are reoptimized at BLYP/dnp level using DMOL^3 program package (DMol^3, Version 970818, Accelrys, San Diego, CA). The "dnp" level basis set is of double-numeric quality (i.e., approximately two atomic orbitals for each one occupied in the free atom) augmented with polarization functions (i.e., functions with angular momentum one higher than that of the highest occupied orbital in the free atom). The "dnp" basis set is as included in DMOL^3 program package.

The global electrophilicity values were evaluated using eq. (1), and the operational forms of μ and η are as in eqs. (2) and (3), respectively. The local softness values of the individual atoms (i.e., s_k^α) are computed through eqs. (6a) and (6b), in which "S" comes from eq. (4). The charge values were evaluated by Hirshfeld population analysis (HPA)[21] using the DMOL^3 program and by Mulliken Population analysis (MPA)[22] using the Gaussian program. Conceptual advantage of HPA over that of MPA is discussed in details in refs. 23–27. To enhance the reliability, the MPA-based charges are evaluated using a new technique adopted by Roy.[24] In this new technique the charges on the H-atoms are summed on the heavy atoms (i.e., C-, O-, and S-atoms here) to which they are bonded. The charges evaluated in this way are found to be more reliable than the normal "condensed-to-individual atom" way.[5]

Results and Discussion

Explanation of the Yield of Acetalization

The experimental yield of acetalization of the 10 systems is given in Table 1. To make the comparison more systematic the 10 systems are divided in the following subgroups:

(i) C_6H_5CHO, p-(OMe)C$_6$H$_4$CHO, p-(Cl)C$_6$H$_4$CHO

(ii) C_6H_5CHO, o-(NO$_2$)C$_6$H$_4$CHO, p-(NO$_2$)C$_6$H$_4$CHO

(iii) C_6H_5CHO, o-(OH)C$_6$H$_4$CHO, m-(OH)C$_6$H$_4$CHO,

$$p-(OH)C_6H_4CHO$$

(iv) C_6H_5CHO, 4−(OH)−3−(OMe)C$_6$H$_3$CHO,

$$2-(Cl)-6-(NO_2)C_6H_3CHO$$

It should be mentioned here that apart from comparison among the members within a group, there are always the scope of cross-comparison (i.e., between systems that belong to different groups). Let us now go for group-wise comparison.

Group (i)

From Table 1 we see that the yield of acetalization varies in the order:

Table 1. Acetalization[a] of Benzaldehyde and Substituted Benzaldehydes.[b]

Serial No.	Aldehydes	Time (hs)	Percentage of yields	
			X_1[c,d]	X_2[c,d]
1	C_6H_5CHO	0.16	97	95
2	p—$(OMe)C_6H_4CHO$	0.33	80	80
3	o—$(NO_2)C_6H_4CHO$	2.50	95	90
4	p—$(NO_2)C_6H_4CHO$	0.50	95	92
5	p—$(Cl)C_6H_4CHO$	0.16	94	95
6	o—$(OH)C_6H_4CHO$	24.0	00	00
7	m—$(OH)C_6H_4CHO$	2.0	62	70
8	p—$(OH)C_6H_4CHO$	2.0	25	35
9	4—(OH)—3—$(OMe)C_6H_3CHO$	0.50	60	60
10	2—(Cl)—6—$(NO_2)C_6H_3CHO$	3.50	85	60

[a]Reactions were monitored by TLC/GC. X_1 = dimethyl acetals; X_2 = diethyl acetals.
[b]Taken from ref. 17.
[c]Confirmed by comparison with IR and ^{1}H-NMR of the authentic sample.
[d]Isolated yields.

