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A Simple Model to Predict Preferable Aldol Products from Unsymmetrical Ketones Using Local Hard−Soft Acid−Base Concept

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Unsymmetrical ketones produce two types of enolate intermediates upon deprotonation, which are known as “less substituted” and “more substituted” ones. The major final aldol product will depend on which one of these two enolate intermediates is more reactive toward the incoming reactant (i.e., aldehyde in the case of aldol condensation reaction) in the next stage of the reaction. As here the active sites belong to two different chemical systems, “local hardness” values are reported to be more reliable (Langenaeker et al. *J. Phys. Chem.* **1995**, *99*, 6424, and Roy et al. *J. Phys. Chem.* **1998**, *102*, 3746) to predict the intermolecular reactivity order of these two intermediates. But in this article we have proposed a very simple model which simultaneously represents both kinds of enolate intermediates. So the present study can be considered as a first one in which an intermolecular problem has been recasted as an intramolecular one, and thus “local softness” and related reactivity descriptors have been used, instead of the “local hardness”, to predict the intermolecular reactivity orders. The generated results show that the model works at satisfactory level.

1. Introduction

In the last 2 decades several global and local reactivity descriptors based on density functional theory (DFT) (ref 1) have been proposed. The global reactivity descriptors, e.g., global hardness (η) and global softness (S) (ref 2a), have been very useful to extend our understanding of the most stable state of a chemical species,[2b] correlation of hardness (or softness) with other chemical parameters,[2c] and also the profile of a reaction path.[2d] The usefulness of local reactivity descriptors found to be more important because it helps to explain the intra- and intermolecular reactivities. Reactivity descriptors, e.g., hardness and softness kernels,[3a,3b] local hardness,[3a,4] local softness,[4] and Fukui functions (FF) (ref 5) have become very useful in understanding the details of different classes of chemical reactions. Studies of nucleophilic reactions become complicated when molecular electrostatic potential (MESP) (ref 6) is used as reactivity descriptors (because the potential always shows the maxima over the nuclei thus masking the real active site), although some alternative methods have been suggested to avoid it.[7] But studies have shown that no such problem appears when local softness or FF’s are used as local reactivity descriptors.

Very recently Mahrwald and Gündogan[8] have shown that when unsymmetrical ketones are subjected to direct aldol additions (i.e., without going through the stable enolate intermediates) with aldehydes in the presence of substoichiometric quantities of $TiCl_4$ at room temperature, aldol additions occur at the encumbered (i.e., more sterically hindered) α-side. When they tried for aldol addition of aldehydes to functionalized unsymmetrical ketones (e.g., 2.4-pentane dione or fluoracetone with benzaldehyde) at the same reaction conditions, no aldol additions occurred at all. The aldol addition at the unsubstituted α-side, through the reaction of 1-chloro-3-pentanone with benzaldehyde, resulted in very poor yields at the same reaction conditions. From the outcome of their study the authors concluded that the electronic effects predominate in determining the yield of the aldol additions. The aldol addition occurs at the less electronegative α-side of unsymmetrical ketones, although, from a stereochemical point of view, it is the more hindered and a more substituted one.

Now if electronic factors really play the predominant role in determining the major final aldol product, then we can argue that it is a case where we can apply local hard−soft acid−base concept based reactivity descriptors to locate the most reactive sites in the intermediate enolate ions. Now the question is which of the local reactivity descriptors (between “local hardness” and “local softness”) would be more suitable for the present purpose? To answer this question we should first look into the exact nature of aldol addition to unsymmetrical ketones. There is also another theoretical study on the reactivity of enolates using local hard−soft acid−base concept which takes care of the interaction energy of the reaction partners.[9]

In section 2 we have discussed precisely what kind of problem (i.e., whether “intramolecular” or “intermolecular”) the aldol condensation of unsymmetrical ketone is. This will help us to understand whether the unsymmetrical ketone itself or the corresponding enolate intermediates should be chosen as the target chemical system of our study. We have proposed a simple model di-enolate to demonstrate it. The local reactivity descriptors used to evaluate the most reactive site have been discussed in brief in section 3. The methodologies adopted in the present study as well as the computational techniques used are discussed in brief in section 4. This section also discusses about the chosen “less substituted” and “more substituted” enolate intermediates which are generated by deprotonation of the unsymmetrical ketones used by Mahrwald and Gündogan[8] in their experimental study. Section 5 contains the results and discussion part. First we have used local softness and related quantities as intramolecular reactivity descriptors to locate the most active sites in the enolate intermediates chosen by Mahrwald and Gündogan[8] in their experimental study and also in the proposed model di-

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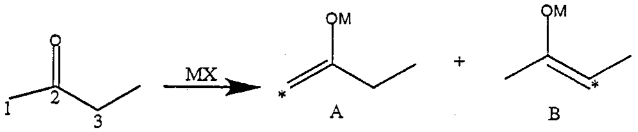

Figure 1. Enolization of a typical unsymmetrical ketone. Here **A** is the "less substituted" and **B** is the "more substituted" enol intermediate generated from the unsymmetrical ketone (see text).

enol intermediates (section 5.A). Then we have made an analysis whether the values thus obtained can produce reliable intermolecular reactivity orders of those enolate intermediates and thus help to predict the major aldol product (subsection 5.B). In subsection 5.C we have discussed whether the experimental observations can be reproduced when the same reactivity descriptors are used on our model di-enolates. Finally in the concluding section (section 6) we have summarized our results and have discussed the areas where the present model has potential future application.

