Regiochemistry of 1,3-dipolar cycloadditions between azides and substituted ethylenes: a theoretical study

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The cycloaddition reactions of 1,3-dipoles such as the simple azides (R–N_3, R = H, CH_3) with substituted ethylenes (H_2C=CHX, X = H, F, Cl, CH_3, OH and CN) as dipolarophiles have been studied by a density functional procedure using the hybrid B3LYP exchange correlation functional and 6-31G(d,p) basis functions. For each system, two distinct transition states have been located corresponding to the relative orientation of two molecules. The energy difference between the two transition states varies from 0.2 to 5 kcal mol^{-1}. The addition thus shows a certain regioselectivity. This observed regiochemistry is explained using recently developed DFT-based reactivity descriptors, such as local softness and Fukui functions.

1. Introduction

Orientation or regioselectivity is an important criterion of mechanism in the field of cycloaddition reactions. Thus clearer understanding of the origin of regioselectivity is crucial for the interpretation of reaction mechanism of a cycloaddition reaction. Diels–Alder and 1,3-dipolar cycloadditions (13DC) constitute one of the most important classes of organic reactions and are among the most versatile and powerful preparative methods for the synthesis of cyclic compounds.[1] The mild reaction conditions, and in particular the high stereospecificity and regioselectivity, made these pericyclic reactions an approach of choice in synthetic organic chemistry. Regioselectivity is a major feature of 13DC since it occurs with any unsymmetrically substituted dipolarophile (DPh). Moreover, the reaction can be driven to yield regiospecific products by suitably changing the substituent in DPh. Owing to its importance in the synthesis of heterocyclic molecules, 13DC has long been drawing the attention of both experimental and theoretical chemists.[2–10] A 1,3-dipole (13DP) can add onto asymmetric dipolarophiles such as substituted ethylenes in two different orientations (see Fig. 1). However, in many cases it has been observed that the reaction proceeds mainly through one reaction path, which is lower in energy.[6,11,12] This introduces regioselectivity in these reactions. Munk and Kim studied the 13DC reactions between enamines as dipolarophiles (DPhs) and phenyl azide as dipole.[13] They observed that the addition was regiospecific. In the preferred cycloadduct the negative end of the azide dipole (N-atom bearing the phenyl group) is directed to that carbon atom of the unsaturated linkage bearing the electron-releasing amino group. Regioselectivity has also been observed in the 13DC between phenyl azide and many other DPhs.[14,15]

If the steric effects are insignificant, the product distribution will be determined by electronic effects occurring at the rate determining step. With respect to the reactivity centres in the azide molecule, it is well known that *electrophilic* attack occurs at the α-nitrogen atom and *nucleophilic* attack at the terminal nitrogen atom.[4] The general characteristics of the 13DC of azides and other 1,3-dipoles (13DP) were discussed a long while back by Huisgen.[2] According to the author, the 13DC occurs by a concerted mechanism in which two new σ bonds are formed simultaneously, although there may be an asynchronicity in the bond formation process. Later Houk and co-workers[5] applied frontier molecular orbital (FMO) perturbation theory in the interpretation of regioselectivity in 13DC. They concluded that identification of the controlling FMO was essential for predicting the regiochemistry of the reaction. In the case of azides, 13DC with electron rich dipolarophiles are said to be 13DP LUMO-controlled and generally the unsubstituted nitrogen end of the azide joins to the unsubstituted terminus in the dipolarophiles. On the other hand, reactions with electron deficient dipolarophiles are 13DP HOMO-controlled and in the majority of cases, the substituted azide N-atom joins to the unsubstituted end of the dipolarophiles. Possible complications may occur in some cases due to strong electrostatic effects and closed shell repulsions. The FMO approach has been found to be fairly successful in explaining various experimental observations. However, the balance of factors leading to a particular regioselectivity is often too close to make a choice of which pair of frontier orbitals to take. Moreover, it was observed that the FMO approach failed to predict the correct regiochemistry in some 13DC reactions.[16] Thus it should be useful to find out the efficacy of other reactivity concepts for the elucidation of the regioselectivity.