$$C_6H_5CHO > p-(Cl)C_6H_4CHO > p-(OMe)C_6H_4CHO$$

The difference in yields of C_6H_5CHO and p-$(Cl)C_6H_4CHO$ is negligible when the product is dimethyl acetal but same when the product is diethyl acetal. If we consider the $+R$ and $-I$ effect of the —Cl group (of which $-I$ effect is the dominant one) and that of the $+R$ effect of the —OMe group, then we agree with Patel and coworkers that electron-withdrawing groups increase the yield of acetalization, whereas the electron donating groups decrease it. From Table 2 it is obvious that s_k^+ values of C_{CHO} are unable to reproduce the experimental trend (in both MPA/6-31G(D,P) and HPA/dnp methods). However, the values of w (Table 3) could

generate the expected trend (except that the w-value of p-$(Cl)C_6H_4CHO$ is higher than that of C_6H_5CHO, which is justified when we consider the fact that in the former there is one strong electron withdrawing group, that is, —Cl).

Group (ii)

Because there is an electron-withdrawing group (i.e., —NO_2) in each of o-$(NO_2)C_6H_4CHO$ and p-$(NO_2)C_6H_4CHO$, we expect the electrophilicity of these two systems to be higher than that of C_6H_5CHO. However, the s_k^+ values of C_{CHO} (see Table 2) indicate the totally opposite trend. It is encouraging that the electrophilicity trend generated by w is as expected in both the methods (Table 3). The arguments in favor of a higher value of w for p-$(NO_2)C_6H_4CHO$ than that of o-$(NO_2)C_6H_4CHO$ are elaborated later. It is worth mentioning here that although the numerical values differ by a very small amount (varying in the second decimal point), they are not negligible when we consider the fact that the values are in atomic units and 1 a.u. = 27.2114 eV.

Now, if we assume that only the electronic factor plays the dominant role in determining the reactivity then we would expect the yield of acetalization to be as per the following trend:

$$C_6H_5CHO < o-(NO_2)C_6H_4CHO \approx p-(NO_2)C_6H_4CHO$$

But from Table 1 we see that the yields of acetalization are almost same. This is possible only if we assume that the favorable condition generated by the electron-withdrawing effect of the —NO_2 group is nullified by the steric hindrance exerted by the same group to the approaching nucleophile (i.e., the alcohol, R′OH) and in the subsequent steps (see ref. 17 for a probable mechanism).

Group (iii)

The values of the yield of acetalization from Table 1 clearly show that it is highest in C_6H_5CHO and zero (i.e., negligible) in

Table 2. MPA- and HPA-Based s_k^+ Values of C_{CHO} (i.e., Carbon Atom of the —CHO Group) of the Aldehydes Chosen in the Present Study.

Aldehydes	Atomic centers	Methods	
		MPA/6–31G(D,P) s_k^+	HPA/dnp s_k^+
1	C_{CHO}	0.6885	0.3528
2	C_{CHO}	0.7623	0.3420
3	C_{CHO}	0.2210	0.2516
4	C_{CHO}	0.2696	0.2934
5	C_{CHO}	0.6170	0.3398
6	C_{CHO}	0.6325	0.3381
7	C_{CHO}	0.7523	0.3595
8	C_{CHO}	0.7988	0.3242
9	C_{CHO}	0.8003	0.3333
10	C_{CHO}	0.0330	0.1833

The values are in atomic units. The numbers (1, 2, 3, etc.) in the first column denote the aldehydes (see Table 1).

Table 3. MPA- and HPA-Based Global Electrophilicity (i.e., W) Values of the Aldehydes Chosen in the Present Study.

Aldehydes	Atomic centers	Methods	
		MPA/6–31G(D,P) W	HPA/dnp W
1	C_{CHO}	0.0427	0.0799
2	C_{CHO}	0.0360	0.0675
3	C_{CHO}	0.0691	0.1173
4	C_{CHO}	0.0808	0.1212
5	C_{CHO}	0.0506	0.0875
6	C_{CHO}	0.0367	0.0721
7	C_{CHO}	0.0401	0.0749
8	C_{CHO}	0.0347	0.0698
9	C_{CHO}	0.0347	0.0676
10	C_{CHO}	0.0814	0.1140

