

1,3-Dipolar cycloadditions of thionitroso compounds (R–N=S): a density functional theory study

Trung Ngoc Le,^{ab} Loc Thanh Nguyen,^{ac} Asit K. Chandra,^d Frank De Proft,^a Paul Geerlings^{*a} and Minh Tho Nguyen^{*d}

^a *Eenheid Algemene Chemie, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium*

^b *Department of Chemistry, University of Danang, Vietnam*

^c *Faculty of Chemical Engineering, HoChi-Minh City University, Vietnam*

^d *Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium*

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The cycloaddition reactions of 1,3-dipoles, including fulminic acid (HCNO) and the simple azides (XNNN, X = H, CH₃, NH₂), with thionitroso compounds (R–N=S, R = H, NH₂) as dipolarophiles have been studied by density function procedures using the hybrid B3LYP exchange correlation function and 6–311G(d,p) basis functions. For each system, two (HCNO) or four (azide) distinct transition structures have been located and the intrinsic reaction coordinate path was constructed. It appears in all cases that activation energies for the cycloadditions are rather low, ranging from 0 to 30 kJ mol^{–1}. The additions are not stereospecific, the energy difference between transition structures having *cis* and *trans* dispositions of the N–R groups being rather small (less than a few kJ mol^{–1}). The addition shows a certain regioselectivity in which the attack of the O-atom of HCNO and N(R) of the azides to the S-atom of the dipolarophile is preferred. This regiochemistry is explained using recently developed DFT-based reactivity descriptors, such as local softness and Fukui functions. The hardness and polarizability profiles of the supersystem along the IRC paths were also discussed.

1. Introduction

Diels–Alder cycloadditions and 1,3-dipolar cycloadditions (13DCs) constitute one of the most important classes of organic reactions and are among the most versatile and powerful preparative methods for cyclic compounds. The mild reaction conditions, and in particular the high stereospecificity and regioselectivity, made these pericyclic reactions the methodology of choice in many heterocyclic syntheses. Although the cycloadducts are different, namely six-membered rings in Diels–Alder and five-membered rings in 13DCs, both types of addition involve the same π -electron balance: $4\pi + 2\pi$. The 2π -unit is usually a system containing a double bond (X=Y) or a triple bond (X≡Y), where X and Y could be any element of the main groups. In view of such a large variety of possibilities, much effort has been devoted, during the last two decades, to the development of synthetic methods using heteroatom systems.¹ In a recent review, Bryce *et al.*² considered the heteroaldehydes (RCH=S, RCH=Se and RCH=Te) and hetero-nitroso compounds (R–N=S and R–N=Se) as new and promising dienophiles in Diels–Alder reactions. While the use of thiocarbonyls (RR'C=S) as dipolarophiles in 13DCs has also recently been investigated by Huisgen and co-workers,³ that involving thionitroso compounds (R–N=S) remains unexplored as yet. According to a recent compilation by Takahashi and Okazaki,⁴ only two experimental studies have been carried out^{5,6} in which thionitroso compounds have been shown to react with 1,3-dipoles such as diazoalkanes and azides. The fact that thionitroso compounds have been much less studied is due no doubt to their low thermodynamic stability. Indeed, thionitrosoalkanes and thionitrosoarenes cannot be isolated, only generated *in situ* and then captured by trapping agents. Recently, different groups^{7–11} have found efficient precursor compounds to R–N=S and thus paved the way for investigating the spectroscopic and mechanistic properties of the emerging functional group.

