Chemoselectivities in Acetalization, Thioacetalization, Oxathioacetalization and Azathioacetalization

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In the present article (experimental as well theoretical) the relative yields of cyclic (*O*,*O*), (*S*,*S*), (*S*,*O*), and (*S*,*N*) acetals, formed from p-(NO$_2$)C$_6$H$_4$CHO and p-(OH)C$_6$H$_4$CHO, are compared. Atomic charges, global electrophilicity descriptor (*w*) [as proposed by Parr et al., *J. Am. Chem. Soc.* **1999**, *121*, 1922] and hard−soft acid−base concept of Pearson (*J. Am. Chem. Soc.* **1963**, *85*, 3533) are used to explain the experimental observations. Although the *w* values can explain the yields, charge and local softness values of the interacting sites explain the plausible reaction mechanism. The bisnucleophiles chosen for acetalization are CH$_2$(OH)−CH$_2$(OH) (glycol), CH$_2$(SH)−CH$_2$(SH) (dithiol), CH$_2$(OH)−CH$_2$(SH) (oxathiol) and CH$_2$(SH)−CH$_2$(NH$_2$) (azathiol). For p-(NO$_2$)C$_6$H$_4$CHO, the experimental yield of cyclic acetals were found to follow the trend as (*S*,*N*) > (*S*,*O*) > (*O*,*O*) > (*S*,*S*), which is also supported by theoretical explanation based on the *w* values and applying the concept of hard−hard (i.e., charge-controlled) and soft−soft (i.e., orbital-controlled) interaction between the interacting sites of the substrates (i.e., aldehydes) and the reactants (bisnucleophiles). Similarly, for p-(OH)C$_6$H$_4$CHO the relative yields of cyclic acetals follow the trend (*S*,*N*) ≈ (*S*,*S*) > (*S*,*O*) > (*O*,*O*). It is argued that the attack on C$_{CHO}$ (i.e., C-atom of the CHO group) in p-(NO$_2$)C$_6$H$_4$CHO by O$_{OH}$ (i.e., O-atom of OH group) or N$_{NH_2}$ (i.e., N-atom of NH$_2$ group) is mainly charge-controlled but the attack on C$_{CHO}$ in p-(OH)C$_6$H$_4$CHO) by S$_{SH}$ (i.e., S-atom of SH group) is orbital-controlled.

1. Introduction

Recently, Patel and co-workers carried out experimental studies on the acetalization of benzaldehyde and substituted benzaldehydes.[1,2] It was observed that the variation of yield depends on the types and positions of the substitutions. Subsequently, in a theoretical investigation Roy et al.[3] showed that it is the global electrophilicity (*w*)[4] (of PhCHO and its different substitutions) that plays a dominant role in the process of acetalization. It is understood that steric factors also cause minor variations in experimental yields for some systems. In a competitive reaction environment, containing a mixture of p-(NO$_2$)C$_6$H$_4$CHO (p-nitrobenzaldehyde), p-(OH)C$_6$H$_4$CHO (p-hydroxybenzaldehyde), CH$_2$OH−CH$_2$OH (glycol) and CH$_2$SH−CH$_2$SH (dithiol), the observed higher yield of cyclic acetal formed from p-(NO$_2$)C$_6$H$_4$CHO and of cyclic thioacetal formed from p-(OH)C$_6$H$_4$CHO, could also be explained on the basis of the difference of *w* values (between aldehydes and acetalizing agents).[3]

In the present study we have reported the yield of formation of cyclic (*O*,*O*), (*S*,*S*), (*S*,*O*) and (*S*,*N*) acetals formed from p-(NO$_2$)C$_6$H$_4$CHO and p-(OH)C$_6$H$_4$CHO. Relevant theoretical explanations are also provided on the basis of atomic charges, global electrophilicity (*w*) and local reactivity descriptors. The acetalizing agents used are CH$_2$OH−CH$_2$OH (glycol), CH$_2$SH−CH$_2$SH(dithiol), CH$_2$(OH)−CH$_2$(SH) (oxathiol), and CH$_2$(SH)−CH$_2$(NH$_2$) (azathiol). Experimental details are provided as Supporting Information. In section 2, a brief theoretical back-

ground of the reactivity descriptors along with their physical interpretation is provided. Methodologies used to compute the values of the reactivity indicators are described in section 3. The observed experimental yields of cyclic acetals are elaborated in different schemes in section 4, which are also backed by theoretical explanation. Finally, in the concluding section (section 5) we have summarized the overall study.