The values are in atomic units. The numbers (1, 2, 3, etc.) in the first column denote the aldehydes (see Table 1).

p-(OH)C$_6$H$_4$CHO. Patel and coworkers[17] have explained that the electron-donating effect of the —OH group is the cause for poor yield of the —OH substituted benzaldehydes, as this disfavors the nucleophilic attack on the C$_{CHO}$ by the nucleophile (i.e., the R′OH). Although the zero yield of acetalization in the case of *o*-(OH)C$_6$H$_4$CHO cannot be explained on the basis of reactivity descriptors only, at least the qualitative trend should be generated by these values. However, from Table 2 we see that the trend generated by s_k^+ values of C$_{CHO}$ is not regular. In the MPA/6-31G(D, P) method *m*-(OH)C$_6$H$_4$CHO and *p*-(OH)C$_6$H$_4$CHO have higher s_k^+ values, which is opposite to our expectation. The s_k^+ values of C$_{CHO}$ in the HPA/dnp method is somewhat as expected, but here also the highest value is for *m*-(OH)C$_6$H$_4$CHO.

When we try to explain yields of acetalization on the basis of *w*-values, these are found to be as expected. In both the methods the *w*-values are highest for C$_6$H$_5$CHO and lowest in *p*-(OH)C$_6$H$_4$CHO. The highest value of *w* for *m*-(OH)C$_6$H$_4$CHO (among the three —OH substituted benzaldehydes) is probably because of the fact that the —OH group in the *m*- position cannot exert + *R* effect as effectively as the *o*- or *p*-substituted isomers. Overall, it can be concluded that according to the global electrophilicity (i.e., *w*) values the highest yield of acetalization should be of C$_6$H$_5$CHO and the second highest is of *m*-(OH)C$_6$H$_4$CHO. This is also similar to what is observed experimentally. The zero yield of acetalization in case of *o*-(OH)C$_6$H$_4$CHO cannot be explained only on the basis of *w* or s_k^+ (of C$_{CHO}$) values. Maybe some other phenomena play important role here. For example, the intramolecular H-bonding between C$_{CHO}$ and the *ortho*-OH group, thus forming a ring structure (i.e., steric hindrance), prevents the nucleophile (i.e., the R′OH) to approach to C$_{CHO}$.

Group (iv)

If we consider only the electron-withdrawing or electron-donating effects of the substituted groups then the highest and the lowest yield of acetalization should be of 2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO and 4-(OH)-3-(OMe)C$_6$H$_3$CHO, respectively. But the experimental yield is highest for C$_6$H$_5$CHO (not as expected only on the basis of electronic factor) and lowest for 4-(OH)-3-(OMe)C$_6$H$_3$CHO (as expected). The lower yield of acetalization of 2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO than that of C$_6$H$_5$CHO, despite the fact that the former has two strong electron-withdrawing groups, may be due to the steric hindrance caused by two bulky groups (in *ortho* positions of the —CHO group) to the approaching nucleophile (i.e., the R′OH).

Now when we analyze the s_k^+ values (of C$_{CHO}$) from Table 2, we found that these values do not reproduce the expected yield of acetalization. In the case of the MPA/6-31G(D,P) method the s_k^+ value (of C$_{CHO}$) is much higher for 4-(OH)-3-(OMe)C$_6$H$_3$CHO and very low for 2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO, none of which is acceptable. Although the s_k^+ value for 4-(OH)-3-(OMe)C$_6$H$_3$CHO is lower than C$_6$H$_5$CHO in the HPA/dnp method, the lowest value for 2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO is again not acceptable. However, we are encouraged to see that the generated values of *w* (Table 3) are as expected in both the methods. Thus, the trend generated by the values of *w* (in both the methods) is as follows:

2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO > C$_6$H$_5$CHO > 4-(OH)-3-(OMe) C$_6$H$_3$CHO

As argued in the previous paragraph, the probable reason of the lower yield of acetalization of 2-(Cl)-6-(NO$_2$)C$_6$H$_3$CHO than that of C$_6$H$_5$CHO, is the steric effect caused by two bulky substituents in the *ortho*-positions of the —CHO group.