2. A New Model to Represent the Aldol Condensation of Unsymmetrical Ketones:

An unsymmetrical ketone forms two typical enolate intermediates upon deprotonation (see Figure 1). Here A is known as the "less substituted" and B is known as the "more substituted" enolate intermediate. The major final product will depend on which of the two intermediates are more susceptible to be attacked by an incoming electrophile (i.e., the aldehydes in the present case) in the next step (at the positions indicated by "*"). So local reactivity descriptors based on hard and soft acid and bases concept can be used to locate the preferable site of electrophilic attack to the enolate intermediates.

But the previous studies by Langenaeker et al.[10] and Roy e et at al.[11] have shown that to compare the intermolecular reactivities (because here the reactive centers belong to two different enolate intermediates) the local hardness parameter is more reliable than the local softness or the Fukui function parameters. The explanation was given that intermolecular reactivity is charge controlled and so is governed by hard−hard interaction.[12] So any hardness related reactivity descriptors will be more suitable to measure this kind of reactivities. On the other hand, the intramolecular reactivity is dominated by the covalent interaction because it is orbital controlled. So any orbital controlled reactivity descriptor (e.g., local softness, Fukui function index) will be more suitable to measure the intramolecular reactivity sequence. However our present problem is special in the sense that although the major product will depend on the relative reactivity of the active sites of two different enolate intermediates, their precursor is common (i.e., the same unsymmetrical ketone). So, we can view it as a problem in which the competition between position 1 and position 3 of the unsymmetrical ketone (see Figure 1) will decide the dominance of a particular product. But in their study Roy et al.[11] have found that for saturated carbonyl compounds (i.e., carbonyl compounds which do not contain any double or triple C−C bonds) the strongest electrophilic and nucleophilic centers are the C_{carb} (carbon atom of the carbonyl group) and O_{carb} (oxygen atom of the carbonyl group), respectively. Other positions show very negligible activities from where no definitive information, regarding the potentiality to be an active site, can be extracted. Thus, reactivities of position 1 and 3 of Figure 1 will be negligible because of the obvious reason that these two carbon atoms are fully saturated.

Thus, we see that the problem has intermolecular feature at the intermediate stage but would have been very straightforward if we could treat it as an intramolecular one using the parent unsymmetrical ketone which, unfortunately, does not provide the required information. Now the question is how to tackle both of this inter- and intramolecular feature simultaneously so that we can use local reactivity descriptors based on hard and soft acid and bases concept? We have suggested a very simple model which may serve this purpose. The model is a di-enolate in which one of the enolate moeity bears the features of the "less substituted" enolate (intermediate A in Figure 1), while the other bears the features of the "more substituted" one (intermediate B in Figure 1). It is shown in Figure 2. Here the enolate moeity inside the left circle bears the features of the "less substituted" enolate intermediate and the moeity inside the right circle bears the features of the "more substituted" one. The number of intervening carbon atoms (denoted by C_n) will be such that the interaction between the two moeity will be negligible. This can be tested by gradually increasing C_n. If the local reactivities of the active sites (denoted by "*") and also the other sites of both the moieties inside the respective circles do not show any change in trend, then we can accept that the saturation point (in terms of C_n) is reached.

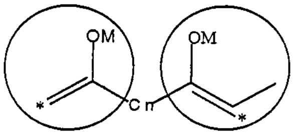

Figure 2. The model di-enolate intermediate. Here the moieties inside the left and right circles represent respectively the "less substituted" and "more substituted" enolate intermediates generated form an unsymmetrical ketone (see Figure 1).

Now the di-enolates, as depicted by the above model, is a single chemical system. This means that we have turned the problem into an intramolecular one. So we can apply local softness (or Fukui function) to evaluate local reactivities of the individual sites. By comparing the reactivities of the active sites in question (indicated by "*" in both the circles) we will be in a position to predict what will be the major aldol product obtained from the unsymmetrical ketones. In subsection 5.C we will discuss in details about the reliability of the present model.

3. Theoretical Background

A. Local Reactivity Descriptors Based on Softness and Fukui Function Indices:

The local softness parameter is in recent days increasingly used as a local reactivity descriptor and is defined as[4]

$$s(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial \mu}\right)_{\nu(\bar{r})} \tag{1}$$

where $\rho(\bar{r})$ is the electron density at the site $\bar{r}$.

Thus, local softness is such a reactivity parameter which describes the response of any particular site of a chemical species (in terms of change in electron density, ρ) when there is any global change in its chemical potential value. The parameter $s(\bar{r})$ obeys the condition

$$\int s(\bar{r})\, d\bar{r} = S \tag{2}$$

where S is known as the global softness of a chemical species, which is inversely related to the global hardness (η) and is defined as[2]

$$S = \frac{1}{2\eta} = \left(\frac{\partial N}{\partial \mu}\right)_{\nu(\bar{r})} \tag{3}$$

So, the global hardness is defined as[2]

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu(\bar{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{\nu(\bar{r})} \tag{4}$$

where E is the total energy, N the number of electrons of the chemical species, and $\nu(\bar{r})$ the external potential (i.e., the potential due to nuclei plus any other, if present). The term "μ" is known as the "chemical potential", which is identified as the negative of the electronegativity[13] as defined by Iczkowski and Margrave.[14]

The operational definitions of η and S are obtained by finite difference approximations to eq 4 as[2]

$$\eta = \frac{\mathrm{IP} - \mathrm{EA}}{2} \tag{5}$$

$$S = \frac{1}{\mathrm{IP} - \mathrm{EA}} \tag{6}$$

where IP and EA are the first vertical ionization potential and electron affinity, respectively, of the chemical species.