2A. Global Reactivity Descriptors

From a qualitative suggestion by Maynard et al.,[5] Parr and co-workers[4] have proposed a global electrophilicity descriptor as follows:

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

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., power = (V^2/*R*), where *V* and *R* represent the potential difference and resistance, respectively). In eq 1, μ is the "chemical potential" and η is "global chemical hardness" of the concerned chemical species. The analytical and operational definitions of μ and η are given as follows,[6]

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

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

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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. In eq 2 and 3 the operational definitions of μ and η are derived by applying the finite difference approximation to the "total energy (E) vs total number of electron (N) plot" of any chemical system. Inverse of η is known as global softness "S" and is represented as

$$S = \frac{1}{\eta} \cong \frac{1}{(\text{IP} - \text{EA})} \qquad (4)$$

It should be noted here that eqs 3 and 4 represent the first analytical as well as operational definitions of chemical hardness and softness proposed qualitatively by Pearson much earlier.[7] In last two decades a number of analytical studies are reported on hard−soft acid−base concept and most of them are based on reactivity descriptors derived from conceptual density functional theory.[8]

2B. Local Reactivity Descriptors

Parallel to the development of global reactivity descriptors some local reactivity descriptors were also proposed which have potential use in predicting local (or site) reactivity (selectivity) of a chemical species. One such descriptor is Fukui function index and is defined as[9]

$$f(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{v(\bar{r})} = \left(\frac{\partial \mu}{\partial v(\bar{r})}\right)_N \qquad (5)$$

Here, $\rho(\bar{r})$ represents the electron density at position $\bar{r}$ of the chemical species. It is named so because of its conceptual similarity with Fukui's frontier molecular orbital theory.[10] After taking care of the discontinuities in the $f(\bar{r})$ versus N plot, the "condensed to atom" approximations of $f(\bar{r})$, when multiplied by global softness (S), provide three condensed local softness values represented by[11]

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

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

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

Here, $p_k(N)$, $p_k(N+1)$ 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[12] of atom "k" toward nucleophilic, electrophilic, and radical attack on it, respectively. Thus, in a molecule the atom "k", for which s_k^+ value is highest, is the most preferred atom to be attacked by a nucleophile. Similarly, highest values of s_k^- and s_k^0 for any atom "k" indicate it to be the most preferable atom for electrophilic and radical attack. We could come to eqs 6a−c because of following analytical relations,

$$s(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial \mu}\right)_{v(\bar{r})} = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{v(\bar{r})} \left(\frac{\partial N}{\partial \mu}\right)_{v(\bar{r})} = f(\bar{r})S \qquad (7)$$

Equations 6a−c can be represented by a generalized expression as follows,

$$s_k^\alpha = f_k^\alpha S \qquad (8)$$

Here, α is $+$, $-$, and 0.

3. Computational Details

To investigate chemoselectivities in the process of acetalization, thioacetalization, oxathioacetalization and azathioacetalization we have chosen in total 6 chemical systems as described in section 1. Out of these six systems two are aldehydes, i.e., p-(NO$_2$)C$_6$H$_4$CHO and p-(OH)C$_6$H$_4$CHO. The other four are CH$_2$OH−CH$_2$OH (glycol), CH$_2$SH−CH$_2$SH(dithiol), CH$_2$(OH)−CH$_2$(SH) (oxathiol) and CH$_2$(SH)−CH$_2$(NH$_2$) (azathiol). The different reaction combinations, as described in the Supporting Information, are designed to single out the nature of chemoselectivity. The obtained yields and the relevant theoretical explanations are elaborated scheme-wise in the next section (section 4).

The geometries were initially optimized at the semiempirical level using CHEM-3D program,[13] followed by re-optimization at the RHF/6-31G(D,P) level using Gaussian-98.[14] In another set of calculations the geometries are re-optimized at BLYP/dnp level using DMOL^3 program package.[15] 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. It is already known that numerical basis sets are much more accurate than the Gaussian basis sets of the same size.[15]

The global electrophilicity values were evaluated by 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)[16] using DMOL^3 program and by Mulliken population analysis (MPA)[17] using Gaussian program. Conceptual advantage of HPA over that of MPA is discussed in details in refs 18−22. There are several other studies that have rigorously shown the superiority of HPA over other population analysis schemes.[23] Although it should also be noted here that Bultinck and Carbo will not fully agree to the above view because of their recent observations on the poor show of HPA in some cases.[24] To enhance the reliability, the MPA based charges are extracted by using a new technique adopted by Roy.[21] In this new technique the charges on the H-atoms are summed on the heavy atoms (i.e., C, O, S and N atoms here) to which they are bonded. The charge values evaluated in this way are found to take care of the artifact of charge partitioning in MPA to some extent and thus is more reliable compared to the normal "condensed-to-individual atom" way.[11]

4. Results and Discussion

As mentioned in section 3, the obtained yields and the relevant explanations are given in the schemes. In Table 1 we have reported the values of q_k (charge), s_k^+ and s_k^- of the relevant atoms. The global electrophilicity (w) values are reported in Table 2. What we observe in Table 1 is that the s_k^+ value of C$_{CHO}$ in p-(OH)C$_6$H$_4$CHO is higher than that of C$_{CHO}$ in p-(NO$_2$)C$_6$H$_4$CHO, although the latter has a higher value of w than that of the former (Table 2). This is just another evidence in favor of the claim by Roy et al.[25] that the trends of global and local (of the strongest atoms in the chemical systems compared) electrophilicities are not always same. It is also clear from Table 1 that the charge values (q_k) of C$_{CHO}$ in p-(OH)-C$_6$H$_4$CHO is lower than that of C$_{CHO}$ in p-(NO$_2$)C$_6$H$_4$CHO, which is also expected because of the electron withdrawing

