Density Functional Approach to Regiochemistry, Activation Energy, and Hardness Profile in 1,3-Dipolar Cycloadditions

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The principle of hard and soft acids and bases has been applied in a local sense to rationalize the regiochemistry in cycloaddition reaction of a few typical 1,3-dipoles with phosphorus-containing dipolarophiles. It has been observed in most cases that the transition state with higher hardness is associated with lower activation energy. The hardness profile has also been investigated for these cycloaddition reactions; while the hardness value goes through a minimum along the reaction coordinate, its minimum does not coincide with the energy maximum.

1. Introduction

The knowledge of the specific sites of interaction between two chemical species, the mechanism of transition-state formation, and the origin of energy barriers are of fundamental importance in determining the path and products of a given chemical reaction. It has recently been found that many important chemical concepts useful for the understanding of chemical reactivity (e.g., electronegativity, hardness, softness) appear naturally within density functional theory (DFT).[1] For example, the electronegativity (χ)[2] and hardness (η),[3] which have long been providing a better understanding of chemical reactivity, have recently been identified as the first and second derivative of energy (E) with respect to the number of electrons (N) of the system. A number of local reactivity descriptors, such as Fukui functions and local softness, have also been defined to extract information about the variations of chemical reactivity from one place to the other inside a molecule.[1] There are numerous applications of these local reactivity descriptors for the interpretation of reaction mechanisms.[4−8] The observed regioselectivity in various cycloaddition reactions, e.g., Diels Alder reactions, excited-state cycloaddition reactions between carbonyls and alkenes, has also been explained[9,10] by using these local reactivity parameters and the local hard and soft acids and bases (HSAB) principle, recently proposed by Gazquez and Mendez.[11] The beauty of this approach lies in the fact that similar to the frontier orbital theory the predictions are made from isolated molecular properties only.

The success of these DFT-based reactivity descriptors for understanding reaction mechanisms strengthens the motivation of using them in the study of the progress of chemical reactions. It is always interesting to see how one reactivity parameter varies with the progress of a chemical reaction and whether it is possible to define a reaction profile in terms of that parameter, in the same way as an energy profile. Such possibilities have already been discussed in the literature using η or chemical potential (μ) as the parameter of interest.[12−16] All these studies were mostly confined to very simple reactions such as tautomerism, isomerization, rotation, or inversion in a molecule. It has been observed that in most of the cases the hardness of the system goes through a minimum near the transition structure. Recently Ghanty and Ghosh[17] made a similar study on the dissociation and isomerization types of reactions and observed that average hardness of the products is higher than that of the reactants for the exchange reactions. In the case of isomerization reactions, they found that hardness is minimum for the transition state. They also considered polarizability of the system as an index and observed that the condition of minimum polarizability can in general be associated with the maximum hardness. During the course of the present study, another work in this direction has been published by Gazquez,[18] and the main proposition of his work is that the activation energy of a chemical reaction depends primarily on the difference between the hardness of the initial state of a reaction and that of the transition state.

In the present work, an attempt has been made to study various aspects of cycloaddition reactions between a 1,3-dipole (henceforth referred to as 13DP) and a phosphorus-containing dipolarophile (hereafter referred to as DPh). These cycloaddition reactions are important in synthetic organic chemistry due to the potential of forming many starting materials for the syntheses of P-heterocycles. The problem of primary importance here concerns the regiochemistry of the cycloaddition. When a dipolarophile A═B and a 1,3-dipole C═D═E approach each other, two cycloadducts are in principle possible (Scheme 1). However, in majority of cases, the reaction proceeds mainly through one transition state and thus introduces regioselectivity. Recently, we have shown[19] that the local HSAB principle can be useful for the interpretation of this observed regioselectivity in many cycloaddition reactions. The purpose of the present study is not only the interpretation of such regiochemistry but also to examine how hardness of the system changes along the reaction coordinate, and thus the possibility of defining a *hardness profile* in this type of reaction is discussed. In view of the recent work by Gazquez,[18] an attempt has also been made to find out some correlation between activation energies and hardness differences between the reactant and the transition state. It should be emphasized that all the earlier relevant studies considered very simple reactions such as isomerization or tautomerism, and thus it is the first attempt to examine the *hardness profile* in the case of more complex multicenter reactions.