Although the theoretical framework based on frontier orbital theory was developed a long while back for explaining the observed regioselectivity in 13DC, theoretical works focusing on the structural, energetics and other aspects of 13DC involving azides and DPhs containing the C=C bond are still very limited. In view of the lack of both qualitative knowledge and quantitative information on the structure, energetics and reactivity of dipolarophiles containing the C=C bond in 13DC with azides, we set out to perform a theoretical study on 13DC of hydrazoic acid (H–N_3) and simple substituted azides (H_3C–N_3) as representative 13DP and substituted ethylenes as representative DPhs. A wide variety of substituent is chosen, from the electron donor 'methyl' to the electron withdrawing 'cyano', to observe the effect of these substituents on the regiochemistry. The objective of this work is twofold: (i) in the first step, we have characterized the structural and energetic aspects of the cycloadditions, R–N=N=N + H_2C=CHX (R = H, CH_3; X = H, F, Cl, CH_3, OH, CN), and in particular their regiochemical behaviour, and (ii) in the second step, an attempt has been made

Table 1 Geometrical parameters obtained at the B3LYP/6-31G(d,p) level for the two transition states (TS_n and TR_r, see Fig. 1) of the cycloaddition reactions between R–NNN and H_2C=CHX. Bond lengths and angles are in Å and degrees, respectively

		R_1		R_2		α		β	
X	R	TS_r	TS_n	TS_r	TS_n	TS_r	TS_n	TS_r	TS_n
H	H	2.14		2.15		99.1		103.2	
	CH_3	2.16		2.17		99.6		102.8	
F	H	2.12	2.11	2.15	2.17	100.7	100.2	102.2	104.5
	CH_3	2.13	2.17	2.17	2.16	100.6	98.4	101.9	102.8
Cl	H	2.18	2.10	2.10	2.16	98.4	99.9	100.9	104.2
	CH_3	2.18	2.10	2.12	2.19	98.4	100.1	100.8	104.2
CH_3	H	2.14	2.10	2.16	2.19	101.2	101.2	101.8	105.2
	CH_3	2.16	2.11	2.18	2.22	100.9	101.1	101.5	105.0
OH	H	2.15	2.02	2.12	2.28	101.4	103.6	99.6	108.0
	CH_3	2.15	2.06	2.14	2.28	101.5	102.5	99.5	107.1
CN	H	2.28	2.03	2.02	2.18	94.6	101.7	99.1	104.9
	CH_3	2.29	2.02	2.04	2.21	94.5	102.2	98.8	105.0

to rationalize the observed regioselectivity by using the reactivity descriptors based on density functional theory (DFT). Since DFT is becoming an efficient and computationally cost effective tool for electronic structure calculations, it is worthwhile to find out how DFT-based reactivity concepts can be used for the interpretation of reaction mechanism and especially the regiochemistry in the present 13DC study. These descriptors have recently been applied successfully in the interpretation of reaction mechanism in a variety of chemical problems.[17–20] In addition, this representative study will be helpful for the understanding of 13DC with larger olefins and specially the intramolecular 13DC which is very important to synthetic organic chemistry.

2. Details of calculations

DFT calculations were performed by using the GAUSSIAN94 set of programs.[21] The hybrid B3LYP functional for exchange and correlation energies[22,23] was employed throughout this work in conjunction with the 6-31G(d,p) one electron basis functions. Geometrical parameters of the 1,3-dipoles, R–NNN (R = H, CH_3), the substituted ethylenes, H_2C=CHX (X = H, F, Cl, CH_3, CN, OH), the transition states (TSs) for cycloadditions and the cycloaddition products were fully optimized and characterized by harmonic vibrational frequency analyses at the indicated level. Atomic charges were evaluated both by Mulliken population analysis and by following the procedure of electrostatic potential (ESP) driven charges. The MK option was used in the GAUSSIAN94 for calculating the ESP atomic charges.