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TABLE 1: MPA and HPA Based Charges (i.e., q_k), s_k^+, and s_k^- Values of the Atoms (Marked *) Relevant in the Present Study (See Text)^a

	methods					
	MPA/6-31G(D,P)			HPA/dnp		
carbonyl systems	q_k	s_k^+	s_k^-	q_k	s_k^+	s_k^-
p-NO$_2$C$_6$H$_4$C*HO	0.5276	0.2696	0.1780	0.1192	0.2934	0.2099
p-OHC$_6$H$_4$C*HO	0.5099	0.7988	0.1653	0.1024	0.3242	0.2233
CH$_2$S*H−CH$_2$S*H	0.0459	0.9043	0.9432	−0.0530	0.6512	0.9077
CH$_2$O*H−CH$_2$O*H	−0.3121	0.6130	0.4728	−0.2315	0.2144	0.4798
CH$_2$O*H−CH$_2$SH	−0.2974	0.0904	0.0878	−0.2308	0.1749	0.4408
CH$_2$OH−CH$_2$S*H	0.0171	1.5737	1.6644	−0.0480	0.7467	0.9261
CH$_2$S*H−CH$_2$NH$_2$	0.0211	1.5699	1.7004	−0.0658	0.6649	0.9398
CH$_2$SH−CH$_2$N*H$_2$	−0.1672	0.1866	0.1770	−0.2197	0.2098	0.4758

^{a} The s_k^+ and s_k^- values are in atomic units.

TABLE 2: MPA and HPA Based Global Electrophilicity (i.e., w) Values of the Chemical Systems Chosen for Comparison of Competitive Acetalization, Thioacetalization, Oxathioacetalization and Azathioacetalization in the Present Study (See Text)^a

	methods	
chemical systems	MPA/6-31G(D,P)	HPA/dnp
p-NO$_2$C$_6$H$_4$CHO	0.0404	0.0606
p-OHC$_6$H$_4$CHO	0.01735	0.0349
CH$_2$SH−CH$_2$CH	0.0103	0.02085
CH$_2$OH−CH$_2$OH	0.00745	0.01905
CH$_2$OH−CH$_2$SH	0.00715	0.01895
CH$_2$SH−CH$_2$NH$_2$	0.0057	0.0167

^{a} The values are in atomic units.

effect of the −NO$_2$ group present in the latter system. The apparent contradictory trends in s_k^+ and q_k values of C$_{CHO}$ have their effect on the reactivity of the two systems. The higher values of charge (of C$_{CHO}$) as well as global electrophilicity (i.e., w) of p-(NO$_2$)C$_6$H$_4$CHO indicate that it will be preferred by a charged but hard (i.e., small sized) nucleophile (to react on C$_{CHO}$) from a distance at the initial stage of the reaction. This is some kind of hard−hard interaction which is charge controlled.[26−28] But the higher s_k^+ value of the C$_{CHO}$ in p-(OH)-C$_6$H$_4$CHO will favor (at least to some extent) the reaction with the uncharged (or less negatively charged) but soft (i.e., large sized) nucleophile in the later stage of the reaction. This can be considered as soft−soft interaction, which is mainly orbital controlled[26] and operates at closer approach. However, it is worth mentioning here that the overall yield of the reaction will depend on the electrophiles as well as the nucleophiles involved.

We also notice from Table 1 that the s_k^+ value of C$_{CHO}$ in p-(OH)C$_6$H$_4$CHO is too high to that of the s_k^+ value of C$_{CHO}$ in p-(NO$_2$)C$_6$H$_4$CHO when evaluated by MPA/6-31G(D,P) method. There is no physical justification in favor of so much difference in the s_k^+ values of C$_{CHO}$ in the two systems and this, probably, can be attributed to the artifact involved in the MPA charge-partitioning scheme. We, therefore, trust more on the s_k^+ values generated by HPA/dnp method.

On the basis of the discussion above, we have given explanations of the obtained yields in the schemes.