Rewriting eq 1 and then combining with eq 3 we can write

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

where $f(\bar{r})$ is the Fukui Function indices and is introduced by Parr and Yang.[5] As $s(\bar{r})$ is obtained by simply multiplying $f(\bar{r})$ with the global softness S, the information contained in them is same i.e., sensitivity of the chemical potential of a system to a local external perturbation.[15] However, $s(\bar{r})$ contains some additional information about the global molecular softness.

As at some integral value of N_0 the derivative $\partial\rho/\partial N$ will, in general, have one value from the right, one from the left and an average, three such indices can be obtained as

$$f^+(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_\nu^+$$

$$\text{(derivative as } N \text{ increases from } N_0 \rightarrow N_0 + \delta) \tag{8a}$$

$$f^-(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_\nu^-$$

$$\text{(derivative as } N \text{ increases from } N_0 - \delta \rightarrow N_0) \tag{8b}$$

$$f^0(\bar{r}) = \frac{1}{2}[f^+(\bar{r}) + f^-(\bar{r})]$$

$$\text{(mean of left and right derivatives)} \tag{8c}$$

When compared with the frontier-electron theory of reactivity as proposed by Fukui and collaborators,[16] we write that[15]

$$f^+(\bar{r}) \approx \rho_{\mathrm{LUMO}}(\bar{r})$$

$$\text{measures reactivity toward a nucleophilic reagent} \tag{9a}$$

$$f^-(\bar{r}) \approx \rho_{\mathrm{HOMO}}(\bar{r})$$

$$\text{measures reactivity toward an electrophilic reagent} \tag{9b}$$

$$f^0(\bar{r}) \approx \frac{1}{2}[\rho_{\mathrm{HOMO}}(\bar{r}) + \rho_{\mathrm{LUMO}}(\bar{r})]$$

$$\text{measures reactivity toward an innocuous (radical) reagent} \tag{9c}$$

here, according to the convention, HOMO represents the "highest occupied molecular orbital: and LUMO the "lowest unoccupied molecular orbital" in the chemical species in question.

Yang and Mortier[17] have proposed approximate atomic $f(\bar{r})$ indices by applying finite difference approximation to the condensed electronic population on any atom. Thus, we have three operational form of approximate atomic $f(\bar{r})$ indices (from eqs 8a−c) which, when multiplied by S, provide three different local softnesses for any particular atom (k). These can be written as

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

$$\text{(suited for studies of nucleophilic attack)} \tag{10a}$$

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

$$\text{(suited for studies of electrophilic attack)} \tag{10b}$$

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

$$\text{(suited for studies of radical attack)} \tag{10c}$$

where $\rho_k(N_0)$, $\rho_k(N_0 - 1)$, and $\rho_k(N_0 + 1)$ represents the electronic population on atom k for the N_0, $N_0 - 1$, and $N_0 + 1$ electron system, respectively.

B. "Relative Electrophilicity" and "Relative Nucleophilicity". Although the eqs 10a−c are found to be very useful in generating the experimentally observed intra- molecular reactivity trends in several previously studied cases,[18,19] recently Roy et al.[11] have reported some mismatch. On the basis of condensed FF (local softness) indices Roy et al. introduced two different local reactivity descriptors, "relative electrophilicity" ($s_k^{\,+}/s_k^{\,-}$) and "relative nucleophilicity" ($s_k^{\,-}/s_k^{\,+}$) of any particular atom k, to locate the preferable site of nucleophilic and electrophilic attack on it, respectively. The rationality of this choice was given that the individual values of $s_k^{\,+}$ and $s_k^{\,-}$ are strongly influenced by the basis set or correlation effects. But the ratios of $s_k^{\,+}$ and $s_k^{\,-}$, involving two differences of electron densities (see eqs 10a,b) of systems differing by one in their number of electrons at constant nuclear framework, are expected to be less sensitive to the basis set and correlation effects.[11] These two newly defined reactivity descriptors are shown to generate improved intramolecular reactivity trends than those obtained from condensed FF indices.[11,20] The general scheme to use these two newly defined local reactivity descriptors to predict the preferable reactive site is as follows,

(i) Choose only the sites (i.e., atoms) having comparable and higher $s_k^{\,+}$ and $s_k^{\,-}$ values, (ii) then compare the $s_k^{\,+}/s_k^{\,-}$ and $s_k^{\,-}/s_k^{\,+}$ values of only those sites and (iii) if for any site $s_k^{\,+}/s_k^{\,-} > s_k^{\,-}/s_k^{\,+}$ then it is the preferred electrophilic and vice versa.

Very recently Roy et al.[21,22] have shown that "relative electrophilicity" ($s_k^{\,+}/s_k^{\,-}$) and "relative nucleophilicity" ($s_k^{\,-}/s_k^{\,+}$), when evaluated through Hirshfeld's population analysis (HPA) (ref 23) technique, produces the more reliable local reactivity trends than when the same reactivity descriptors are evaluated through Mulliken population analysis (MPA) (ref 24) technique. Without going into details of that aspect we here simply state that in the present study we will be using HPA technique.