The classical barrier height ($\Delta E_o^{\ddagger}$) associated with each TS was calculated from expression (1), where E_i's correspond to the

$$\Delta E_o^{\ddagger} = E_{AB} - (E_A + E_B) \tag{1}$$

energy of the species '*i*' including the zero point vibrational energy (ZPVE). It is well known that the computed vibrational frequencies generally overestimate those from experiment. This overestimation is due to the combined effect of neglecting the anharmonicity for the potential energy function and the inadequacy of the computational method. Scaled frequencies are, therefore, used for estimating experimental fundamental frequencies.[24,25] B3LYP vibrational frequencies were scaled by 0.9806 for estimating the ZPVE, as proposed in ref. 25. The heats of reaction (ΔH(298 K)) for the two possible products were calculated from the energies and vibrational frequencies calculated at the optimized geometries for both the possible products and the isolated reactants. The vibrational contribution to the thermal corrections was calculated from the unscaled harmonic vibrational frequencies because the scaling factor obtained by fitting to the ΔH_{vib}(298 K) was very close to unity.[25] Translation and rotational motions were taken as classical. Thermal corrections were estimated at 298 K and 1 atm pressure.

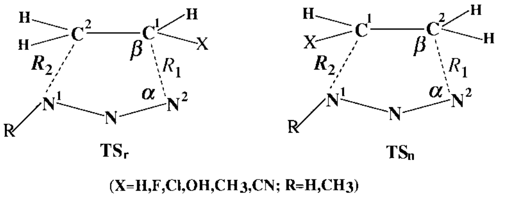


Fig. 1 Two possible modes of cycloadditions between azides and substituted ethylenes.

3. Results and discussion

The results obtained from our theoretical calculations are presented in two different sections. While the first is confined to the structural and energetic aspects of the 13DC, the second section is devoted to an analysis of the reaction mechanism and regiochemistry by using the DFT-based reactivity descriptors.

3.1 Structure and energetics

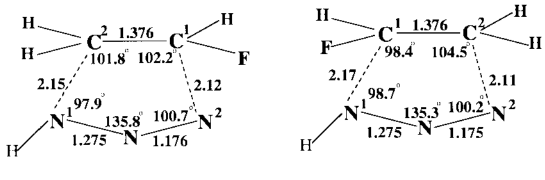
As discussed earlier, there are two possible orientations for the 13DC between azides and substituted ethylenes. Thus two transition states do exist corresponding to the two different modes of cycloadditions. The TS where the substituted N-atom of the azide joins to the substituted C-atom of ethylene is referred to as TS_n, whereas the TS where the substituted N-atom of the azide joins to the unsubstituted carbon atom of ethylene is designated as TS_r (see Fig. 1). It should be pointed out here that there are two possible mechanisms for these 13DC, namely the concerted and biradical paths. General opinion, however, is in favour of a concerted reaction path.[26] In the present work, only the concerted approach has been considered. In fact, starting from the TS, many points have been located along the intrinsic reaction coordinate (IRC) path for the 13DC with ethylene and fluoroethylene to observe whether the TSs actually correspond to the 13DC. The IRC calculations confirmed that the TSs were exclusively related to the cycloaddition of azides and substituted ethylenes. We were unable to locate any diradical formation along the IRC path.

Table 1 presents some key geometrical parameters of the transition states for the 13DC optimized at the B3LYP/6-31G(d,p) level. Fig. 2, as a representative example, shows some important geometrical parameters for the two TSs associated with the 13DC between HN_3 and fluoroethylene. In the case of R–NNN + H_2C=CH_2, the bond lengths of the two newly forming N···C bonds are nearly the same (2.14 *vs.* 2.15 Å), whereas they differ significantly when one of the hydrogen

Table 2 Energy costs [in eV] for transferring an electron from the azide [A] to the dipolarophile [B] and *vice versa*

	HNNN		H_3C–NNN	
B	IE − EA[a]	IE − EA[b]	IE − EA[a]	IE − EA[b]
$H_2C{=}CHF$	14.13	12.33	13.19	12.24
$H_2C{=}CHCl$	13.26	12.01	12.31	11.90
$H_2C{=}CHCH_3$	14.03	11.73	13.09	11.64
$H_2C{=}CHOH$	14.57	11.30	13.62	11.21
$H_2C{=}CHCN$	11.68	12.68	10.73	12.59

[a] $IE_{dipole} - EA_{dipolarophile}$. [b] $(IE_{dipolarophile} - EA_{dipole})$.