Analysis of the Higher *w*-Value for *p*-(NO$_2$) C$_6$H$_3$CHO Than That for *o*-(NO$_2$)C$_6$H$_4$CHO

We see from eq. (1) that the working formula of *w* is:

$$w = \frac{\mu^2}{2\eta}.$$

By further expanding μ and η in terms of ionization potential (*IP*) and electron affinity (*EA*) we can rewrite eq. (1) as follows:

$$w = \frac{\mu^2}{2\eta} = \frac{\left[\dfrac{-(IP + EA)}{2}\right]^2}{2\left(\dfrac{IP - EA}{2}\right)} = \frac{(IP + EA)^2}{4(IP - EA)}. \tag{9}$$

Now for any chemical system we can further rewrite eq. (9) in terms of the energies of the neutral (i.e., E_N), the anionic (i.e., E_N^-), and the cationic (i.e., E_N^+) species as:

$$w = \frac{(IP + EA)^2}{4(IP - EA)} = \frac{[(E_{N^+} - E_N) + (E_N - E_{N^-})]^2}{4[(E_{N^+} - E_N) - (E_N - E_{N^-})]}$$

$$= \frac{(E_{N^+} - E_{N^-})^2}{4(E_{N^+} + E_{N^-} - 2E_N)}. \tag{10}$$

From the right-hand side of eq. (10) it is obvious that between two systems A and B, the value of *w* will be more positive for that one in which (a) the numerator is higher in value. This is possible when E_N^- is a more negative valued quantity, which means that the corresponding anion is more stable. (b) The denominator is positive but numerically lower in value. Now, to be positive the condition is $-2E_N > E_N^+ + E_{N^-}$, as all E_N, E_N^+, and E_N^- are negative valued quantities.

Keeping in mind the first criteria, that is, E_N^- is a more negative valued quantity than the corresponding E_N^+, and the second criteria, that is, $-2E_N > E_N^+ + E_{N^-}$, we see from Table 4 that the corresponding E_N value is more negative for *p*-(NO$_2$)C$_6$H$_4$CHO than that of *o*-(NO$_2$)C$_6$H$_4$CHO. The physical meaning is that *p*-(NO$_2$)C$_6$H$_4$CHO is more stable than *o*-(NO$_2$)C$_6$H$_4$CHO, which is justified when we consider the steric effect caused by bulky *ortho* —NO$_2$ group on —CHO in the later one. Similarly, the more negative E_N^- value of *p*-(NO$_2$)C$_6$H$_4$CHO indicates that the delocalization of the negative charge is energetically more favorable when the —NO$_2$ group is in the *p*-position than when it is in the *o*-position (which is again justified from structure-stability criteria). These are the reasons why the global electrophilicity value (*w*) is higher in the case of *p*-(NO$_2$)C$_6$H$_4$CHO.

Table 4. Energy Values of Neutral (i.e., E_N), Cationic (i.e., E_{N^+}) and Anionic (i.e., E_{N^-}) species of p—$NO_2C_6H_4CHO$ and o—$NO_2C_6H_4CHO$ in Both MPA/6–31G(D,P) and HPA/dnp Methods.

	Methods					
	MPA/6–31G(D,P)			HPA/dnp		
Chemical systems	E_N	E_{N^+}	E_{N^-}	E_N	E_{N^+}	E_{N^-}
o—$NO_2C_6H_4CHO$	−546.90173	−546.57058	−546.88204	−550.16765	−549.81655	−550.20204
p—$NO_2C_6H_4CHO$	−546.91009	−546.56446	−546.90241	−550.17563	−549.82160	−550.21323

The values are in atomic units.