In view of the lack of both qualitative knowledge and quantitative information on the reactivity of thionitroso compounds as dipolarophiles (DPh), we set out to perform a theoretical study on their behaviour in 13DCs with fulminic acid (HC≡N⁺–O[–]) and simple substituted azides (R–N=N⁺=N[–]) as representative 1,3-dipoles (13DPs). The objective of this work is twofold: (i) in the first step, we have characterized various structural and energetic aspects of the R–N=S + HC≡N⁺–O[–] and R–N=S + R'–N=N⁺=N[–] reactions, in particular their regiochemical and stereochemical behaviour, and (ii) in the second step, we have attempted to rationalize the observed regioselectivity by using reactivity descriptors and principles based on density functional theory (DFT) such as the total softness (*S*), the Fukui function [*f*(*r*)] and the local hard and soft acids and bases (HSAB) principle (for reviews on conceptual aspects of DFT, see ref. 12, 13). Recently, we have applied with considerable success these novel concepts to interpret the regioselectivity in many pericyclic reactions such as [2+1]¹⁴ and [2+2] reactions,¹⁵ 1,3-dipolar [2+3] cycloadditions¹⁶ and Diels–Alder [2+4] reactions.¹⁷ In this work, the variation of these reactivity descriptors along the minimum energy reaction pathways has also been explored in detail. Moreover reaction path and DFT descriptor calculations provide an interesting framework to test the maximum hardness principle, which states that molecules tend to rearrange themselves so as to achieve maximum hardness and suggests that hardness will be minimised when the energy of a system is maximised under constant chemical potential (μ) and external potential [*v*(*r*)], as originally formulated by Pearson.¹⁸

2. Details of calculations

All the calculations were performed with the aid of the Gaussian 94 set of programs.¹⁹ The hybrid B3LYP function for exchange and correlation energies^{20,21} was employed throughout this work in conjunction with the 6–311G(d,p) one electron

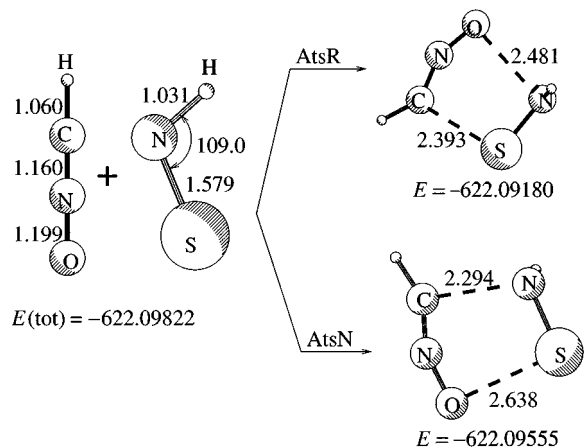


Fig. 1 Geometries, total energy (E in hartree with ZPE corrections) of the reactants and two transition structures for the HCNO + HN=S addition (A) computed at the B3LYP/6-311G(d,p) level. Complete geometrical data are available from the authors.

basis functions. Geometrical parameters of the 1,3-dipoles, HCNO and X-NNN ($X = \text{H}, \text{CH}_3$ and NH_2), and the thionitroso species $\text{R}-\text{N}=\text{S}$ ($\text{R} = \text{H}, \text{NH}_2$), and the transition structures for cycloadditions were fully optimized and characterized by harmonic vibrational frequency analyses at the indicated level. Starting from a transition structure of interest, the intrinsic reaction coordinate (IRC) pathway has also been constructed in order to verify further its identity and also to map out a minimum energy reaction pathway. Along such a pathway, the electronic properties of the supersystem have been computed for a selected number of points. In this way, the profiles of hardness and polarizability have been established. Definitions and working equations of these quantities will be given in the corresponding sections. Throughout this paper, bond lengths are given in angstroms, bond angles in degrees, total energies in hartree, zero point vibrational and relative energies in kJ mol^{-1} , and polarizability and hardness, unless noted otherwise, in atomic units.

3. Results and discussion

3.1 Structure and energetics

In general, each transition structure (ts) is referred to by four or five letters; for example, **AtsN** stands for the ts of the addition **A** with a normal (**N**) regio-approach of both partners. Similarly, **AtsR** indicates the ts of the same addition with a reverse (**R**) approach. In terms of energies, a normal ts is defined as lying lower than the corresponding reverse ts.

In the addition of $\text{X}-\text{NNN}$ to $\text{R}-\text{N}=\text{S}$, there is an additional differentiation in the spatial disposition of both nitrogen groups ($\text{XN}-$ and $\text{RN}-$); in these cases, the fifth letter (**c** or **t**) refers to a *cis* (**c**) or *trans* (**t**) configuration of them relative to a plane formed by the heavy atoms. 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 only been considered.