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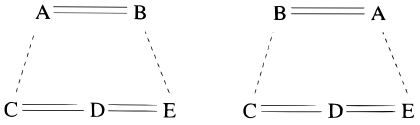
SCHEME 1



2. Theory and Computational Details

The fundamental expression of DFT for the change in energy from one ground state to another is

$$dE = \mu\, dN + \int \rho(r)\, \delta v(r)\, dr$$

where μ, $\rho(r)$, and $v(r)$ are the chemical potential, electron density, and external potential of the system, respectively. Hence both μ and $\rho(r)$ can be considered as a response function to the dN and $\delta v(r)$ perturbations, respectively. The first partial derivative of μ with respect to N, the total number of electrons, is the global hardness (η).[20]

$$2\eta = \left[\frac{\partial \mu}{\partial N}\right]_{v(r)} = \left[\frac{\partial^2 E}{\partial N^2}\right]_{v(r)} = \frac{1}{S}$$

where S is the global softness. Due to the discontinuity of the energy versus N curve, one generally makes a finite difference approximation to obtain η and S. In the finite difference approximation,[20] η and S can be written as

$$\eta = \frac{(\mathrm{IE} - \mathrm{EA})}{2}$$

$$S = \frac{1}{(\mathrm{IE} - \mathrm{EA})}$$

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

Now coming to the local reactivity descriptors, the Fukui function $f(r)$ is defined as the first derivative of the electron density $\rho(r)$ of a system with respect to the number of electrons N at constant external potential $v(r)$:[21]

$$f(r) = \left[\frac{\partial \rho(r)}{\partial N}\right]_{v(r)} = \left[\frac{\delta \mu}{\delta v(r)}\right]_N$$

It has been argued[13] that the greater the Fukui function value, the greater the reactivity of a site. Local softness $s(r)$ is defined as

$$s(r) = \left[\frac{\partial \rho(r)}{\partial \mu}\right]_{v(r)} = \left[\frac{\partial \rho(r)}{\partial N}\right]_v \left[\frac{\partial N}{\partial \mu}\right]_v = Sf(r)$$

The condensed form of Fukui functions of an atom, say k, in a molecule with N electrons has been proposed by Yang and Mortier:[22]

$$f_k^+ = [q_k(N+1) - q_k(N)] \qquad \text{for nucleophilic attack}$$

$$f_k^- = [q_k(N) - q_k(N-1)] \qquad \text{for electrophilic attack}$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)] \qquad \text{for radical attack}$$

where q_k is the gross electronic population of atom k in a molecule. In view of the relation $s(r) = Sf(r)$, the corresponding condensed local softness parameters can easily be calculated from the condensed Fukui function and global softness. Gazquez and Mendez[11] proposed a local version of the well-known HSAB principle, which essentially indicates that the interaction between A and B is favored when it occurs through those atoms having approximately equal softness values.

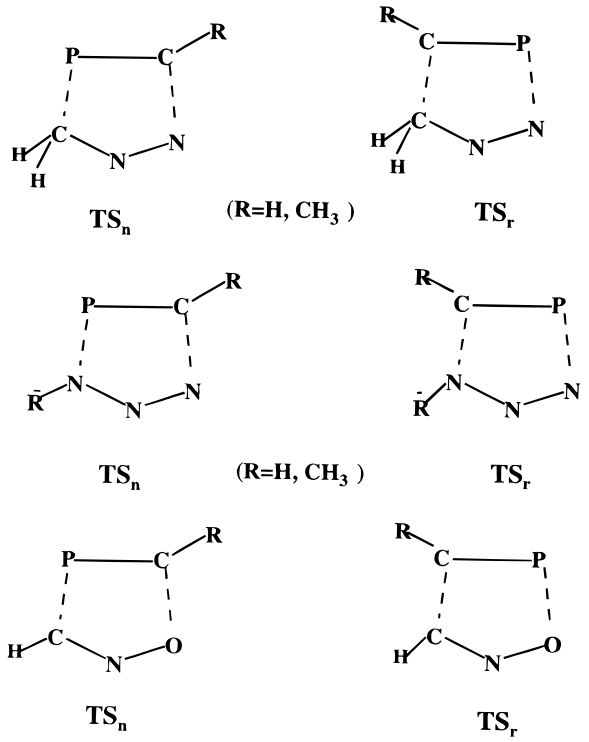


Figure 1. Two possible transition states for the cycloaddition between 1,3-dipole and dipolarophile. TS_n is the lower energy transition state, and the reaction proceeds mainly through this transition state.