Competitive Acetalization and Thioacetalization

In a separate study Patel and coworkers[18] have shown that when equimolar mixtures of p-$(NO_2)C_6H_4CHO$ and p-$(OH)C_6H_4CHO$ are subjected to competitive reaction with a mixture of p-$(NO_2)C_6H_4CHO$ and p-$(OH)C_6H_5CHO$ (1 equiv.), 1,2-ethanediol (4 equiv.), triethylorthoformate, and TBATB (0.01 equiv.) in THF, almost complete (97%) cyclic thioacetalization, that is, 1,3-dithiolane formation occurs with p-$(OH)C_6H_4CHO$, whereas, p-$(NO_2)C_6H_4CHO$ was cyclic acetalized (i.e., form 1,3-dioxalane) to 80%. As discussed in the introductory section, we have used the global electrophilicity values (i.e., w) to explain the above reaction. In Table 5 the values of w are shown. Here we see that the values are highest for p-$(NO_2)C_6H_4CHO$ and lowest for 1,2-ethanediol (i.e., $CHOH$—CH_2OH) in both the methods. It is a rational argument (in conceptual physical-organic chemistry) that a substrate of high electrophilicity will react more effectively with a reactant of low electrophilicity (i.e., of high nucleophilicity), which has also been pointed out by Maynard et al.[12] Thus, when both CH_2OH—CH_2OH and CH_2SH—CH_2SH (i.e., 1,2-ethanedithiol) are used as reactants, p-$(NO_2)C_6H_4CHO$ will prefer to react with the former than the later. For the same reason p-$(OH)C_6H_4CHO$ will react more effectively with CH_2SH—CH_2SH. This is exactly what was observed by Patel and coworkers[18] in their experimental study.

Table 5. MPA- and HPA-Based Global Electrophilicity (i.e., w) Values of the Chemical Systems Relevant for Comparison of Competitive Acetalization in the Present Study (See Text).

	Methods	
	MPA/6–31G(D,P)	HPA/dnp
Chemical systems	w	w
p—$NO_2C_6H_4CHO$	0.0808	0.1212
p—OHC_6H_4CHO	0.0347	0.0698
CH_2SH—CH_2SH	0.0206	0.0417
CH_2OH—CH_2OH	0.0149	0.0381

The values are in atomic units.

Conclusion

The present article can be considered as a novel case study in which global and local reactivity descriptors, based on a hard–soft acid-base concept, are used to explain the acetalization products observed by Patel and coworkers in their experimental study.[17] The generated values of reactivity descriptors clearly demonstrate that the global electrophilicity values (i.e., w) of C_6H_5CHO, and its different substitutions are more reliable in explaining the reaction yields than the local electrophilicity values (i.e., s_k^+) of C_{CHO}. In ref. 15, Roy has argued that approximating global reactivity of any chemical system to the local reactivity of its strongest site (i.e., atom) is not logical (especially for systems having more than one comparatively strong reactive site). This is because out of the four series of compounds studied in ref. 15 (altogether 11 carbonyl compounds) trends were not as expected in two series [i.e., series (iii) and series (iv), which contain C_6H_5CH =$CHCHO$ and $C_6H_5COC_6H_5$, respectively]. The global electrophilicity values (i.e., w) of these two compounds were found to be higher than other members in the respective series, although the trends generated by local philicity values (w_k^+) were as expected. Both of these systems have more numbers of comparatively strong reactive sites (i.e., atoms) than other members in the respective series. Thus, although w values of these two systems are highest in the respective series, w_k^+ values of $C_{C=O}$ (i.e., carbon atom of the carbonyl group) are lowest, and are expected when intermolecular electrophilicity trends are assumed to follow the electrophilicity trend of the $C_{C=O}$ (carbon atom of the carbonyl group) only. It should be stressed here that in ref. 15 expected intermolecular electrophilicity trends were based only on the local electrophilicity of $C_{C=O}$ (see ref. 15, Section 4, 9th line, i.e., first line after the four series of systems) and not on the basis of any experimental study (as the present one). A multitude of qualitative effects, for example, inductive, resonance, polarizability, etc., exerted by other parts of the molecule on $C_{C=O}$, were considered to decide the expected local electrophilicity of $C_{C=O}$. That might be the reason when the trends generated by w and w_k^+ values were compared with the expected ones, the former apparently failed [in series (iii) and (iv)], while the latter was found to be successful.