(a) The $\text{HC}\equiv\text{N}^+-\text{O}^- + \text{HN}=\text{S}$ addition (A). Fulminic acid was chosen from among the numerous 13DPs for the purpose of comparison; its reaction with acetylene is often considered as a prototype 13DC, whose characteristics have been well established using both MO²² and DFT methods.²³ Fig. 1 summarizes the selected geometrical parameters and total energies of the two transition structures **AtsN** and **AtsR**. Thus, the normal approach of both partners as shown in **AtsN** is identified with an attack of the O-atom of fulminic acid to the S-atom of $\text{HN}=\text{S}$. Within fulminic acid, the O-end thus behaves as a new

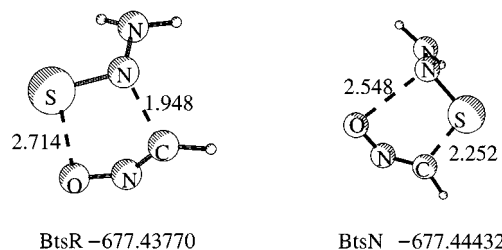


Fig. 2 Geometries and total energy (E in hartree with ZPE corrections) of the transition structures for the HCNO + H₂N-N=S addition (B) computed at the B3LYP/6-311G(d,p) level. The geometry of H₂N-N=S is: $r(\text{N}=\text{S}) = 1.622 \text{ \AA}$, $r(\text{N}=\text{N}) = 1.296 \text{ \AA}$ and $\text{NNS} = 118.5^\circ$. The total energy of HCNO + H₂N-N=S is: -677.46457 a.u. with ZPE. Complete geometrical data are available from the authors.

bond donor centre and the C-end as a new bond acceptor. There is an overall charge (electron) transfer from the dipole to the dipolarophile, as computed using the ESP atomic net charges. These atomic charges are evaluated by following the procedure of electrostatic potential driven charges and by using the MK option²⁴ in the Gaussian program, using the one-electron 6-311G(d,p) basis set. Potential driven charges were found to be less basis set dependent and are moreover easier to obtain than Atoms-in-Molecules charges, being of comparable quality.²⁵ The energy difference between both ts's amounts to about 10 kJ mol^{-1} , suggesting a high regioselectivity favouring the normal approach over the reverse. The addition *via* **AtsN** is associated with an energy barrier of only 7 kJ mol^{-1} , which is much smaller than that of 56 kJ mol^{-1} computed separately for the fulminic acid plus acetylene reaction using B3LYP/6-311G(d,p)+ZPE treatment. Separate calculations at the CCSD(T)/6-311++G(2df,2p) level of MO theory of the latter reaction give an energy barrier of 59 kJ mol^{-1} . This result thus lends support to the B3LYP values.

(b) The $\text{HC}\equiv\text{N}^+-\text{O}^- + \text{H}_2\text{N}-\text{N}=\text{S}$ addition (B). The NH_2 group has been chosen as a substituent due to the fact that dialkylamino-thionitroso compounds are perhaps the only example of isolable derivatives of this functional group.^{26,27} In addition, these compounds exhibit a rather peculiar electronic structure due to the large contribution of the zwitterionic resonance structure (ii) involving a reverse charge distribution implying a certain degree of double bond character of the N-N bond⁴ (*cf.* Scheme 1).



Scheme 1

The main calculated results are recorded in Fig. 2. Contrary to the unsubstituted case, the normal regio-approach *via* **BtsN** now involves the nucleophilic attack of C to S. When comparing the intermolecular $\text{C} \cdots \text{S}$ distance in this case with the one of the reverse addition in (a), a shortening of this distance is observed (2.25 \AA vs. 2.39 \AA in **AtsR**). Such a late ts is naturally associated with a larger energy barrier of 54 kJ mol^{-1} (vs. 13 kJ mol^{-1} *via* **AtsN**). This increase can simply be understood in terms of charge transfer. As mentioned above, the addition occurs normally with a charge transfer from the 13DP to the DPh. Therefore any group which favours that trend will activate the addition. The amino group tends to induce an opposite effect on the electronic movement and thus deactivates the reaction. In fact, in **BtsN** there is actually an electron transfer of almost 0.07 e from H₂NNS to HCNO. In other words, electron donating substituents on the 13DP and electron withdrawing substituents on the DPh are expected to favour the 13DC. In view of the rather small energy barrier in the unsubstituted case