4. Methodology and Computational Details

The parent unsymmetrical ketones used by Mahrwald and Gündogan[8] and the corresponding "less substituted" and "more substituted" enolate intermediates are depicted in Figure 3. Here, for the sake of calculation we have considered enol intermediates

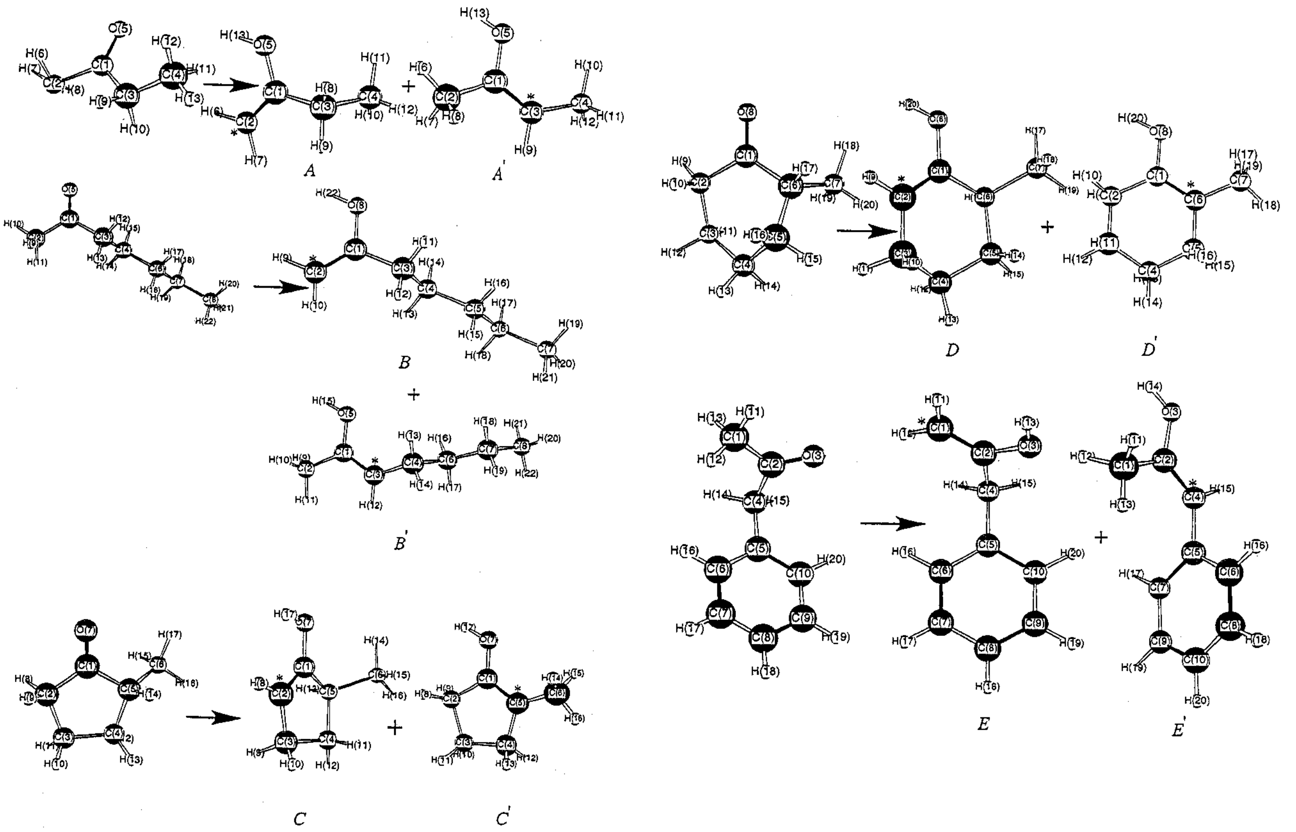

Figure 3. The unsymmetrical ketones considered in the present study. The corresponding "less substituted" (**A**, **B**, **C**, etc.) and "more substituted" (**A′**, **B′**, **C′**, etc.) enol intermediates are also shown. Here the double bonds are represented by the solid lines (e.g., $C_1{=}C_2$ in **A**, $C_1{=}C_3$ in **A′**, etc.) and the single bonds are represented by the hollow lines. The "*" indicates the "less substituted" and "more substituted" α-carbon atoms.

instead of the enolate ones. This means that the enolate $-OM$ has been replaced by enolic $-OH$. We can justify this change by arguing that both M^+ and H^+ are Lewis acids. This replacement is more justified in the present case as the study by Mahrwald and Gundogan[8] is a direct aldol addition and no stable enolate is formed. But we can always imagine the occurrence of a transient keto−enol tautomerism. The atoms are numbered for simplicity of discussion and the most active sites of the enol intermediates, relevant in the present study, are indicated by "*" (see also Figures 1 and 2). Similarly the model di-enols, with number of intervening carbon atoms (C_n) extending up to 4 (i.e., $n = 1{-}4$), are shown in Figure 4 and named as di-enol-1 ($n = 1$), di-enenol-2 ($n = 2$), etc. From Figure 3 we can argue that although the most active sites (indicated by "*") in the two kinds of enol intermediates of the unsymmetrical ketones have different chemical environment, they have the similarity in one aspect. That is the noninterference (or negligible interference) of the chemical environment of one active site to that of the other. This justifies that the proposed model can be applied in general to all the unsymmetrical ketones chosen in the present study. The results obtained in our study will justify that we may not be wrong in our argument.