The higher positive charge on C$_{CHO}$ in p-(NO$_2$)C$_6$H$_4$CHO [than on C$_{CHO}$ in p-(OH)C$_6$H$_4$CHO] and high negative charge on O$_{OH}$ (in CH$_2$OH−CH$_2$OH) makes the charge-controlled hard−hard interaction very effective. The hard−hard interaction between C$_{CHO}$ [in p-(OH)C$_6$H$_4$CHO] and O$_{OH}$ (in CH$_2$OH−CH$_2$OH) is not that effective because of lower positive charge on C$_{CHO}$ in the former (this will be particularly true when a

SCHEME 1: Experiment 1 in the Supporting Information
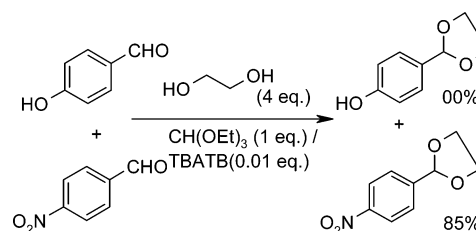
competitor like p-(NO$_2$)C$_6$H$_4$CHO is already there in the reaction medium). Also, the difference of global electrophilicity between p-(NO$_2$)C$_6$H$_4$CHO and CH$_2$OH−CH$_2$OH is significantly higher than that between p-(OH)C$_6$H$_4$CHO and CH$_2$OH−CH$_2$OH. These two factors favor the (O,O) acetal formation of p-(NO$_2$)C$_6$H$_4$CHO (Scheme 1). It seems that the higher s_k^+ value of C$_{CHO}$ in p-(OH)C$_6$H$_4$CHO (by HPA/dnp method) has no influence on the yield.

SCHEME 2: Experiment 2 in the Supporting Information
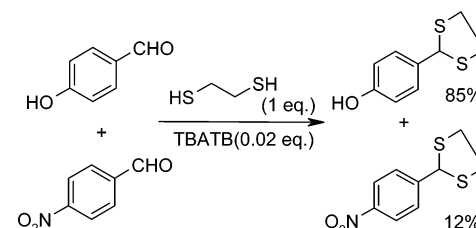
Here, because of large size and negligible negative charges (in HPA/dnp method), S-atoms in CH$_2$SH−CH$_2$SH behave like soft bases. So, the interaction of C$_{CHO}$ (having comparatively lower positive charge on it) in p-(OH)C$_6$H$_4$CHO with S$_{SH}$ (in CH$_2$SH−CH$_2$SH) is mainly orbital controlled and soft−soft in nature. On the contrary, comparatively higher positive charge on C$_{CHO}$ of p-(NO$_2$)C$_6$H$_4$CHO makes the soft−soft interaction with CH$_2$SH−CH$_2$SH less effective. Thus, the major product is expected cyclic (S,S) acetal of p-(OH)C$_6$H$_4$CHO.

SCHEME 3: Experiment 3 in the Supporting Information
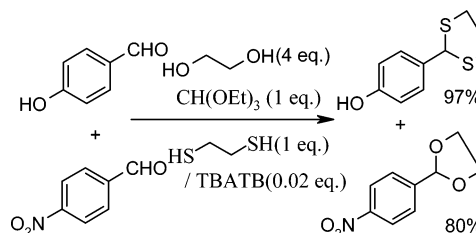
Here, because of the competitive reaction condition p-(NO$_2$)-C$_6$H$_4$CHO will form (O,O) acetal with CH$_2$OH−CH$_2$OH and p-(OH)C$_6$H$_4$CHO will form (S,S) acetal with CH$_2$SH−CH$_2$SH. The reason is that the highest global electrophilicity of p-(NO$_2$)C$_6$H$_4$CHO plus higher positive charge of C$_{CHO}$ will favor it to react with the lowest electrophilic (i.e., the strongest nucleophilic) CH$_2$OH−CH$_2$OH (which has also higher negative charge on the O$_{OH}$-atoms) in a charge-controlled hard−hard way. Similarly, p-(OH)C$_6$H$_4$CHO will react with CH$_2$SH−CH$_2$-SH in an orbital-controlled soft−soft pathway (see the explanations in Schemes 1 and 2 above).

SCHEME 4: Experiment 4 in the Supporting Information
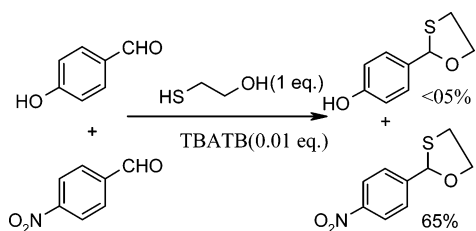
As per explanations in the previous schemes it is expected that the initial attack by O_{OH} (in CH_2SH-CH_2OH) to the deactivated carbonyl group (i.e., C_{CHO}) of p-$(NO_2)C_6H_4CHO$ will take place in the first step (which is charge-controlled). This is then followed by an intramolecular nucleophilic attack by the S_{SH} on the oxycarbenium ion as shown in Figure 1.

Here as both the first and third steps are energetically favorable, the yield of (S,O) acetal of p-$(NO_2)C_6H_4CHO$ is higher. The probable reaction mechanism shown above is also consistent with the product distribution in Schemes 1 and 3. Also, it has been experimentally found that (O,O) acetal can easily be converted to (S,O) acetal (because third step is energetically more favorable in case of transthio-acetalization process, as S_{SH} is a better nucleophile than O_{OH}).

