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Regioselectivity of Oxetane Formation in the Photocycloaddition of Lowest ^{3}(n,π*) State of Carbonyl Compounds: Interpretation Using Local Softness

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The principle of hard and soft acid−base (HSAB) has been used extensively in the past to study the behavior of chemical systems.[1,2] Within the framework of the density functional theory (DFT), several global and local quantities related to the chemical reactivity appeared naturally and were expressed in the form of simple mathematical expressions.[3] In other words, a sound mathematical formulation of the HSAB principle, which was well known, was possible through the development of the DFT. Accordingly, the assumption that soft acids prefer to bind with soft bases, and hard acids with hard bases, could now be shown quantitatively. Pioneering work by Yang and Parr,[4] and Gazquez and Mendez,[5] made this principle to use in a local sense by defining various local reactivity indices, such as the Fukui function and local softness and hardness. The Fukui function and local softness can be used to measure the reactivity of a particular site in a molecule. Recently, the regioselectivity of various aldehydes and ketones and substituted benzynes in their ground electronic state toward nucleophilic and electrophilic attack has been interpreted in terms of Fukui function and local softness and hardness.[6-8] In the present note, we apply for the first time the HSAB principle in a local sense to interpret the regioselectivity in photocycloaddition of the lowest *triplet* state of ketones with several partners containing a double bond (referred hereafter as "enes").

The condensed Fukui functions of an atom, *k*, in a molecule with *N* electrons is given by[9]
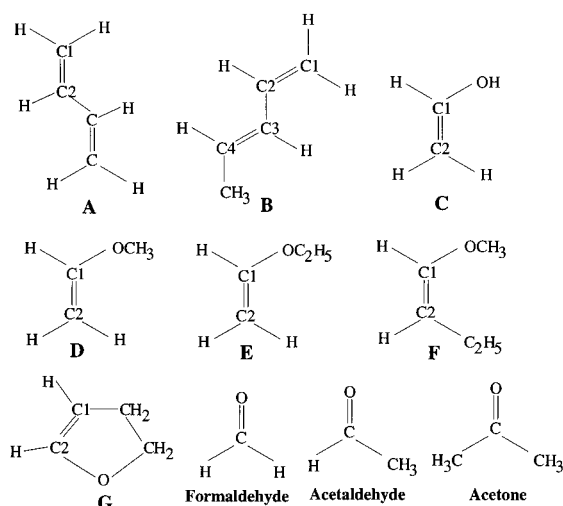
$$f_k^+ = q_k(N+1) - q_k(N)$$

$$f_k^- = q_k(N) - q_k(N-1)$$

$$f_k^0 = (q_k(N+1) - q_k(N-1))/2$$

where superscripts +, −, and 0 refer to the nucleophilic, electrophilic, and radical attack, respectively, and q_k is electronic population of the atom *k* in the molecule. The

Scheme 1

A= 1,3 butadiene, B= pent-2,4-diene, C= hydroxy ethylene, D= methoxy ethylene, E= ethoxy ethylene, F= 1-methoxy but-1-ene, G= 1,2 dihydroxy furan

corresponding condensed local softness parameters are defined as[4]

$$s_k^i = f_k^i S$$

where $i = +, -$ or o, and S is the global softness which is the inverse of hardness (η). In the DFT formalism, hardness is defined as
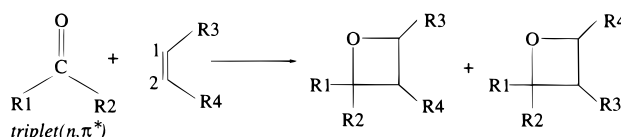
$$2\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} = 1/S$$

where E is the energy of the N electron system. In the finite difference approximation, S can be expressed as

$$S = \frac{1}{IE - EA}$$

where IE and EA are the first vertical ionization energy and electron affinity of the molecule, respectively.

A general representation of the photocycloaddition reaction under consideration can be given as:

This type of cycloaddition is observed from both lowest excited singlet and triplet (n,π*) states of carbonyl compounds.[10] Two different isomers of oxetanes can be formed depending on whether C1 in the ene makes a bond with the O or C atom of the excited carbonyl group. The reaction is known to be regioselective. The ratio of both product isomers as expected is highly dependent on the nature of substituents R3 and R4. The carbonyls and enes considered in the present study are shown in Scheme 1.