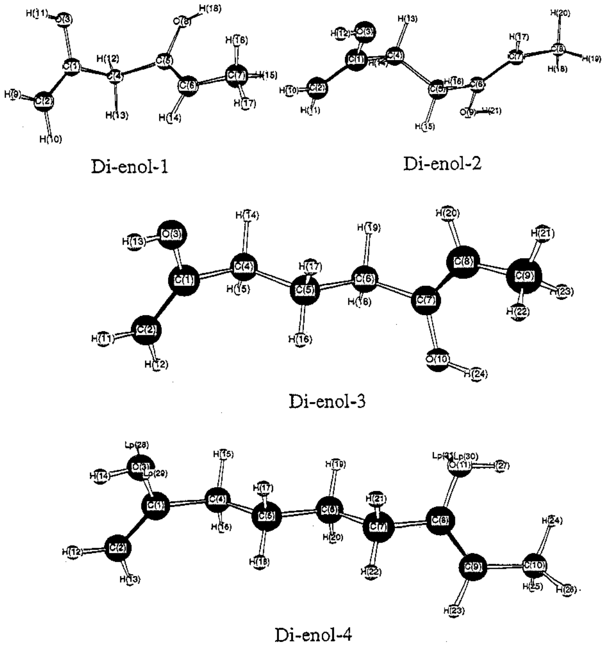

Figure 4. The four model di-enol intermediates with increasing number of intervening carbon atoms (i.e., C_n). Here di-enenol-1 has one intervening carbon atom, di-enenol-2 has two intervening carbons atoms, etc. (See text).

Optimized geometries at DFT levels are used. The geometries are optimized at two different levels, BLYP/dnd and BLYP/dnp. Here in BLYP method gradient corrected exchange and correlation functionals are used. The exchange functional is as proposed by Becke[25] and the correlation functional is as suggested by Lee, Yang and Parr.[26] 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 highest occupied orbital in free atom). The "dnd" level basis set is similar to "dnp" basis except that no "p" functions are used on hydrogen. Abbreviations for the methods that will be used are BLYP/dnd ≡ A1 and BLYP/dnp ≡ A2. 'The size of the "dnd" level basis set is comparable to Gaussian 6-31G* basis sets, and "dnp" basis sets are comparable to 6-31G** sets. However, it is reported that numerical basis set is much more accurate than a Gaussian basis set of the

TABLE 1: s_k^+, s_k^-, s_k^+/s_k^-, and s_k^-/s_k^+ Values (Evaluated through Hirshfeld's Population Analysis Technique) of the More Active Atomic Positions of Different Enol Intermediates Considered in the Present Study[a]

enol intermediates	atomic center	s_k^+	s_k^-	s_k^+/s_k^-	s_k^-/s_k^+
A	C_1	0.16318	0.32094	0.50845	1.96677
	C_2	0.26942	0.63054	0.42729	2.34035
	O_5	0.24157	0.40228	0.60049	1.66531
	H_{13}	0.47648	0.13557	3.51455	0.28453
A′	C_1	0.09583	0.35302	0.27146	3.68378
	C_3	0.16499	0.50040	0.32971	3.03297
	O_5	0.26004	0.37323	0.69674	1.43526
	H_{13}	0.62990	0.15385	4.09428	0.24424
B	C_1	0.16284	0.21379	0.76168	1.31288
	C_2	0.24726	0.43358	0.57028	1.75354
	O8	0.19156	0.27448	0.69791	1.43286
	H_{22}	0.36989	0.10165	3.63882	0.27481
B′	C_1	0.14473	0.32651	0.44327	2.25599
	C_3	0.16738	0.44058	0.37992	2.63217
	O_5	0.19031	0.33903	0.56132	1.78151
	H_{15}	0.40140	0.14126	2.84151	0.35193
C	C_1	0.13828	0.30504	0.45330	2.20605
	C_2	0.20441	0.47678	0.42873	2.33248
	O_7	0.26165	0.35915	0.72853	1.37263
	H_{17}	0.59780	0.12808	4.66735	0.21425
C′	C_1	0.08561	0.33425	0.25612	3.90446
	C_5	0.10905	0.39750	0.27435	3.64500
	O_7	0.25600	0.35143	0.72847	1.37274
	H_{17}	0.64451	0.14750	4.36969	0.22885
D	C_1	0.16562	0.31637	0.52349	1.91026
	C_2	0.21286	0.48199	0.44163	2.26434
	O_8	0.20065	0.38273	0.52427	1.90741
	H_{20}	0.36070	0.13058	2.76219	0.36203
D′	C_1	0.12908	0.33656	0.38352	2.60744
	C_6	0.13921	0.39337	0.35390	2.82567
	O_8	0.20215	0.34696	0.58263	1.71636
	H_{20}	0.42217	0.14615	2.88869	0.34618
E	C_1	0.20452	0.36756	0.55641	1.79722
	C_2	0.09857	0.16617	0.59316	1.68588
	O_3	0.13066	0.22270	0.58673	1.70435
	H_{13}	0.28831	0.09544	3.02083	0.33103
E′	C_2	0.29443	0.29508	0.99779	1.00221
	C_4	0.18825	0.33546	0.56116	1.78201
	O_3	0.19509	0.32830	0.59425	1.68280
	H_{14}	0.11595	0.14005	0.82791	1.20786

[a] The s_k^+ and s_k^- values are in atomic units. The basis set used is "dnp". To identify the enol intermediates denoted by **A**, **A′**, **B**, **B′**, etc., see Figure 3