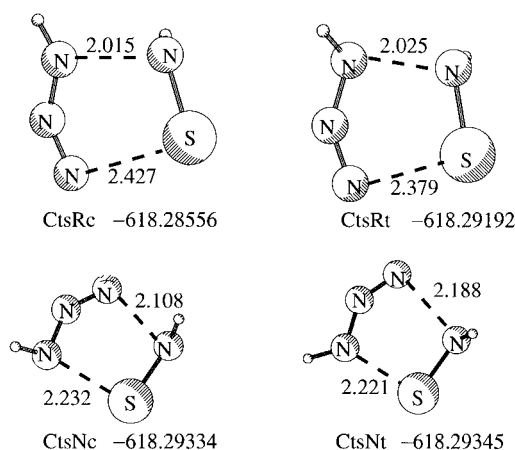
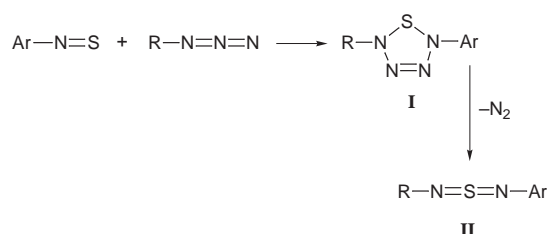


Fig. 3 Characteristics of the transition structures for $\text{HN}=\text{N}^+=\text{N}^- + \text{HN}=\text{S}$ addition (C) computed using B3LYP/6-311G(d,p). The geometry of the $\text{HN}=\text{N}^+=\text{N}^-$ is: $r(\text{N}=\text{N}^+) = 1.239 \text{ \AA}$, $r(\text{N}^+=\text{N}^-) = 1.131 \text{ \AA}$, $\text{NNN} = 171.5^\circ$ and $\text{HNN} = 110.1^\circ$. The total energy of $\text{HN}=\text{N}^+=\text{N}^- + \text{HN}=\text{S}$ is: -618.30483 a.u. with ZPE. Complete geometrical data are available from the authors.

(see above), reactions involving substrates having the latter substituents are likely to be barrier-free processes. In the present case, the energy difference between the **BtsN** and **BtsR** remains large (17 kJ mol^{-1}), indicative of a highly regioselective transformation.

(c) The $\text{HN}=\text{N}^+=\text{N}^- + \text{HN}=\text{S}$ addition (C). Okazaki and co-workers⁴⁻⁶ have studied the 13DC of $\text{R}-\text{N}=\text{S}$ with azides. Although the primary cycloadducts are too unstable with respect to loss of molecular nitrogen, the isolated product (**II**) does correspond to an initial formation of thiatetrazoline intermediate (**I**), (cf. Scheme 2).



Scheme 2

As stated above, the presence of two substituent groups at nitrogen centers induces in this case an additional stereochemical difference. As a matter of fact, four different ts's have been located and are shown in Fig. 3. Beside the regio-difference **N** and **R**, as in the previous case, the stereo-difference is specified by the *cis* (**c**) and *trans* (**t**) disposition of both N-H groups with respect to the average plane of the five-membered ring. While the five-atom skeleton deviates from planarity, the H-atoms occupy almost axial positions. A few points are worthy to note:

(i) The normal regio-approach (**N**) is identified with an attack of the HN group of azide at the S-atom of $\text{HN}=\text{S}$. The intermolecular distances ($\text{N} \cdots \text{S}$ and $\text{N} \cdots \text{N}$) are now closer to each other.

(ii) In both normal (**N**) and reverse (**R**) cases, the *trans* (**t**) configuration is consistently favoured over the *cis* (**c**), in particular in the reverse case. This is undoubtedly due to a larger steric repulsion between groups on neighbouring atoms. The nearly equal energies of both **CtsNc** and **CtsNt** on the other hand suggest a negligible 1,3-interaction between the N-substituents.

(iii) The energy difference between the **CtsNt** and **CtsRt** amounts to only 4 kJ mol^{-1} .