In this work, four 1,3-dipoles including H_2CNN, HCNO, HNNN, and H_3CNNN, and two dipolarophiles, HCP and H_3C-CP, are taken for studying cycloadditions between them. The geometries of all these molecules were fully optimized, and then vertical ionization energies and electron affinities were calculated at the optimized geometry by following ΔSCF procedure. Then η and S were estimated from the finite difference formula mentioned above. The transition structures (TS) of both the normal (TS_n) and reverse (TS_r) (see the next section for the definition of TS) cycloadditions between all the 13DP and DPh were also located and subsequently characterized by vibrational frequency calculations. An intrinsic reaction coordinate (IRC) calculation was performed to identify a few other points along the reaction coordinate. In all cases IRC calculations were performed near the transition structure, because it would be increasingly difficult to estimate the hardness of the system from the finite difference approximation when the two reactants are far apart but still interacting. Subsequently, η was estimated at each point along the reaction coordinate to draw the hardness profile. All the calculations were performed by using the density functional procedure with the B3LYP exchange correlation functional and 6-31G(d,p) basis functions. Atomic charges were evaluated by using the procedure of electrostatic potential driven charges. The Gaussian-94 program package[23] was used for all the calculations, and the MK option was used for the evaluation of atomic charge.

3. Results and Discussion

As mentioned earlier, there are two possible paths, in principle, for each [3+2] cycloaddition, and accordingly two transition states are also possible (Figure 1). The lower energy TS is defined as TS_n (normal) and the other one as TS_r (reverse).

TABLE 1: Global Hardness (η), Global Softness (S), and Local Softness Values for Nucleophilic (s^+) and Electrophilic (s^-) Attack As Calculated from the B3LYP Results. Data Are in au

molecule	η	S	atom (k)	s_k^-	s_k^+
HN^1NN^2	0.236	2.12	N^1	1.00	0.59
			N^2	0.92	1.17
H_2CNN^1	0.195	2.57	C	2.03	0.14
			N^1	1.19	1.27
HCNO	0.262	1.91	C	0.95	1.30
			O	0.86	0.68
$H_3CN^1NN^2$	0.217	2.30	N^1	0.96	0.89
			N^2	0.93	1.18
HCP	0.220	2.27	C	0.78	−0.01
			P	1.42	1.88
$H_3C\text{-}C^1P$	0.206	2.42	C^1	0.64	0.07
			P	1.42	1.84

However, it has been observed from many studies[24−26] that the cycloaddition reactions proceed mainly through one path, and thus these reactions are regiospecific or at least regioselective. For example, in the case of [3+2] cycloaddition between diazoalkenes and alkyl-substituted phosphaalkynes,[27] only one cycloadduct has been formed, and in the case of HC≡P + H_2-CNN[25] the reaction proceeds mainly through the TS_n (Figure 1), which also corresponds to the lower energy TS. It should be pointed out here that there are two possible mechanisms for these cycloadditions, namely, the concerted and the biradical path. In the present work, only the concerted approach has been considered.

Now to explain this observed regioselectivity, the two reactants, 13DP and DPh, are first classified as nucleophile or electrophile and then the local HSAB principle is applied. Starting from the idea that the softnesses of the interacting atoms should be as close as possible, a quantity has been defined for the regioselectivity that could be a measure of predominance of one approach over the other. When atoms i and j of a molecule A are involved in the formation of a cycloadduct with atoms k and l of another molecule B, one can define the following as a measure of regioselectivity:

$$\Delta_{ij}^{kl} = (s_i - s_k)^2 + (s_j - s_l)^2$$

where s_i's are the appropriate type of atomic softnesses (if s_i and s_j are electrophilic, then s_k and s_l are obviously nucleophilic). Δ can be considered as a measure how extensively the HSAB principle is satisfied. The reaction path associated with lower Δ value will be the preferred one. From the ionization energies and electron affinities of the 13DP and DPh it is observed that the direction of charge transfer is favorable from the 13DP to the DPh. Similar observations were made earlier for the cycloaddition between 13DP and many other types of DPh.[24] Dipolarophiles are thus considered as electrophiles and 1,3-dipoles as nucleophiles in these cycloaddition reactions. Hence the appropriate Δ quantities for the two types of cycloadditions between 13DP (C═D═E) and DPh (A═B) defined in Figure 1 are

$$\Delta_n = (s_C^- - s_A^+)^2 + (s_E^- - s_B^+)^2$$

and

$$\Delta_r = (s_C^- - s_B^+)^2 + (s_E^- - s_A^+)^2$$

where Δ_n and Δ_r correspond to TS_n and TS_r respectively.