Outcome of the work of ref. 15 prompted Roy and his collaborators to carry on the study further. Through analytical reasoning and numerical demonstrations it was shown in ref. 16 that the

points raised in ref. 15 is justified. Using 15 different organic chlorides it was shown that for systems having more than one comparatively strong electrophilic sites the local philicity value of the strongest site does not always generate a reliable global intermolecular electrophilicity trends. Systems where it does and systems where it does not are also shown in ref. 16. But for systems having only one distinctly strong electrophilic site the local philicity index does generate the global electrophilicity trend.

The systems chosen in the present study are different from those chosen in ref. 15 from the structure–reactivity point of view (although these are also carbonyl compounds, that is, C_6H_5CHO and its different substitutions). None of the systems in ref. 15 contains any substitutions in the Ph-ring. In the present study all the systems (except C_6H_5CHO) contain a substituted Ph-ring. Also, types of substitutions [group (i) and (iv)] as well as positions of substitutions [group (ii) and (iii)] also vary between members within a group. Because of this, the electronic effects exerted by the substituted groups are interrupted to a different extent by the intervening Ph-ring carbon atoms before these effects are felt by the C_{CHO}. Thus, the number of reactive centers in the Ph-ring, apart from C_{CHO}, will be different within the group members depending upon types and positions of substitutions. So, following the arguments laid out in refs. 15 and 16 (as mentioned above), we can understand why global electrophilicity values (w) explain the reaction yield better than local softness values (s_k^+) in the present study.

The authors would like to restate here that DFT-based local reactivity descriptors (i.e., s_k^+, f_k^+, w_k^+) are more reliable for studying intramolecular reactivity (i.e., site selectivity) of a molecule, which has been well established in the last 2 decades. But until now there has been no suitable descriptor (based on DFT), which is very reliable in explaining global reactivity (i.e., intermolecular reactivity). However, the global electrophilicity descriptor (i.e., w), as proposed by Parr et al.[11] seems to be promising, at least for electrophilic interaction. Of course, like most of the other reactivity descriptors (e.g., charge, electrostatic potential, etc.) the values of w also cannot explain the yields quantitatively.

The study also reveals that although the electronic factor plays the major role in determining the reactivity of the aldehydes (as was also claimed by Patel and coworkers[17]), the role of the steric factor cannot be altogether ruled out in all the cases. This is obvious from the minor variations of the yield of acetalization among the members within a group (in all the four groups). In particular, the zero yield of acetalization of o-$(OH)C_6H_4CHO$ and lower yield of acetalization of 2-(Cl)-6-$(NO_2)C_6H_3CHO$ than that of C_6H_5CHO cannot be explained on the basis of w-values alone. The probable reason of the zero yield of acetalization of o-$(OH)C_6H_4CHO$ has been cited as the intramolecular hydrogen bonding between ─CHO and the ─OH group in the *ortho* position. Also, the lower yield of acetalization for 2-(Cl)-6-$(NO_2)C_6H_3CHO$ has been attributed to the high steric effects, caused by two *ortho* groups on the approaching nucleophile. Unfortunately, neither of these two effects can be taken care of by w-values. In fact, the greatest demerit of the conceptual DFT-based reactivity descriptors is that they cannot take care of the effects caused by the steric bulk and only take care of the electronic effects. Because of this deficiency, the role of the conceptual

DFT-based reactivity descriptors remains mainly to be descriptive rather than predictive in the case of intermolecular interaction between large chemical systems. Maybe a combined study of reactivity descriptors as well as energetics (taking care of the stability of the transition states also) will make these points clear.