(iv) The energy barrier for the most favoured process through **CtsNt** is calculated to be 30 kJ mol^{-1} , a value significantly larger than that in $\text{HCNO} + \text{HNS}$ discussed above.

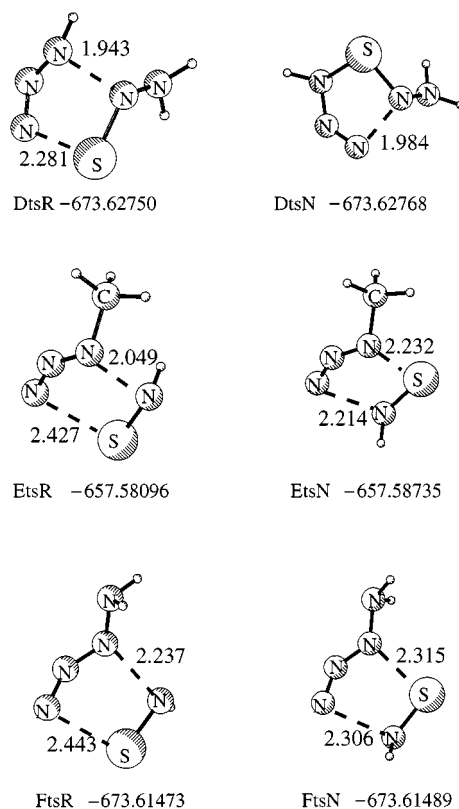


Fig. 4 B3LYP/6-311G(d,p) optimized geometries and total energies of the ts for reactions (D), (E) and (F). Sums of the total energies of the separated reactants are: (D): -673.67118 a.u. , (E): -657.59478 a.u. , (F): -673.61630 a.u. with ZPE corrections. Complete geometrical data are available from the authors.

(v) According to the electron population analysis, the charge transfer occurs in the direction $13\text{DP} \rightarrow \text{DPh}$ with an amount comparable to the $\text{HCNO} + \text{HNS}$ case for both normal and reverse approaches.

(vi) Overall, the preference for the regio-isomers formed from **CtsN** is consistent with the experimental observation in Scheme 2.

(d) Additions of substituted systems. In this section, we will briefly present the results obtained on three 13DCs of substituted systems, namely:



In each case, four different ts's have also been located corresponding to both normal (**N**) and reverse (**R**) regio-approaches as well as to both *trans* (**t**) and *cis* (**c**) stereo-approaches of both reaction partners. A *cis* (**c**) ts is consistently higher in energy than its corresponding *trans* (**t**) ts, in particular in the reverse (**R**) ts's where both terminal nitrogen ($\text{R}-\text{N}$) groups are going to form a novel chemical bond. While the energy difference between a **tsRc** and a **tsRt** varies from 5 kJ mol^{-1} in reaction (D), via 17 kJ mol^{-1} in (E) to 22 kJ mol^{-1} in (F), that between a **tsNc** and a **tsNt** is quite small; both structures have almost the same energetic content. It can thus be predicted that the 13DC of azides with thionitroso compounds is not at all stereospecific (the term stereospecificity refers to the preferential formation of one stereoisomer over the others); both stereoisomers of the cycloadduct are likely to be formed in comparable amounts. For the sake of simplicity in the presentation of data, Fig. 4 displays only the *trans* (**t**) ts's of the three reactions under consideration. A few points can be noted in addition:

Table 1 Energy cost [IE(A) – EA(B), in eV] for transferring an electron from A to B and the net charge transfer at the transition structures for the cycloadditions between 1,3-dipoles and R–N=S

Dipole	HNS			H ₂ N–NS		
	IE – EA ^a	tsN ^b	tsR ^b	IE – EA ^a	tsN ^b	tsR ^b
HNNN	9.62(11.26)	0.08	0.10	10.75(10.62)	–0.04	0.01
H ₃ C–NNN	8.70(10.98)	0.11	0.14			
H ₂ N–NNN	9.00(10.51)	0.15	0.16			
HCNO	9.57(12.52)	0.09	0.08	10.70(11.88)	–0.07	–0.02

^a IE_{dipole} – EA_{dipolarophile} (IE_{dipolarophile} – EA_{dipole}) using B3LYP calculations. ^b Charge transfer calculated using electrostatic potential driven charges. A positive value corresponds to an electron transfer to RN=S.