On the other hand S_{SH} is attacking first to the carbonyl group (i.e., C_{CHO}) of the p-$(OH)C_6H_4CHO$ followed by an intramolecular attack of O_{OH} as shown in Figure 2.

In Figure 2 the first step is energetically favorable (and is assumed to be predominantly orbital-controlled) as has been observed in Schemes 2 and 3. But the third step, i.e., the attack of O_{OH} to an electron rich thiocarbenium moiety is not favorable and we believe it to be the rate-determining step.

Now, because the rate-determining step in case of oxathio-acetal [i.e., (S,O) acetal] formation of p-$(NO_2)C_6H_4CHO$ (the first step in Figure 1) is energetically favorable to that of the rate-determining step in case of p-$(OH)C_6H_4CHO$ (third step in Figure 2), the yield of (S,O) acetal formation in case of the former is higher than that of the latter (Scheme 4). Higher global electrophilicity of p-$(NO_2)C_6H_4CHO$ also favors the oxathio-acetal formation.

SCHEME 5: Experiment 5 in the Supporting Information
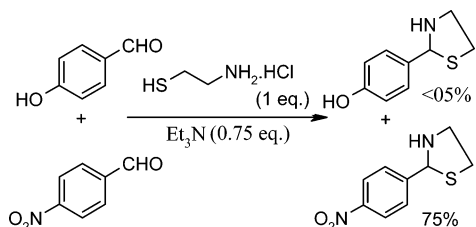
Explanation in favor of the higher yield of azathioacetalization of p-$(NO_2)C_6H_4CHO$ is similar to Scheme 4. The probable reaction mechanism for (N,S) acetal formation of p-$(NO_2)C_6H_4$-CHO is shown in Figure 3.

Here the first step is the rate-determining step. The probable mechanism of (N,S) acetal formation of p-$(OH)C_6H_4CHO$ is similar to the corresponding mechanism in Scheme 4 (Figure 2). Because, the rate-determining step in the formation of (N,S) acetal of p-$(OH)C_6H_4CHO$ is energetically less favorable when compared to that of p-$(NO_2)C_6H_4CHO$ and also the fact that the latter is a stronger electrophile than the former, the yield follows the above trend.
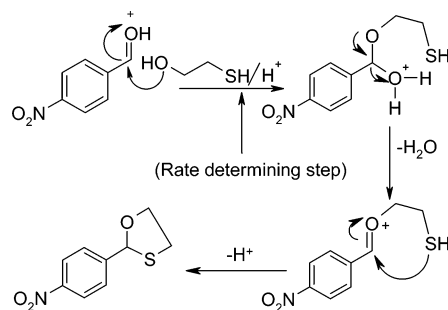
Figure 1. Mechanism I.
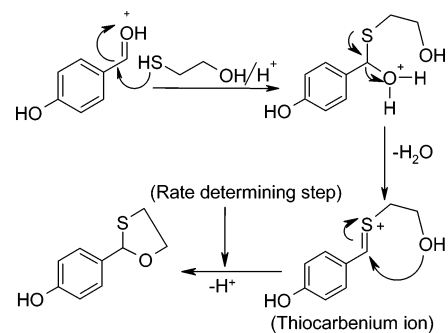
Figure 2. Mechanism II.
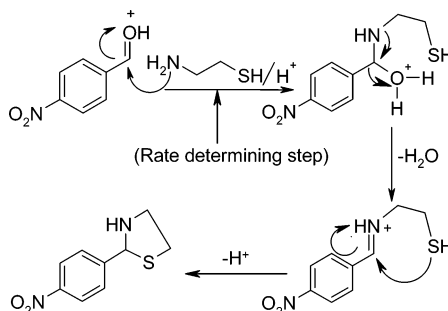
Figure 3. Mechanism III.

**SCHEME 6: Experiment 6 in the Supporting Information**
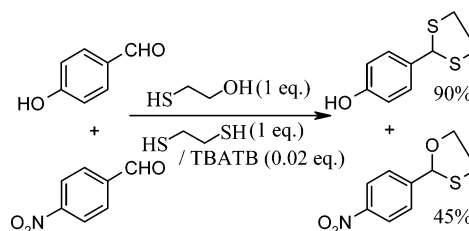
The obtained yields can be explained in the same line of arguments as in Scheme 3. The C_{CHO} of p-$(NO_2)C_6H_4CHO$ will be attacked first by O_{OH} of CH_2OH-CH_2SH in a predominantly charge-controlled pathway (Figure 1 in Scheme 4.). The reaction of p-$(OH)C_6H_4CHO$ with CH_2SH-CH_2SH is mainly orbital-controlled.

Here (Scheme 7) the explanation is similar to Scheme 6. The N_{NH_2} of $CH_2SH-CH_2NH_2$ will attack the C_{CHO} of p-$(NO_2)C_6H_4$-CHO in a predominantly charge-controlled pathway. The reaction between p-$(OH)C_6H_4CHO$ and CH_2SH-CH_2SH is, as usual, predominantly orbital-controlled.