TABLE 2: The Most Active Nucleophilic Sites of the Enol Intermediates as Obtained by Comparing the s_k^- and s_k^-/s_k^+ Values from Table 1[a]

enol intermediates	when s_k^- values are compared	when s_k^-/s_k^+ values are compared
A	C_2	C_2
A′	C_3	C_1*[b]
B	C_2	C_2
B′	C_3	C_3
C	C_2	C_2
C′	C_5	C_1*
D	C_2	C_2
D′	C_6	C_6
E	C_1	C_1
E′	C_4	C_4

[a] To identify the enol intermediates denoted by **A**, **A′**, **B**, **B′**, etc., see Figure 3. [b] Here "*" indicates that the trend does not match with the experimental observation.

same size.[27] Both "dnd" and "dnp" are as included in DMOL^3 program.[27]

To be sure that the geometry corresponding to the minimum energy is reached, frequencies are simultaneously checked while optimizing the geometries (until there is no imaginary frequency in optimized geometry). Local softness values (both s_k^+ and s_k^-) are evaluated using eqs 10a,b. The methods used are A1 and A2, and the population analysis technique adopted is HPA (i.e., stockholders' charge partitioning technique) available in the DMOL^3 Program.

5. Results and Discussion

A. Predictions of the Most Reactive Sites Using Local Reactivity Descriptors. *(i) Active Sites in the Enol Intermediates Generated From Unsymmetrical Ketones.* In Table 1 we have presented the s_k^+, s_k^-, s_k^+/s_k^-, and s_k^-/s_k^+ values of the most reactive sites (both for electrophilic and nucleoplilic attack) of the two types of enol intermediates. The values are generated using "dnp" basis set (we want to mention that as "dnp" is a superior basis set to "dnd" we are reporting the values obtained by "dnp" basis set only. The values obtained by using "dnd" basis set are with us and will be supplied upon request. This is true for model di-enol intermediates also). It is clear from Table 1 that the carbon atoms which belong to the C═C bond and the O atom of the −O−H group are preferably nucleophilic in nature. The enolic H atom is the most electrophilic among all the atoms which also justify that it is acidic in nature. In Table 2 we have summarized the results obtained from Table 1. It is obvious from Table 2 that although there are three preferable nucleophilic atoms in each of the enol intermediates (i.e. the carbon atoms belonged to the C═C bond and the O atom of the −O−H group) only the "less substituted" and "more substituted" C atoms of the corresponding enol intermediates (marked by "*" in Figure 3) display maximum nucleophilicity in most cases. The observations is true when we compare either s_k^- or s_k^-/s_k^+ values. This helps us to argue why these are the most probable sites where electrophilic attack by an aldehyde will take place in the next step of aldol condensation. Only in the "more substituted" enol intermediates of two cases (i.e., **A′** and **C′** in Table 2) the values obtained by s_k^-/s_k^+ are not as expected. In both these two cases the carbon atoms attached to the enolic-OH group appear to be more nucleophilic than the "more substituted" α-carbon atoms (C_3 in **A′** and C_5 in **C′**) when s_k^-/s_k^+ values are considered.

(ii) Active Sites in the Proposed "Two-in-One" Model Di-enol Intermediates. The values of s_k^+, s_k^-, s_k^+/s_k^- and s_k^-/s_k^+ of the more active atomic sites of model di-enol intermediates have been presented in Table 3. Here depending on the number of intervening carbon atoms (see section 2) the model di-enols have been termed as di-enol-1 (one intervening carbon atom), di-enol-2 (two intervening carbon atoms), etc. Here for di-enol-1 the values clearly shows that the carbon atoms belonged to the C═C bonds and the two enolic O atoms are nucleophilic in nature. However, if we analyze s_k^- and s_k^-/s_k^+ values in the same way as mentioned in section 3. B, we find that C_2 and C_6 show much higher nucleophilicity than the other four atoms. It is to be mentioned that these two carbon atoms are analogous to the "less substituted" and "more substituted" carbon atoms of the parent unsymmetrical ketone (see Figure 1). This justifies why in the next step of aldol addition the electrophilic attack by the aldehydes will take place in these two positions. The two enolic H atoms (H_{11} and H_{18}) appear to be highly electrophilic, justifying the acidic nature of these two atoms in the enol intermediate. Thus, all the characteristics of an enol intermediate, which is believed to be the precursor of the final aldol product, are maintained in our proposed model.

The predominant nucleophilicity of the 'less substituted' and 'more substituted' carbons atoms is maintained even when we

TABLE 3: s_k^+, s_k^-, s_k^+/s_k^-, and s_k^-/s_k^+ Values (Evaluated through Hirshfeld's Population Analysis Technique) of the More Active Atomic Positions of the Model Di-enol Intermediates (See Figure 4) Proposed in the Present Study[a]