Table 1 shows the global hardness and softness and local softnesses for electrophilic and nucleophilic attack of the DPh and 13DP considered in the present investigation. In the case of diazomethane and HCNO, the carbon atom has a much larger softness for electrophilic attack than the terminal nitrogen or oxygen atoms, respectively, whereas for the HNNN, the nitrogen atom attached to the H atom has a larger softness for electrophilic attack. For both dipolarophiles, HCP and H_3C-CP, the phosphorus has a larger softness for nucleophilic attack than the carbon. Table 2 presents the activation energies corresponding to the two possible transition structures and the corresponding Δ values estimated from the above-mentioned expression. TS_n is lower in energy than the TS_r, and the reaction proceeds mainly through TS_n. Now, it is clear from Table 2 that Δ_n is consistently lower than Δ_r for all the cycloaddition reactions considered here. Thus the transition state formed by maintaining the local HSAB principle is always lower in energy. This clearly explains the observed regioselectivity of these cycloaddition reactions.

TABLE 2: Activation Energies (E_{act} in kcal/mol) of the Cycloaddition Reactions between 1,3-Dipole and Dipolarophile and the Corresponding Δ Values (See Text for Definition)

		E_{act}		Δ	
dipole	dipolarophile	TS_n	TS_r	Δ_n	Δ_r
HCNO	HCP	5.63	6.53	1.61	1.96
	CH_3CP	7.39	10.99	1.40	1.73
H_2CNN	HCP	5.86	6.92	1.45	4.63
	CH_3CP	9.47	12.37	1.28	4.24
HNNN	HCP	8.77	11.12	1.63	1.94
	CH_3CP	12.38	14.85	1.41	1.71
H_3CNNN	HCP	7.94	10.10	0.76	1.01

TABLE 3: Hardness (η) and Polarizability (α)[a] of the Two Transition States of the Cycloaddition Reactions between 1,3-Dipoles and Dipolarophiles. Data Are in au

		η		α	
dipole	dipolarophile	TS_n	TS_r	TS_n	TS_r
HCNO	HCP	0.1888	0.1880	65.08	66.04
	CH_3CP	0.1679	0.1776	81.97	80.81
H_2CNN	HCP	0.1700	0.1667	71.66	73.58
	H_3C-CP	0.1626	0.1616	87.25	88.16
HNNN	HCP	0.1870	0.1852	66.01	66.85
	CH_3CP	0.1754	0.1762	81.29	81.51
H_3CNNN	HCP	0.1813	0.1794	80.32	81.28

[a] α values were calculated using 6-311++G(3df,2p) basis set and taking the arithmetic average of the three diagonal elements of the polarizability tensor.

Table 3 records the hardness and polarizability of both the transition states. It is interesting to observe that in most of the cases the lower energy TS_n also has larger hardness and lower polarizability compared to TS_r. In the case of HCNO + CH_3-CP, the lower energy TS_n has lower hardness and higher polarizability. As the maximum hardness principle (MHP)[28] is valid only under constant chemical and external potential, this observation does not violate the MHP. However, it is also difficult to explain this observation from the parameters considered in the present study, and further work with enhanced sophistication is required to explain it. From the hardness and polarizability of the transition structures, it seems that maximum hardness is associated with minimum polarizability. This corroborates well with the observations of Ghanty and Ghosh[17,29] and others.[30,31] It is also interesting to notice that η of the TS is always lower than both the reactants. According to the recent proposition of Gazquez,[18] activation energy is mainly determined by the hardness difference between the reactants and the transition state; the lower the difference, the lower the activation energy. However, no general correlation between hardness

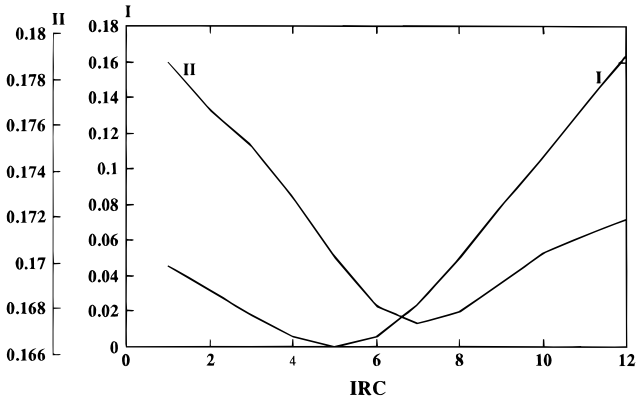


Figure 2. Change in relative energy ($E_{TS} - E$ in au), curve I, and hardness (in au), curve II, along the intrinsic reaction coordinate near the transition state (TS_n) of the cycloaddition reaction $H_2CNN + HCP$. Relative energies are scaled by a factor of 10.