Geometry optimization of the carbonyl compounds in their lowest triplet (n,π*) state and the enes in their ground electronic state have been carried out by the DFT method using B3LYP exchange correlation functionals[11]

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Table 1. The Global Softness, S, and Condensed Local Softnesses, s_k^+ or s_k^- in atomic units, and Ionization Energies (IE) and Electron Affinities (EA) in kcal/mol Calculated at the B3LYP/6-31G(d,p) Level for All the Molecules Shown in Scheme 1. Values Within Parantheses Were Derived from Mulliken Charges.

molecule	S	s_{C1}^-	s_{C2}^-	IE	EA
A	2.638	0.981 (0.351)	0.208 (0.065)	199.4	−38.4
B	2.743	0.930 (0.338)	0.110 (0.034)	188.6	−40.2
		0.409 (0.105)[a]	0.697 (0.264)[b]		
C	2.109	0.317 (0.196)	1.163 (0.360)	207.1	−90.4
D	2.252	0.297 (0.135)	1.059 (0.354)	197.4	−81.2
E	2.281	0.309 (0.129)	1.060 (0.353)	194.4	−80.7
F	2.442	0.374 (0.194)	0.944 (0.270)	182.8	−74.2
G	2.330	0.488 (0.178)	0.708 (0.298)	187.1	−82.3
		s_C^+	s_O^+		
formaldehyde	3.582	0.949 (0.066)	1.591 (1.673)	201.5	36.3
acetaldehyde	4.158	0.611 (0.058)	1.972 (1.862)	179.8	28.8
acetone	4.680	0.613 (0.050)	2.243 (2.038)	164.0	29.9

[a] s_{C3}^-. [b] s_{C4}^-.

Table 2. The Values of Δ_{ij}^{CO} for the Addition of the Enes Shown in Scheme 1 to the Triplet State of the Carbonyls. Values within Parantheses Were Derived from Mulliken Charges

ene		formaldehyde	acetaldehyde	acetone	expt.
A	Δ_{12}^{CO}	1.913 (2.667)	3.247 (3.316)	4.275 (3.984)	
	Δ_{21}^{CO}	0.921 (1.748)	1.444 (2.283)	1.756 (2.846)[a]	ref 15
B	Δ_{12}^{CO}	2.194 (2.761)	3.568 (3.421)	4.650 (4.100)	
	Δ_{21}^{CO}	1.142 (1.783)	1.338 (2.323)	1.979 (2.890)[a]	ref 16
	Δ_{34}^{CO}	1.092 (1.987)	1.668 (2.556)	2.433 (3.150)[a]	
	Δ_{43}^{CO}	1.461 (2.498)	2.451 (3.130)	3.368 (3.782)	
C	Δ_{12}^{CO}	0.583 (1.740)	0.741 (2.274)	1.254 (2.836)[a]	ref 17
	Δ_{21}^{CO}	1.669 (2.268)	3.043 (2.867)	4.012 (3.489)	
D	Δ_{12}^{CO}	0.708 (1.745)	0.932 (2.280)	1.502 (2.843)[a]	ref 17
	Δ_{21}^{CO}	2.467 (2.448)	3.006 (3.070)	3.986 (3.714)	
E	Δ_{12}^{CO}	0.691 (1.757)	0.922 (2.282)	1.492 (2.845)[a]	ref 17
	Δ_{21}^{CO}	1.655 (2.466)	2.966 (3.090)	3.939 (3.736)	
F	Δ_{12}^{CO}	0.750 (1.985)	1.130 (2.553)	1.745 (3.147)[a]	ref 18
	Δ_{21}^{CO}	1.482 (2.229)	2.665 (2.827)	3.603 (3.449)	
G	Δ_{12}^{CO}	0.883 (1.903)	1.615 (2.461)	2.374 (3.044)[a]	ref 19
	Δ_{21}^{CO}	1.275 (2.289)	2.212 (2.894)	3.972 (3.521)	

[a] Corresponding product is most favorable as observed experimentally in the given references.

with the 6−31G(d,p) basis set. The entire calculation was performed using the GAUSSIAN-94 program package.[12] The energies of ($N + 1$) and ($N − 1$) ions were calculated with geometries of the corresponding neutral molecule (N electron system) optimized at the B3LYP/6−31G(d,p) level. This is done to ensure that the external potential due to the nuclei in the molecule remains unchanged; the use of the vertical electron affinities and ionization energies is a necessary condition to calculate the Fukui function and local softness. Since it is now well established that molecular electrostatic potential (MEP) derived charges produce more realistic electronic population than Mulliken charges, we have calculated the MEP-derived charges using the Merz−Singh−Kollman scheme.[13] However, for the purpose of comparison, the Fukui function and softness were also calculated using the Mulliken charges. Table 1 lists the IE and EA of all the molecules shown in Scheme 1 calculated at the B3LYP/6-31G(d,p) level of theory.