model di-enol intermediates	atomic center	s_k^+	s_k^-	s_k^+/s_k^-	s_k^-/s_k^+
di-enol-1	C_1	0.13253	0.16933	0.78268	1.27766
	C_2	0.23684	0.38487	0.61538	1.62500
	C_5	0.11566	0.19202	0.60231	1.66029
	C_6	0.16435	0.33368	0.49254	2.03030
	O_3	0.17155	0.23906	0.71759	1.39355
	O_8	0.15384	0.25898	0.59402	1.68345
	H_{11}	0.35305	0.10154	3.47684	0.28762
	H_{18}	0.23740	0.09324	2.54599	0.39277
di-enol-2	C_1	0.14632	0.17804	0.82183	1.21680
	C_2	0.23863	0.38324	0.62267	1.60599
	C_6	0.10631	0.19719	0.53913	1.85484
	C_7	0.14489	0.32894	0.44049	2.27022
	O_3	0.17947	0.23720	0.75663	1.32166
	O_9	0.15404	0.24492	0.62894	1.58998
	H_{12}	0.36009	0.09831	3.66279	0.27302
	H_{21}	0.27178	0.09088	2.99057	0.33438
di-enol-3	C_1	0.14476	0.18139	0.79806	1.25304
	C_2	0.23326	0.38213	0.61043	1.63819
	C_7	0.11077	0.19956	0.55507	1.80159
	C_8	0.14652	0.33114	0.44248	2.26000
	O_3	0.17495	0.23649	0.73978	1.35176
	O_{10}	0.15004	0.24059	0.62363	1.60352
	H_{13}	0.34638	0.09319	3.71698	0.26904
	H_{24}	0.25817	0.08645	2.98644	0.33485
di-enol-4	C_1	0.15299	0.18467	0.82848	1.20703
	C_2	0.23487	0.38009	0.61792	1.61832
	C_8	0.11355	0.20319	0.55882	1.78947
	C_9	0.14194	0.32959	0.43064	2.32211
	O_3	0.17690	0.23935	0.73908	1.35304
	O_{11}	0.15299	0.24622	0.62136	1.60937
	H_{14}	0.33945	0.09114	3.72459	0.26849
	H_{27}	0.26087	0.08516	3.06316	0.32646

[a] The s_k^+ and s_k^- values are in atomic units.

TABLE 4: Trends of the Intermolecular Reactivities of the Enol Intermediates as Obtained by Comparing the s_k^- and s_k^-/s_k^+ Values (Taken from Table 1) of the Relevant Atomic Centers in Which We Are Interested

enol intermediates	atomic center	s_k^- values	s_k^-/s_k^+ values	trends using s_k^- values	trends using s_k^-/s_k^+ values
A	C_2	0.63054	2.34035		
				A > **A′***[a]	**A** < **A′**
A′	C_3	0.50040	3.03297		
B	C_2	0.43358	1.75354		
				B < **B′**	**B** < **B′**
B′	C_3	0.44058	2.63217		
C	C_2	0.47678	2.33248		
				C > **C′***	**C** < **C′**
C′	C_5	0.39750	3.64500		
D	C_2	0.48199	2.26434		
				D > **D′***	**D** < **D′**
D′	C_6	0.39337	2.82567		
E	C_1	0.36756	1.79722		
				E > **E′** *	**E** > **E′***
E′	C_4	0.33546	1.78201		

[a] Here "*" indicates that the trend does not match with the experimental observations.

increase the number of intervening carbon atoms in the model di-enol intermediates. This is evident when we analyze the values of di-enol-2, di-enol-3, and di-enol-4. The 'less substituted' and 'more substituted' carbons atoms in these model systems are C_2 and C_7 (di-enol-2), C_2 and C_8 (di-enol-3), and C_2 and C_9 (di-enol-4), respectively. The enolic H atoms in these model systems also show high electrophilicity indicating the acidic character of the enolic H atom. The very fact that there is no significant change in the numerical values of local reactivity descriptors from di-enol-2 onward justify our argument that we have attained the level of saturation in terms of the number of intervening carbon atoms. Moreover the qualitative trend of the nucleophilicity and electrophilicity does not alter with the increase of intervening carbon atoms. Thus, it seems that model di-enol intermediate with only one intervening carbon atom (i.e., di-enol-1) is sufficient enough to be considered for the present study.

B. Prediction of Predominant Aldol Product Directly from "Less Substituted" and "More Substituted" Enol Intermediates Generated From Unsymmetrical Ketones. In section 2 we discussed with a probable explanation why local softness and related reactivity descriptors are not very reliable to compare the intermolecular reactivity sequences. Thus, the use of such local reactivity descriptors to predict the predominant aldol product by comparing the reactivities of two active sites which belong to two different chemical systems (i.e., "less substituted" and "more substituted" enol intermediates generated from an unsymmetrical ketone) may lack rigorous theoretical support. Nevertheless it may be interesting to carry on such an analysis because it will test the validity of the above argument and also a comparison can be made with the trends obtained from the proposed model di-enol intermediates discussed in the next section (i.e., section 5C).

In Table 4 we have summarized the reactivity trends by comparing the s_k^- and s_k^-/s_k^+ values of the relevant reactive sites in the "less substituted" (denoted by **A**, **B**, **C**, etc.) and "more substituted" (denoted by **A′**, **B′**, **C′**, etc.) enol–intermediates. Here the accepted line of argument is that "higher s_k^- or, to be more precise, higher s_k^-/s_k^+ value means higher reactivity of the atomic site in question which, in the next step of aldol addition, leads to predominant aldol product". On the basis of above argument we see from Table 4 that when s_k^- values are compared we get the experimental trend (i.e., the "more substituted" aldol product is the predominant one) only in one case and that is from heptane-2-one (i.e., by comparing **B** and **B′**). However, when we use s_k^-/s_k^+ values for comparison we get the experimental trend in four cases. Only in the case of 3-phenyl propan-2-one the generated trend is opposite to that of the experimental one because here the "less substituted" α-carbon atom (C_1) in **E** appears to be more nucleophilic than the 'more substituted' α-carbon atom (C_4) in **E′**. One plausible reason may be the fact that the C═C bond in the "more substituted" form (**E′**) is in direct conjugation with the phenyl (Ph-) ring. So the more substituted α-carbon atom (C_4) in **E′** may loose some of its electron share due to delocalization in the Ph- ring and thus decreasing its nucleophilicity.