(i) As in the fulminic acid case, introduction of the amino group in the dipolarophile results in a remarkable increase of the energy barrier which amounts to 114 kJ mol^{–1} in reaction (D) as compared with 30 kJ mol^{–1} in (C). There is actually a small but noticeable charge transfer from the dipolarophile to the dipole.

(ii) In contrast, introduction of a methyl or amino group in the azide results in a marked decrease of the energy barrier. This quantity is now reduced to 19 kJ mol^{–1} in reaction (E), H₃C–NNN + HN=S, and virtually vanishes in reaction (F), H₂N–NNN + HN=S. As expected, the amino group exerts a stronger electron donating effect than the methyl group. The charge transfer to the dipolarophile becomes substantial, being 0.11 e in (E) and 0.15 e in (F) (*cf.* Table 1).

(iii) In reactions (D) and (F), both normal and reverse approaches result in energetically similar ts's. In other cases, a difference still persists. However, in view of the rather small size of the energy barriers, they are expected to disappear in systems having larger and/or stronger substituents. Then the regiochemistry is presumably no longer determined by the ts's but rather by the thermodynamic stability of the products. Here we can only state that in substituted systems, the 13DC might be much less regioselective than those considered here.

In summary, the calculated structural and energetic results for the five different 13DCs are consistent with each other, pointing toward a certain regioselectivity but a nonstereospecificity in the formation of the cycloadducts. In the following section, a deeper analysis of the regiochemistry of the addition will be carried out using DFT-based descriptors.

3.2 Regiochemistry of the addition: testing the local HSAB principle

In the previous paragraph it was shown that, although two paths are possible in principle, in reality for most of the 13DCs, one path (normal) is associated with a lower energy barrier than the other (reverse) and the reaction proceeds mainly through the lower energy ts, thereby introducing regioselectivity in these reactions (*cf.* ref. 28, 29). For example, in the case of the cycloaddition between diazoalkenes and alkyl-substituted phosphalkynes,³⁰ only one cycloadduct is formed, and in the case of HC=P + H₂CNN,³¹ the reaction proceeds mainly through that ts which is lower in energy. This occurs when the C-atom of H₂CNN joins to the P-atom of HCP.

DFT-based reactivity descriptors such as Fukui functions and local softness have recently been found to be very useful for explaining regiochemistry in addition reactions.^{15–17} As a detailed discussion of these reactivity parameters can be found elsewhere,^{12,32,33} only the relevant expressions used for the evaluation of different quantities are given here.

The global hardness (η) and softness (S) are calculated from eqn. (1) and (2),³⁴ where IE and EA are the first vertical ionization energy and electron affinity of the molecule, respectively.

$$\eta = \frac{(IE - EA)}{2} \quad (1)$$

$$S = \frac{1}{(IE - EA)} \quad (2)$$

The condensed forms of the Fukui functions of an atom k in a molecule with N electrons has been proposed by Yang and Mortier [eqn. (3)],³⁵ where q_k is the gross electronic population

$$\begin{aligned} f_k^+ &= [q_k(N+1) - q_k(N)] && \text{for nucleophilic attack} \\ f_k^- &= [q_k(N) - q_k(N-1)] && \text{for electrophilic attack} \end{aligned} \quad (3)$$

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 Mendez³⁶ 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. Critical evaluations in recent years^{17,37} confirmed these results, prompting us to adopt this approach when discussing regioselectivity.

To explain this 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 (say nucleophilic) are involved in the formation of a cycloadduct with atoms k and l of another molecule B (say electrophilic), we defined^{15–17} the quantity Δ_{ij}^{kl} [eqn. (4)] as a measure of regioselectivity, where the

$$\Delta_{ij}^{kl} = (s_i^- - s_k^+)^2 + (s_j^- - s_l^+)^2 \quad (4)$$

s is the appropriate type of atomic softness. The reaction path associated with the lower Δ value will be the preferred one if the HSAB principle is satisfied. Due to the complex form of Δ and the neglect of stereoelectronic effects, a direct correlation between Δ values and the differences in activation energies could not be expected. From ionization energies and electron affinities of the 13DP and DPh (R–N=S), it is observed that the direction of charge transfer (electron flow) is more favourable from the 13DP to the DPh in a normal approach. As discussed in the previous section in most of the cases the net charge flow was indeed found from the 13DP to the R–N=S. The energy cost (neglecting reorganization effects) for an electron transfer from the 13DP to R–N=S and *vice versa* and the net electronic charge on 13DP are given in Table 1. Similar observations were made earlier for the cycloaddition between 13DP and many other types of DPh.²⁸ R–N=S can thus be considered as the electrophile and the 1,3-dipoles as the nucleophiles in the 13DC.