TSr TSn

Fig. 2 Key geometrical parameters of the two transition states for the cycloadditions between hydrazoic acid and fluoroethylene optimized at the B3LYP/6-31G(d,p) level.

atoms of ethylene is substituted. The difference is especially significant when X = OH and CN. The angle *α* for the two TSs in the 13DC with cyanoethylene is quite different, whereas the maximum difference in angle *β* is observed for the 13DC with vinyl alcohol. For a particular DPh, the geometrical parameters (R_1, R_2, α, β) of the two TSs do not change much when one goes from HNNN to H_3C–NNN. In comparison to the isolated reactant, reactant structures, except the N–N–N angle, do not change significantly in the TSs. The N–N–N bond angle, however, changes from nearly 170° in the isolated R–NNN to about 135° in the TSs. This change in bond angle introduces loss of electron conjugation in the R–NNN molecule, which partly contributes to the reaction barrier. It should also be mentioned that the hydrogen atoms and the substituent in ethylene move away from the R–NNN molecule in the TSs.

The energy costs for transferring an electron from the azides to the substituted ethylenes or *vice versa* are listed in Table 2. The energy cost is estimated from the ionization energy (IE) and electron affinity (EA) of the isolated azide and the substituted ethylene. IE and EA are calculated by a ΔSCF procedure, *i.e.* by performing separate SCF calculations for the neutral, cationic and anionic systems at the optimized geometry of the neutral system. It is clear from Table 2 that for both the azides and for all the substituted ethylenes but cyanoethylene, the energy cost is less for transferring an electron from the DPh to the azide. Thus in all cases but the cyano substituted ethylene, azides behave as *electrophiles* and substituted ethylenes behave as *nucleophiles*. The reversal in behaviour in the case of cyanoethylene is probably due to the strong electron withdrawing character of the cyano group. In view of the strong basis set dependence of EA, a larger basis set 6-311+G(2d,p) has also been applied for the estimation of IE and EA of the azides and the substituted ethylenes to verify the *nucleophilic* and *electrophilic* character of the two reactants. Although the magnitude of EA changes substantially with the introduction of the larger basis set, the overall conclusions are the same as mentioned above from the smaller 6-31G(d,p) basis set. The observation was verified further from the Mulliken and electrostatic potential driven charge distribution at the TS. A significant amount of electronic charge transfer from the DPh to the azide has been observed in all cases but CN-substituted ethylene. Thus the 13DC's studied here are 13DP LUMO controlled, except that, in the case of cyanoethylene the process is 13DP HOMO controlled. Similar conclusions were also reached by Houk and co-workers.[5]

Table 3 Classical barrier heights ($\Delta E_o^{\ddagger}$ in kcal mol^{-1}) for the cycloaddition reactions R–NNN + $H_2C{=}CHX$ (R = H, CH_3 and X = H, F, Cl, CH_3, OH, CN). See Fig. 1 for the definition of the two transition states TS_n and TS_r

	R = H		R = CH_3	
X	TS_r	TS_n	TS_r	TS_n
H	19.63		18.33	
F	22.72	20.29	21.14	18.66
Cl	22.38	21.56	20.77	19.88
CH_3	21.36	20.86	20.02	19.87
OH	25.30	20.19	23.84	19.19
CN	19.56	20.33	17.62	17.88

Table 4 The negatives of the heats of reaction [$-\Delta H$(298 K), in kcal mol^{-1}] for the cycloaddition reactions R–NNN + $H_2C{=}CHX$ (R = H, CH_3 and X = H, F, Cl, CH_3, OH, CN). PD_n and PD_r are the cycloadducts formed through TS_n and TS_r, respectively. See Fig. 1 for the definition of the two transition states TS_n and TS_r. The last column under each 13DP (PD_n/PD_r) presents the expected product ratio calculated from the Arrhenius exponential factor

	R = H			R = CH_3		
X	PD_r	PD_n	PD_n/PD_r	PD_r	PD_n	PD_n/PD_r
H	21.3			24.0		
F	20.6	26.2	60.5	23.5	28.6	65.9
Cl	18.5	23.9	4.0	21.5	26.7	4.5
CH_3	20.2	20.3	2.3	23.0	21.4	1.3
OH	18.1	21.3	5592	20.9	23.2	2572
CN	14.3	15.0	0.3	17.3	17.3	0.6