A careful look at the yield of (S,O) and (S,N) acetals of p-$(NO_2)C_6H_4CHO$ in Schemes 4–7 makes it obvious that the yields of (S,N) acetals are higher than that of (S,O) acetals. A plausible explanation may be the higher difference of global electrophilicity between p-$(NO_2)C_6H_4CHO$ and CH_2SH-CH_2-

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SCHEME 7:   Experiment 7 in the Supporting Information
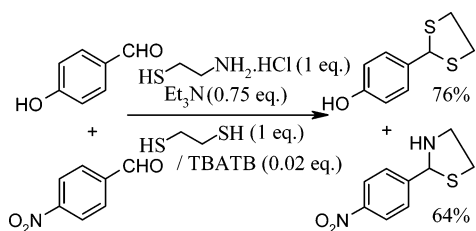
NH_2 than that of p-$(NO_2)C_6H_4CHO$ and CH_2SH-CH_2OH (which indicates that CH_2SH-CH_2NH_2 is a stronger nucleophile than CH_2SH-CH_2OH). Also a higher s_k^- value of N_{NH_2} in CH_2SH-CH_2NH_2 than that of O_{OH} in CH_2SH-CH_2OH makes the rate-determining step energetically more favorable in case of the former. Thus for p-$(NO_2)C_6H_4CHO$ the preferential attack by the nucleophiles to the C_{CHO} follows the trend, N_{NH_2} > O_{OH} > S_{SH}. This trend is further evidenced from the series of competitive reactions as shown in Scheme 8 below.

**SCHEME 8:   Experiments 8−13 in the Supporting Information**
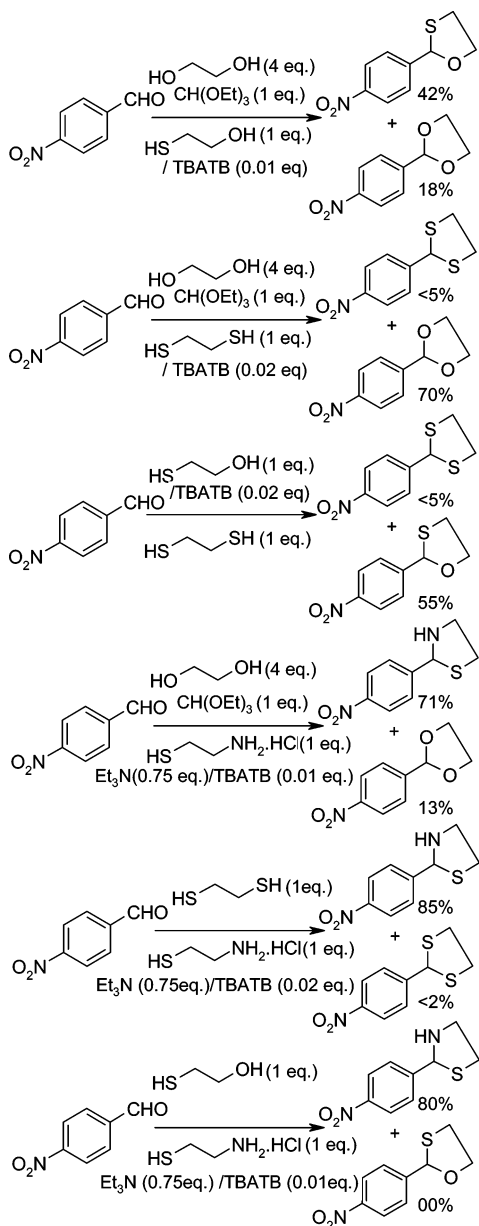
Instead of explaining the yields of the reactions individually a general approach seems to be more convincing. The trends of the yields of (*O*,*O*), (*S*,*S*), (*S*,*O*), (*S*,*N*) acetals, as shown above, could be explained on the basis of two considerations: (i) The attack on C_{CHO} of p-$(NO_2)C_6H_4CHO$ by O_{OH} and N_{NH_2} nucleophiles is predominantly charge-controlled because of the high positive charge on C_{CHO} and negative charges on O_{OH} and N_{NH_2}. As S_{SH} has negligible negative charge on it, the attack on C_{CHO} by S_{SH} is much less effective either as charge-controlled or as orbital-controlled pathway. (ii) The difference of global electrophilicity (w) between p-$(NO_2)C_6H_4CHO$ and the nucleophiles. The more is the difference the better is the yield because lower is the w value stronger is the nucleophile.