The reason behind the difference of global electrophilicity values of o- and p-nitrobenzaldehydes is also discussed through analytical reasoning and a structure–stability relationship. The competitive formation of cyclic acetal and cyclic thioacetal between p-(NO_2)─C_6H_4CHO and p-(OH)─C_6H_4CHO is also explained using global electrophilicity values in the same line of arguments of Maynard et al.[12] It is argued that the highest value of w for p-(NO_2)─C_6H_4CHO makes it the most effective substrate (i.e., the strongest electrophile) to be attacked by CH_2OH─CH_2OH, having lowest value of w (i.e., the strongest nucleophile). This has been cited as the reason why in a competitive reaction mixture p-(NO_2)─C_6H_4CHO forms cyclic acetal as the major product, whereas for p-(OH)─C_6H_4CHO the dominant product is cyclic thioacetal. The authors intend to carry on a separate study exploring in details the justification of the above argument.

References

1. Parr, R. G.; Pearson, R. G. J Am Chem Soc 1983, 105, 7512.
2. Ghosh, S. K.; Berkowitz, M. J Chem Phys 1985, 83, 2976.
3. Yang, W.; Parr, R. G. Proc Natl Acad Sci USA 1985, 82, 6723.
4. Parr, R. G.; Yang, W. J Am Chem Soc 1984, 106, 4049.
5. Yang, W.; Mortier, W. J. J Am Chem Soc 1986, 108, 5708.
6. Roy, R. K.; Krishnamurti, S.; Geerlings, P.; Pal, S. J Phys Chem A 1998, 102, 3746; Roy, R. K.; Proft, F. de ; Geerlings, P. J Phys Chem A 1998, 102, 7035.
7. Krishnamurty, S.; Pal, S. J Phys Chem 2000, 104, 7639.
8. (a) Pal, S.; Chandrakumar, K. R. S. J Am Chem Soc 2000, 122, 4145; (b) Chandrakumar, K. R. S.; and Pal, S. J Phys Chem 2002, 106, 5737.
9. Geerlings, P.; de Proft, F.; Langenaeker, W. Chem Rev 2003, 103, 1793.
10. Hohenberg, P; Kohn, W. Phys Rev B 1964, 136, 864.
11. Parr, R. G.; von Szentpaly, L.; Liu, S. J Am Chem Soc 1999, 121, 1922.
12. Maynard, A. T.; Huang, M.; Rice, W. G.; Covel, D. G. Proc Natl Acad Sci USA 1998, 95, 11578.
13. Chattaraj, P. K.; Maiti, B.; Sarkar, U. J Phys Chem 2003, 107, 4973.
14. Perez, P.; Toro–Labbe, A.; Aizman, A.; Contreras, R. J Org Chem 2002, 67, 4747.

15. Roy, R. K. J Phys Chem 2004, 108, 4934.

16. Roy, R. K.; Usha, V.; Pauloviè, J.; Hirao, K. J Phys Chem 2005, 109, 4601.

17. Gopinath, R.; Haque, Sk. J.; Patel, B. K. J Org Chem 2002, 67, 5842.

18. Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. Org Biomol Chem 2004, 2, 1670.

19. Fukui, K.; Yonezawa, T.; Shingu, H. J Chem Phys 1952, 20, 722; Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. J Chem Phys 1954, 22, 1433.

20. Frisch, M. J.; Trucks, G. W.; Schlegel, Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.;

Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head–Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

21. Hirshfeld, F. L. Theoret Chim Acta 1977, 44, 129.

22. Mulliken, R. S. J Chem Phys 1955, 23, 1833.

23. Roy, R. K.; Pal, S.; Hirao, K. J Chem Phys 1999, 110, 8236.

24. Roy, R. K.; Hirao, K.; Pal, S. J Chem Phys 2000, 113, 1372.

25. Roy, R. K.; Tajima, N.; and Hirao, K. J Phys Chem 2001, 105, 211.

26. Roy, R. K. J Phys Chem A 2003, 107, 397.

27. Roy, R. K. J Phys Chem A 2003, 107, 10428.