Classical barrier heights, $\Delta E_o^{\ddagger}$, associated with the two modes of cycloadditions and corresponding to the two TSs, TS_n and TS_r, are given in Table 3. Table 3 shows that TS_n, where the substituent bearing carbon atom of ethylene joins to the substituted N-atom of azides, is lower in energy than TS_r, where the substituted nitrogen atom of azides joins to the unsubstituted carbon atom of ethylene. Only in the case of cyanoethylene is the reverse true. This contrasting behaviour is certainly due to the difference in reactivity among the DPhs; cyanoethylene acts as an *electrophile* towards azide, whereas other DPhs act as *nucleophiles*. The difference in barrier heights corresponding to two different orientations of cycloaddition range from 0.5 to 5.1 kcal mol^{-1} in the case of HNNN and from 0.2 to 4.6 kcal mol^{-1} in the case of H_3C–NNN. This difference in barrier height introduces a high regioselectivity in the process of cycloadditions for most of the cases. For the 13DC with HN_3, the activation barriers corresponding to TS_n increase in the order X = OH < F < CH_3 < Cl. In the case of H_3C–N_3, however, fluoroethylene has a lower activation barrier than vinyl alcohol. In both cases, the cycloaddition with cyanoethylene has the lowest activation barrier. For a particular DPh, the barrier heights are always lower for the H_3C–NNN in comparison to those of HNNN. Barrier heights are also found to be much higher than those observed in the case of cycloadditions between hydrazoic acid and hetero-dipolarophiles, such as HCP, H_3C–CP, H_2CNH *etc.*[27]

The heats of reaction, ΔH(298 K), for all the 13DC studied here are presented in Table 4. The reactions are found to be exothermic in nature. Except for the cycloaddition between cyanoethylene and azides, in all other cases the product formed through the lower energy TS_n is invariably associated with larger heats of reaction. For a particular DPh, the exothermicity is always higher for the H_3C–N_3 in comparison to HN_3. The 13DC with fluoroethylene is most exothermic (see the entries under PD_n in Table 4), whereas the 13DC with cyanoethylene is least exothermic. As these 13DC's are exothermic, from Hammond's postulate, one expects a more reactant like structure of the TS. This conforms well with our earlier observation that the reactant structures do not change significantly in the TSs.

The regioselectivities in the 13DC's discussed here were determined from the relative energies of the two TSs associated with the two modes of cycloadditions. Since in these reactions the same pair of reactants goes to form two different cycloadducts, the Arrhenius preexponential factor can be expected to be identical. Indeed, we observed from our theoretical calculations that the entropy values of TS_n and TS_r differ insignificantly. For example, the entropy values of TS_n and TS_r are 76.53 and 76.09 cal mol^{-1} k^{-1}, respectively for the 13DC between HN_3 and $H_2C{=}CHF$. Thus the relative amounts of the two product cycloadducts can be assumed to be proportional to the Arrhenius exponential factor $[\exp(-\Delta E_o^{\ddagger})/RT]$. The expected product ratios, PD_n/PD_r, calculated from the Arrhenius exponential factor $(\exp[(E_{TSr} - E_{TSn})/RT])$ are given in Table 4. High regioselectivity can be observed in the case of fluoroethylene and vinyl alcohol. In fact, the 13DC with vinyl alcohol seems to be regiospecific. The absence of experimental results does not allow us to make any direct comparison. Nevertheless, phenyl azides are known to produce regiospecific cycloadducts with styrene. High regioselectivity has been observed in many other 13DC's between phenyl azide and DPh with a C=C bond.[15,26]

3.2 Regiochemistry of the addition

The theoretical results reported in the preceding section show a definite regiochemistry in the 13DC's between azides and substituted ethylenes. We have used the DFT-based reactivity descriptors such as Fukui functions and local softness for the interpretation of regioselectivity. These concepts have been found to be very useful for explaining regiochemistry in addition reactions.[17–20] Since detailed discussions about these reactivity parameters can be found elsewhere,[28,29] only the relevant expressions used for the evaluation of different quantities are given here.