Thus, in the present study we see the yield of formation of different cyclic acetals from p-$(NO_2)C_6H_4CHO$ follow the trend as below:
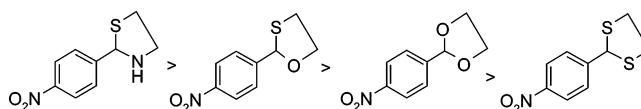
**SCHEME 9:   Experiments 14−16 in the Supporting Information**
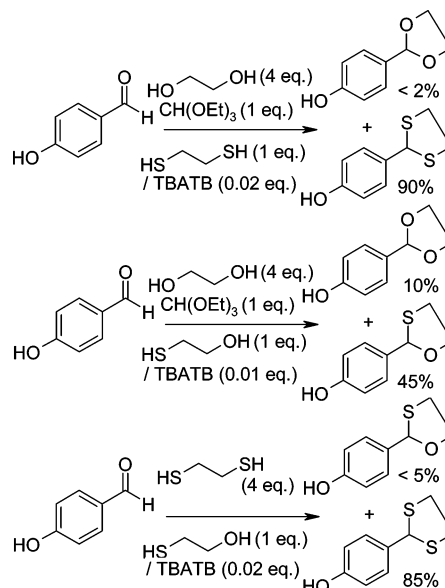
As discussed in Schemes 2 and 3, the formation of (*S*,*S*) acetal is preferred over (*O*,*O*) acetal because of favorable orbital-controlled reaction between p-$(OH)C_6H_4CHO$ and CH_2SH-CH_2SH, which is not the case when the nucleophile is CH_2OH-CH_2OH. Similarly, formation of (*S*,*O*) acetal is preferred over (*O*,*O*) acetal because of the favorable orbital-controlled attack of S_{SH} on the C_{CHO} of p-$(OH)C_6H_4CHO$ (Figure 2, Scheme 4). Again, the yield of (*S*,*S*) acetal is much higher than that of (*S*,*O*) acetal because the third step of Figure 2 will be energetically more favorable in case of CH_2SH-CH_2SH as S_{SH} is a better electron donor (to the thiocarbenium ion) than O_{OH}.

The explanation for the higher yield of (*S*,*N*) acetal over those of (*O*,*O*) and (*S*,*O*) acetals (Scheme 10) is similar to that of Scheme 9. Here also orbital-controlled attack on C_{CHO} by S_{SH} takes place in the first step when the nucleophiles are CH_2SH-CH_2NH_2 and CH_2SH-CH_2OH. This step is not favorable when the nucleophile is CH_2OH-CH_2OH. The third step will be energetically more favorable when the nucleophile at the other end is N_{NH_2} (than when it is O_{OH}) because N_{NH_2} is a better nucleophile than O_{OH}. However, the slightly higher yield of

SCHEME 10: Experiments 17−19 in the Supporting Information
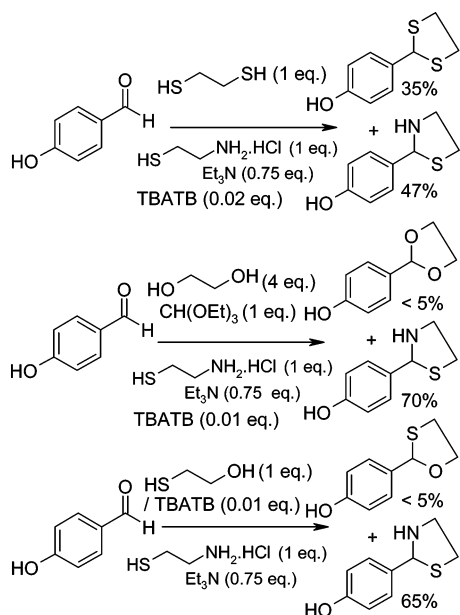
(S,N) acetal than that of (S,S) acetal is not clearly understood because the yield of the latter is expected to be more. Maybe the difference of *w* values between *p*-(OH)C$_6$H$_4$CHO and nucleophiles (which is more when the nucleophile is CH$_2$SH−CH$_2$NH$_2$; see Table 2) plays a role here. But the results seem to be not that erratic when we consider ±5% error in the experimental procedure of evaluation of yield.

Thus the yields of different acetals obtained from *p*-(OH)-C$_6$H$_4$CHO follow the trend as
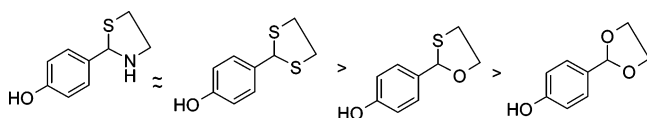
5. Conclusion