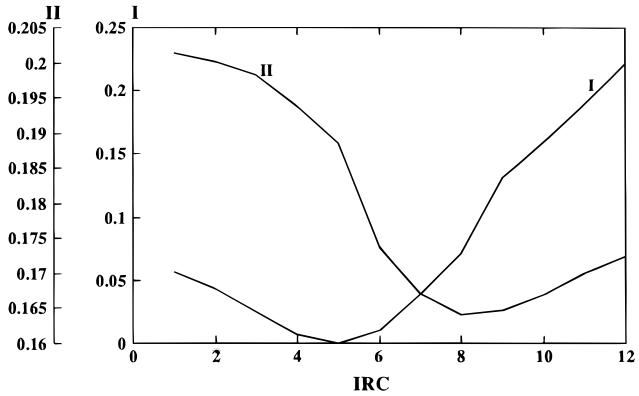


Figure 3. Change in relative energy ($E_{TS} - E$ in au), curve I, and hardness (in au), curve II, along the intrinsic reaction coordinate near the transition state (TS_n) of the cycloaddition reaction HCNO + HCP. Relative energies are scaled by a factor of 10.

difference and activation energy has been observed from the present calculations. For a particular 13DP, activation energy is always higher for the cycloadditon of CH_3CP in comparison to that of HCP. But hardness differences between reactants and the transition structures are not always higher for CH_3CP than HCP. Moreover, for a particular couple of 13DP and DPh, the hardness difference between the reactants and the TS will certainly be lower for TS_r (associated with higher activation energy in comparison to TS_n), which is contrary to the proposition of Gazquez. However, we must mention that the present study is limited only to a few systems, and to draw a final conclusion, one definitely needs to study a variety of other systems.

To examine the possibility of defining a *hardness profile* in this type of cycloaddition reaction, the hardness values were calculated at some selected points along the intrinsic reaction coordinate corresponding to TS_n for the reactions H_2CNN + HCP, HCNO + HCP, and HNNN + HCP. The points considered are around the TS_n and on both the reactant and product sides (with a step length of 0.01 au along the IRC vector). It should be mentioned that η does not change regularly if one goes far away from the TS to the reactant side, and many local minima appear in the hardness profile. We believe this is mainly due to the error in the estimation of η from the finite difference approximation when the two reactants are far apart but still interacting. Figures 2, 3, and 4 show how the energies and hardness values change near the transition state (TS_n) for the above-mentioned three reactions. In all cases, the maxima in the energy profile (minima in the figures) do not coincide

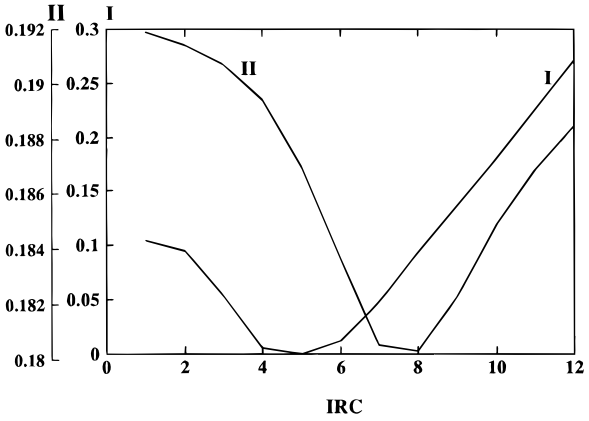


Figure 4. Change in relative energy ($E_{TS} - E$ in au), curve I, and hardness (in au), curve II, along the intrinsic reaction coordinate near the transition state (TS_n) of the cycloaddition reaction between HNNN and HCP. Relative energies are scaled by a factor of 10.

with the minima in the hardness profile. Comparing to the energy profile, the minima in the hardness profile appear around three steps later (toward the product side) along the IRC. However, the hardness indeed goes through a minimum along the reaction coordinate, and thus it is possible to define a *hardness profile* for these types of cycloaddition reactions. It is also interesting to observe that the general nature of the hardness profile for all three reactions is almost the same. It appears that the general Hammond postulate can also be applied to the *hardness profiles* (the hardness of the TS being closer to that of the product).

4. Conclusions

It is shown that regioselectivity of the cycloaddition reactions between 1,3-dipoles and dipolarophiles can be explained by using local softness and the local HSAB principle. The transition structure formed by maintaining the local HSAB principle is invariably lower in energy, and the reaction proceeds mainly through this TS. In the majority of cases the TS_n with lower energy is also associated with larger hardness and lower polarizability. It has also been observed that the hardness goes through a minimum along the reaction coordinate, and thus it is possible to define a *hardness profile*. The minimum in *hardness profile* appears more toward the product side compared to the maximum in energy profile, in line with the general idea of the Hammond postulate.

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