The global hardness (η) and softness (S) are calculated from the expressions[30] (2) and (3), where IE and EA are the first

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

$$S = \frac{1}{(\mathrm{IE} - \mathrm{EA})} \tag{3}$$

vertical ionization energy and electron affinity of the molecule, respectively.

The condensed form of Fukui functions of an atom, say k, in a molecule with N electrons has been proposed by Yang and Mortier[31] and expressed as (4), where q_k is the gross electronic

$$\begin{aligned} f_k^+ &= [q_k(N + 1) - q_k(N)] && \textit{for nucleophilic attack} \\ f_k^- &= [q_k(N) - q_k(N - 1)] && \textit{for electrophilic attack} \\ f_k^0 &= [q_k(N + 1) - q_k(N - 1)] && \textit{for radical attack} \end{aligned} \tag{4}$$

population of atom k in a molecule. In view of the relation $f(r) = s(r)/S$, the corresponding condensed local softness parameters can easily be calculated from the condensed Fukui function and global softness.

Gazquez and Mendez[32] proposed a local version of the well known HSAB principle which essentially indicates that the interaction between A and B is favoured when it occurs through those atoms having approximately equal softness values.

For explaining this regioselectivity, the two reactants, 13DP and DPh, are classified as *nucleophile* or *electrophile* and then the local HSAB principle has been 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 (say *nucleophilic*) are involved in the formation of a cycloadduct with atoms k and l of another molecule B (say *electrophilic*), one can define[18–20] eqn. (5) as a measure of regioselectivity,

$$\Delta_{ij}^{kl} = (s_i^- - s_k^+)^2 + (s_j^- - s_l^+)^2 \tag{5}$$

where s_i's are the appropriate type of atomic softnesses. Δ can be considered as a measure of how extensively the HSAB principle is satisfied. The reaction path associated with the lower Δ value will be the preferred one. As discussed in the previous section, azides behave as *electrophiles* and substituted ethylenes as *nucleophiles* for all the 13DC studied here, except in the case of cyanoethylene where azides behave as *nucleophiles*. Thus in all the 13DC but with cyanoethylene local softnesses for *electrophilic* attack are considered for the DPh and local softnesses for *nucleophilic* attack are taken for the azides for estimating the Δ from expression (5). In the case of cyanoethylene, the situation is reversed, atomic softnesses for *electrophilic* and *nucleophilic* attack are considered for the azides and the substituted ethylenes respectively.

Table 5 Global softness (S), local Fukui functions for *nucleophilic* (f^+) and *electrophilic* (f^-) attack and local softness values for *nucleophilic* (s^+) and *electrophilic* (s^-) attack as calculated from the B3LYP/6-31G(d,p) results. Data are given in atomic units

Molecule	S	Atom (k)	f_k^-	f_k^+	s_k^-	s_k^+
HN^1NN^2	2.12	N^1	0.47	0.28	1.00	0.59
		N^2	0.43	0.55	0.92	1.17
$H_3C{-}N^1NN^2$	2.30	N^1	0.42	0.39	0.96	0.89
		N^2	0.41	0.51	0.93	1.18
$H_2C^2{=}C^1HF$	2.00	C^1	0.22	0.20	0.44	0.40
		C^2	0.59	0.50	1.17	1.01
$H_2C^2{=}C^1HCl$	2.19	C^1	0.06	0.01	0.14	0.03
		C^2	0.48	0.60	1.06	1.31
$H_2C^2{=}C^1HCH_3$	2.11	C^1	0.27	0.19	0.57	0.40
		C^2	0.55	0.51	1.15	1.08
$H_2C^2{=}C^1HOH$	2.09	C^1	0.10	0.11	0.21	0.22
		C^2	0.57	0.53	1.19	1.11
$H_2C^2{=}C^1HCN$	2.36	C^1	0.23	0.15	0.54	0.35
		C^2	0.39	0.38	0.92	0.91