The present article represents a combined study (experimental as well as theoretical) of chemoselectivities involved in the acetalization, thioacetalization, oxathioacetalization and aza-thioacetalization of *p*-(NO$_2$)C$_6$H$_4$CHO and *p*-(OH)C$_6$H$_4$CHO. The main objective is to investigate the trends of cyclic (O,O), (S,S), (S,O) and (S,N) acetal formation with the variation of substitution on the Ph ring of C$_6$H$_5$CHO. The obtained yields of the products suggest that for *p*-(NO$_2$)C$_6$H$_4$CHO the order follows
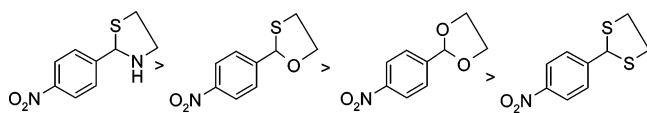
whereas for *p*-(OH)C$_6$H$_4$CHO the trend is
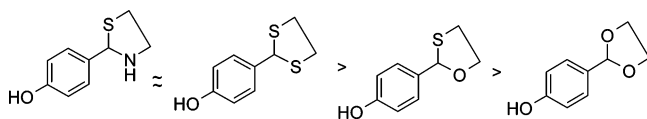
The above yields could be explained theoretically upon consideration of a multiple of factors together:

(i) global electrophilicity difference between the electrophiles [i.e., *p*-(NO$_2$)C$_6$H$_4$CHO and *p*-(OH)C$_6$H$_4$CHO] and the nucleo-philes [i.e., CH$_2$OH−CH$_2$OH, CH$_2$SH−CH$_2$SH, CH$_2$(OH)−CH$_2$(SH), and CH$_2$(SH)−CH$_2$(NH$_2$)]

(ii) type of attack on the most electrophilic atom (i.e., C$_{CHO}$) by the most nucleophilic atoms (i.e., O$_{OH}$, S$_{SH}$ and N$_{NH_2}$) [This helps us to understand whether the attack is charge-controlled or orbital-controlled.]

(iii) energetics at the different stages of the reaction

Unambiguous preference of *p*-(NO$_2$)C$_6$H$_4$CHO for CH$_2$OH−CH$_2$OH and that of *p*-(OH)C$_6$H$_4$CHO for CH$_2$SH−CH$_2$SH (Schemes 1−3, 6, 7, 9 and some reactions in Schemes 8 and 10) clearly shows that only global electrophilicity (*w*) difference between the electrophiles and the nucleophiles is not sufficient to explain the observed yields. Had it been so, we would have expected higher yield of (S,S) acetal product from *p*-(NO$_2$)C$_6$H$_4$-CHO than that from *p*-(OH)C$_6$H$_4$CHO, owing to the higher difference of the global electrophilicity values between *p*-(NO$_2$)C$_6$H$_4$CHO and CH$_2$SH−CH$_2$SH (See Table 2). On the contrary, the reaction in Scheme 4 clearly suggests the high preference of O$_{OH}$ (in CH$_2$OH−CH$_2$OH) toward C$_{CHO}$ in *p*-(NO$_2$)C$_6$H$_4$CHO and that of S$_{SH}$ (in CH$_2$SH−CH$_2$SH) toward C$_{CHO}$ in *p*-(OH)C$_6$H$_4$CHO. These evidences led us to invoke the long known concept of charge-controlled attack in the former and orbital-controlled attack in the latter case.[26] The above assumption is also justified because of the high negative charge on O$_{OH}$ (in CH$_2$OH−CH$_2$OH) but almost neutral S$_{SH}$ (in CH$_2$-SH−CH$_2$SH). In reactions where the involved nucleophiles have different groups at the two ends (e.g., CH$_2$OH−CH$_2$SH and CH$_2$-SH−CH$_2$NH$_2$) the observed yields could be explained by giving preference to that type of attack which leads to energetically more favorable transition state in the rate-determining step (e.g., reactions in Schemes 4 and 5 and last reactions in Schemes 8 and 10). In such cases also the reactions are assumed to be initiated by the attack of O$_{OH}$ or N$_{NH_2}$ to the C$_{CHO}$ of *p*-(NO$_2$)C$_6$H$_4$CHO and by S$_{SH}$ to the C$_{CHO}$ of *p*-(OH)C$_6$H$_4$CHO.

We emphasize here that an energetic study, which includes the evaluation of activation energy in the rate-determining step, is not warranted in the present case. This is because activation energy provides an account of the stability of the transition state (with respect to the reactants), which can be considered as "the effect" of the phenomena involved in the process of chemical reaction. We are here to find out "the cause", rather than "the effect" (as the reaction yields obtained in the experimental study serve that purpose), which influences the stability of the transition state. Although, in general, both the steric and electronic factors contribute to the stability of the transition state, the contribution of the former is negligible in the present study as in both the substrates [*p*-(NO$_2$)C$_6$H$_4$CHO and *p*-(OH)C$_6$H$_4$-CHO] the substituted groups (−NO$_2$, −OH and −CHO) are in para-position. Thus, it seems to be physically meaningful to assume that electronic factors are the sole contributors to the stability of the transition state (and thus control the reactivity) that influences the yields of the reactions studied here. This is exactly what is considered in the present study.

Chemoselectivities in Acetalization

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Supporting Information Available: Experimental details. This material is available free of charges via the Internet at http://pubs.acs.org.

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