Table 2 presents the global softnesses and the softnesses of the atoms involved in the cycloaddition for all the 13DPs and DPhs included in the present study. For the azides (X–NNN), the global softness increases in the order X = H < X = CH₃ <

$X=\text{NH}_2$. As pointed out above, the activation energies for the cycloadditions between azides and $\text{H}-\text{N}=\text{S}$ decrease in the same order $X = \text{H} > X = \text{CH}_3 > X = \text{NH}_2$. At the atomic level the nitrogen atom attached to the X of the azide has a larger softness for electrophilic attack, whereas the sulfur atom in $\text{R}-\text{N}=\text{S}$ has a much larger softness for nucleophilic attack than the nitrogen atom. Both the nitrogen and sulfur atoms become less electrophilic in $\text{H}_2\text{N}-\text{NS}$ compared to $\text{H}-\text{N}=\text{S}$, due no doubt to the effect of the electron donating tendency of the amino group. The less electrophilic character of the two atoms of $\text{H}_2\text{N}-\text{N}=\text{S}$ involved in cycloaddition as compared to $\text{H}-\text{N}=\text{S}$ gives rise to a significant increase in activation energy for the reaction with $\text{H}_2\text{N}-\text{N}=\text{S}$.

Table 3 shows the Δ values calculated *via* eqn. (4) corresponding to **tsN**(Δ_{N}) and **tsR**(Δ_{R}) (*cf.* Fig. 1–4 for the transition states) respectively. These Δ values are calculated using the appropriate atomic softnesses (s_{k}^- for 13DP and s_{k}^+ for $\text{R}-\text{N}=\text{S}$) listed in Table 2. One can easily notice from Table 3 that for almost all the cases considered here, Δ_{N} is consistently lower than Δ_{R} . Thus the transition state formed by maintaining the local HSAB principle is lower in energy. This clearly explains the regioselective nature of the 13DC with $\text{R}-\text{N}=\text{S}$. Only in the case of (F), $\text{H}_2\text{N}-\text{NNN} + \text{HNS}$, is Δ_{N} slightly larger than Δ_{R} , although **tsN** is marginally lower in energy than **tsR**. Note that the whole

Table 2 Global softness (S) and local softness values for nucleophilic (s^+) and electrophilic (s^-) attack as calculated from the B3LYP/6–311G(d,p) results. Data are given in atomic units

Molecule	S	Atom (k)	s_{k}^-	s_{k}^+
HN^1NN^2	2.14	N^1	1.07	0.37
		N^2	0.96	1.10
$\text{H}_3\text{C}-\text{N}^1\text{NN}^2$	2.36	N^1	1.00	0.78
		N^2	0.97	1.05
$\text{H}_2\text{N}-\text{N}^1\text{NN}^2$	2.40	N^1	0.91	0.55
		N^2	0.97	1.13
HCNO	1.95	C	1.04	1.58
		O	0.89	0.71
HNS	3.33	N	0.78	0.68
		S	2.33	2.42
$\text{H}_2\text{N}-\text{N}^1\text{S}$	3.15	N^1	0.53	0.47
		S	1.81	2.06

Table 3 Energy barriers (E_{act} in kJ mol^{-1}) of the cycloaddition reactions between 1,3-dipole and dipolarophile and the corresponding Δ values (see text for definition)