The energy required to transfer one electron from the ene to the carbonyl is much less than that of the reverse process. This essentially means that the ene acts as a nucleophile in the photocycloaddition reaction with triplet carbonyl compounds. Hence, the s_k^- and f_k^- of the enes, and s_k^+ and f_k^+ carbonyl compounds, should be used to interpret their reactivity in the photocycloaddition reaction. In other words, the enes considered here act as electron rich molecules to the triplet ketones. This conclusion is in agreement with the known behavior of these enes toward the triplet ketones.[10] Table 1 also shows the condensed Fukui functions, local softness, and the global softness of the molecules shown in Scheme 1. For comparison, the values of these parameters derived from Mulliken charges are also tabulated. The global softness, S, for the enes and triplet carbonyl compounds are quite different. Hence, according to Gazquez et al.,[5] the Fukui function may not be a good criterion for measuring the reactivity; one should rather consider the local softness. Data tabulated in Table 1 show that even though the values of the local quantities calculated using the Mulliken charges are different from those calculated using MEP derived charges, the overall trend remains similar. The first step of this triplet cycloaddition reaction with an electron-rich ene is a triplet biradical formation via the attack of carbonyl oxygen to one of the carbon atoms involved in the double bond. After the $T_1 \rightarrow S_0$ intersystem crossing, the two radical centers form a bond to give the final product, oxetane, in its ground singlet state.[10,14] Table 1 shows that in all cases the desired biradical (through C····O attack) is formed when the bond formation takes place between the softest electrophilic center of the carbonyl group with the softest nucleophilic center of enes. However, if we consider the entire process as a single-step reaction, we need to define a quantity which can provide the information about the regioselectivity of such four-center reaction. We define such quantity as

$$\Delta_{ij}^{CO} = (s_C^+ - s_i^-)^2 + (s_O^+ - s_j^-)^2 \qquad (1)$$

equation where i, j indicate two carbon atoms of the ene involved in the cycloaddition. Δ_{ij}^{CO} indicates the square deviation of the softness values when atom C_i and C_j of the enes form bonds with the carbonyl C and O atoms, respectively. Hence, a Δ_{ij}^{CO} is associated with every product. A similar quantity has recently been used to predict the selectivity of [4 + 2] cycloaddition reaction in the ground electronic state.[8] From the HSAB principle in a local sense, the smaller value between Δ_{ij}^{CO} and Δ_{ji}^{CO} indicates the corresponding process to be favored.

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For example, if $\Delta_{ij}^{CO} > \Delta_{ji}^{CO}$, the oxetane formation by attaching C_j and C_i with C and O of the carbonyl compound, respectively, will be more favorable. Table 2 records the values of Δ_{ij}^{CO} for the photocycloaddition of triplet carbonyl compounds along with other enes shown in Scheme 1. Available experimental results are also shown in Table 2. Interestingly, in all cases experimentally observed predominant products are consistently associated with lower values of Δ_{ij}^{CO}. The most intriguing example is the reaction of ketones with methylbutadiene (**B**) which has possibilities of four different kinds of product formation. Table 2 shows that $\Delta_{34}^{CO} < \Delta_{43}^{CO}$ and $\Delta_{21}^{CO} < \Delta_{12}^{CO}$. This essentially indicates that the possible products are where C and O of the carbonyl group are attached to (i) C3 and C4, and (ii) C2 and C1, respectively. This is in good agreement with experimental results. It is worthwhile to mention that Δ_{ij}^{CO} values calculated from the Mulliken charges follow the similar trend to those obtained from the charges derived from MEP. Thus, the Mulliken charges can also be used to measure the reactivities of various chemical systems, even though their actual magnitudes are different from that derived from MEP.

In conclusion, we intend to say that the HSAB principle can be applied, in a local sense, to predict products formation in a photochemical reaction. The overall good agreement between the calculated results and experimental facts suggests that the HSAB principle in a local sense is able to predict correctly the reactivities of the various atoms and regioselectivity during a photocycloaddition reaction. The predominant product seems to be formed obeying the local HSAB principle. The fact that the major product can be predicted by just looking at the softness values of the isolated molecules makes the latter useful reactivity indices for this type of reactions.