Table 5 presents the global softnesses, condensed Fukui functions and softnesses of the atoms involved in the cycloaddition for all the 13DP and DPh included in the present study. Global softnesses are estimated from expression (3), whereas condensed Fukui functions and softnesses are calculated by using expressions (4) and global softnesses. ESP atomic charges are used for the evaluation of atomic softnesses. At atomic level the substituent (R) bearing nitrogen atom (N^1) of azide has a larger softness for *electrophilic* attack and the other terminal nitrogen atom (N^2) has a larger softness for *nucleophilic* attack. This observation corroborates well the experimental observation. In the case of substituted ethylene, the unsubstituted carbon atom has a larger softness for *electrophilic* attack. The Δ_{ij}^{kl} values for both the TSs are listed in Table 6. It is interesting to notice from Table 6 that for each 13DC the lower energy TS (TS_r when X = CN and TS_n for others) is invariably associated with a lower Δ value. Thus TSs formed by maintaining the local HSAB principle are always lower in energy. It is really gratifying that a combination of DFT-based reactivity descriptors and the local HSAB principle can explain the observed regiochemistry in the 13DC. Especially, this approach successfully explains why cyanoethylene prefers an orientation different from the other substituted ethylenes. A closer look at Table 5 reveals that minimization of Δ (corresponding to the lower energy TS) also leads to a situation where the most *electrophilic* centre of the azides (the unsubstituted terminal nitrogen atom) joins to

Table 6 Δ-values (see eqn. (5) in the text for the definition of Δ) associated with the two transition states for each of the cycloaddition reactions between R–NNN and $H_2C{=}CHX$ (R = H, CH_3 and X = H, F, Cl, CH_3, OH, CN)

	R = H		R = CH_3	
X	TS_n	TS_r	TS_n	TS_r
F	0.02	0.86	0.20	0.62
Cl	0.21	1.27	0.58	1.11
CH_3	0.00	0.67	0.10	0.44
OH	0.15	1.28	0.47	1.03
CN	0.43	0.33	0.38	0.34

Table 7 Hardness (in a.u.) values of the transition states for the cycloaddition reactions R–NNN + $H_2C{=}CHX$ (R = H, CH_3 and X = H, F, Cl, CH_3, OH, CN). See Fig. 1 for the definition of the two transition states TS_n and TS_r

	R = H		R = CH_3	
X	TS_n	TS_r	TS_n	TS_r
H	0.193		0.183	
F	0.191	0.186	0.183	0.179
Cl	0.184	0.180	0.179	0.174
CH_3	0.186	0.183	0.177	0.176
OH	0.182	0.176	0.173	0.170
CN	0.180	0.174	0.173	0.169

the most *nucleophilic* centre of the substituted ethylenes (the unsubstituted carbon atom). Now, a look at Table 1 shows that in TS_n, R_1 is always shorter than R_2. This means the bond between the most *electrophilic* N-atom of the azide and the most *nucleophilic* carbon atom of the substituted ethylene forms earlier than the other novel bond.

Table 7 presents the hardness values of the two TSs for each of the cycloaddition reactions studied here. In all the cases but cyanoethylene, the lower energy TS, TS_n, has a larger hardness than the other TS, TS_r. In the case of cyanoethylene, the higher energy TS, TS_n, has the larger hardness. Of course, it does not violate the maximum hardness principle (MHP) of Parr and Chattaraj.[33] This is because the principle holds good only when the external potential and chemical potential remain constant. However, from the general trend and from the observations by others[27] it seems that the harder the TS, the more preferable it is.

4. Concluding remarks

The cycloaddition reactions between R–NNN and substituted ethylenes have been studied. In all the cases, a certain regioselectivity has been observed favouring the formation of one cycloadduct over the other. The energy barrier of addition is moderate and higher than that observed with heteronuclear dipolarophiles. The energy barrier is lowest in the case of 13DC with cyanoethylene and highest for the 13DC with chloroethylene. The cycloadditions are found to be exoergic. The regiochemistry of the cycloadditions has been explained successfully by using the density functional theory based reactivity descriptors, such as local softnesses and local HSAB principle. It has been observed that the transition state formed by maintaining the local HSAB principle is always lower in energy. In most of the cases, a lower energy transition state is also found to be associated with a large hardness. The 13DC between azides and vinyl alcohol appears to be regiospecific.

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