C. Prediction of Predominant Aldol Product from the Proposed Model Di-enol Intermediates. In section 2 we have argued that the model di-enol intermediate, being a single chemical entity (although internally it bears the features of both the enol intermediates generated from the corresponding unsymmetrical ketone), is a fit case where we can use local sofness related reactivity descriptors for comparison of intramolecular reactivity sequence. We have discussed the "less substituted" and "more substituted" carbon atoms (which are relevant in the present study to determine the predominant aldol product) of the four model di-enol intermediates (see Figure 4) in subsection 5.A. The trends of s_k^- and s_k^-/s_k^+ values of those atoms (as obtained from Table 3) is summarized in Table 5. Here also the accepted line of arguments, to predict the predominant aldol product, is the same as that of subsection 5.B and that is "the active site which has higher s_k^-, or to be more precise, higher s_k^-/s_k^+ value is more reactive toward the attacking electrophile

TABLE 5: Trends of the Intramolecular Reactivities of the Model Di-enol Intermediates as Obtained by Comparing the s_k^- and s_k^-/s_k^+ Values (taken from Table 3) of the Relevant Carbon Atoms in Which We Are Interested (See Text for Details): s_k^-/s_k^+

model di-enol intermediates	atomic center	s_k^- values	values	trends using s_k^- values	trends using s_k^-/s_k^+ values
di-enol-1	C_2	0.38487	1.62500	$C_2 > C_6$*	$C_2 < C_6$
	C_6	0.33368	2.03030		
di-enol-2	C_2	0.38324	1.60599	$C_2 > C_7$ *	$C_2 < C_7$
	C_7	0.32894	2.27022		
di-enol-3	C_2	0.38213	1.63819	$C_2 > C_8$ *	$C_2 > C_8$
	C_8	0.33114	2.26000		
di-enol-4	C_2	0.38009	1.61832	$C_2 > C_9$ *	$C_2 < C_9$
	C_9	0.32959	2.32211		

[a] Here "*" indicates that the trend does not match with the experimental observations.

(i.e., aldehyde) and so will generate the predominant aldol product". On the basis of the above argument we see that the observed trends go against the experimental ones in all cases when s_k^- values are used for comparison. Here it seems that "less substituted" aldol products should be the predominant ones, although the experimental study shows that the predominant aldol products are the "more substituted" ones. It is interesting to observe that the trends become corrected in all the cases when s_k^-/s_k^+ values are considered for comparison. Thus, the corrected trends using s_k^-/s_k^+ further justifies the argument that it is a more reliable intramolecular reactivity descriptor than s_k^-. Also the results justify our claim that the model di-enol intermediates can successfully predict the predominant aldol products generated from unsymmetrical ketones.

6. Conclusion

In this article we have shown how the proposed "two-in-one" model di-enol intermediate successfully represents the "less substituted" and "more substituted" enol intermediates generated from an unsymmetrical ketone. When "local softness" based reactivity descriptors (i.e., s_k^-/s_k^+) are used to evaluate the reactivities of the relevant atoms (i.e., the "less substituted" and "more substituted" α-carbon atoms which take part in aldol addition reactions) in the proposed model, it could successfully predict the predominant aldol product (i.e., the more substituted one) as observed by the experimental study. The model also displays other important aspects of an enol intermediate i.e., acidic nature of the enolic H atoms, high nuclephilicity of the carbon atoms belonged to C═C bond and the O atoms of the enolic −OH group (probably because of the presence of lone pair of electrons on the O atom). However, it should be mentioned that the local reactivity indicator values evaluated in the present study can only predict qualitative trend and it will be unwise to try to predict the quantitative yields (i.e., the experimental yields as obtained by Mahrwald and Gundogan[8]) from the numerical values of these indicators. It is noteworthy that although it is advised not to use local softness related reactivity descriptors to predict intermolecular reactivity trends,[10,11] the present study shows that "relative nucleophilicity" (s_k^-/s_k^+) does that job satisfactorily baring a single exception (see section 5.B).

Although the proposed model have been used to predict the preferable aldol product generated from unsymmetrical ketones, the logic behind its proposal can be extended to other reactions which involve two or more reactive intermediates generated from a common substrate and as long as electronic effects play the key role in determining the predominant product. In this context we should mention that the recent studies have demonstrated the negligible effect of solvent on the numerical values of condensed Fukui functions.[28]

It will be of interesting if the reverse models, e.g., "one-into-two", "one-into-three", etc., can be constructed to treat the big chemical systems having more than one similar kinds of reactive functionalities (or read "reactive centers" for simplicity). For big chemical systems (e.g., biomolecules and polymers), the calculation of local softness and related reactivity descriptors is very much time-consuming (sometimes impossible) because it involves the evaluation of global softness. But if we break it into different fragments where each fragment carries one reactive center and then compare the reactivities of those sites using local hardness values (as proposed by Langenaeker et al.[10]), then some interesting results may be extracted. Care should be taken so that only those reactive centers which are far apart from one another in the original chemical system (i.e., the neighborhood of one active center does not have much chemical or physical impact on the other active center) goes to different parts after fragmentation. Of course the authors' idea in this direction is in a premature stage and efforts are being made to elucidate it.

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