Reaction	Dipolarophile	Dipole	E_{act}		Δ	
			tsN	tsR	Δ_{N}	Δ_{R}
(A)	HNS	HCNO	7.0	16.9	2.47	1.95
(C)		HNNN	30.2	33.9	1.90	2.28
(E)		$\text{H}_3\text{C}-\text{NNN}$	19.5	36.3	2.10	2.21
(F)		$\text{H}_2\text{N}-\text{NNN}$	3.7	4.1	2.36	2.16
(B)	$\text{H}_2\text{N}-\text{NS}$	HCNO	53.2	70.6	1.22	1.69
(D)		HNNN	114.2	114.7	1.22	1.57

Table 4 Hardness (η) and polarizability (α)^a of the two transition structures of the cycloaddition reactions between 1,3-dipoles and dipolarophiles

Reaction	Dipolarophile	Dipole	η		α	
			tsN	tsR	tsN	tsR
(A)	HNS	HCNO	0.1403	0.1358	47.29	47.92
(C)		HNNN	0.1589	0.1557	46.60	47.42
(E)		$\text{H}_3\text{C}-\text{NNN}$	0.1521	0.1455	60.21	61.13
(F)		$\text{H}_2\text{N}-\text{NNN}$	0.1483	0.1384	57.84	59.31
(B)	$\text{H}_2\text{N}-\text{NS}$	HCNO	0.1419	0.1426	62.82	62.58
(D)		HNNN	0.1657	0.1646	57.95	59.13

^a α values were calculated at the B3LYP/6–311G(d,p) level, taking the arithmetic average of the three diagonal elements of the polarizability tensor. All values are given in atomic units.

prediction is made purely from isolated molecular properties and thus some odd cases may appear when perturbations due to the presence of the other molecule are significant or some stronger factor exists, such as a stereoelectronic effect or a nuclear repulsion. In the case (F), the differences in both energy barriers and Δ values are really small, making predictions more difficult. Moreover, examples have been reported of 1,3-dipolar additions involving fulminic acid where frontier MO theory, of which the present approach can be considered as a generalization, fails to arrive at the correct prediction in regioselectivity.³⁸ A closer look at Tables 2 and 3 reveals that in the normal approach the softest center for electrophilic attack in the 13DP joins to the softest center for nucleophilic attack (S atom) in $\text{R}-\text{N}=\text{S}$. This result suggests an asynchronous mechanism in which the interaction between the two softest centers proceeds faster than the other two centers. This also supports the same observation made from the two intermolecular bond lengths at the transition states in the previous section. These results are in line with our previous work on Diels–Alder reactions.¹⁷

3.3 Testing the maximum hardness principle

The hardness and polarizability of the transition states are listed in Table 4. While hardness is calculated from the finite difference formula given in eqn. (1), polarizability (α) is calculated according to eqn. (5), as the arithmetic average of the three

$$\alpha = (a_{xx} + a_{yy} + a_{zz})/3 \quad (5)$$

diagonal elements of the polarizability tensor, the a_{ii} ($i = x, y, z$) values being obtained *via* the finite field method.³⁹

It is interesting to note that among the two 13DC transition structures, the lower energy **tsN** has higher hardness and lower polarizability than its **tsR** counterpart, except for the $\text{H}_2\text{N}-\text{NS} + \text{HCNO}$ reaction. Thus the ts formed by maintaining the HSAB principle is harder, lower in polarizability and, of course, lower in energy. Similar observations were made very recently for other 13DCs⁴⁰ as well. The inverse relationship between hardness and polarizability of the transition structures is in line with earlier softness–polarizability proportionality results on atoms⁴¹ and corroborates well with the observation made by Ghanty and Ghosh^{42,43} from their study on various exchange and isomerization reactions and also by others.^{44,45}

As a whole these results prompted us to look for the hardness profile of our reactions. The possibility of defining a *hardness profile* along a reaction path has been discussed many times in recent years for a variety of chemical problems.^{46–49} Very recently, Chandra and Nguyen⁴⁰ studied the change of hardness along the intrinsic reaction coordinate for a few 13DC reactions with phosphorous containing dipolarophiles. They indeed observed a minimum in the *hardness profile*, but it was observed⁴⁰ that the hardness minimum is shifted more towards the product side compared to the energy minimum. We have calculated the hardness at various points along the IRC paths for the **tsN** of the HNNN + RNS and HCNO + RNS reactions. In both the cases the variation of hardness is studied

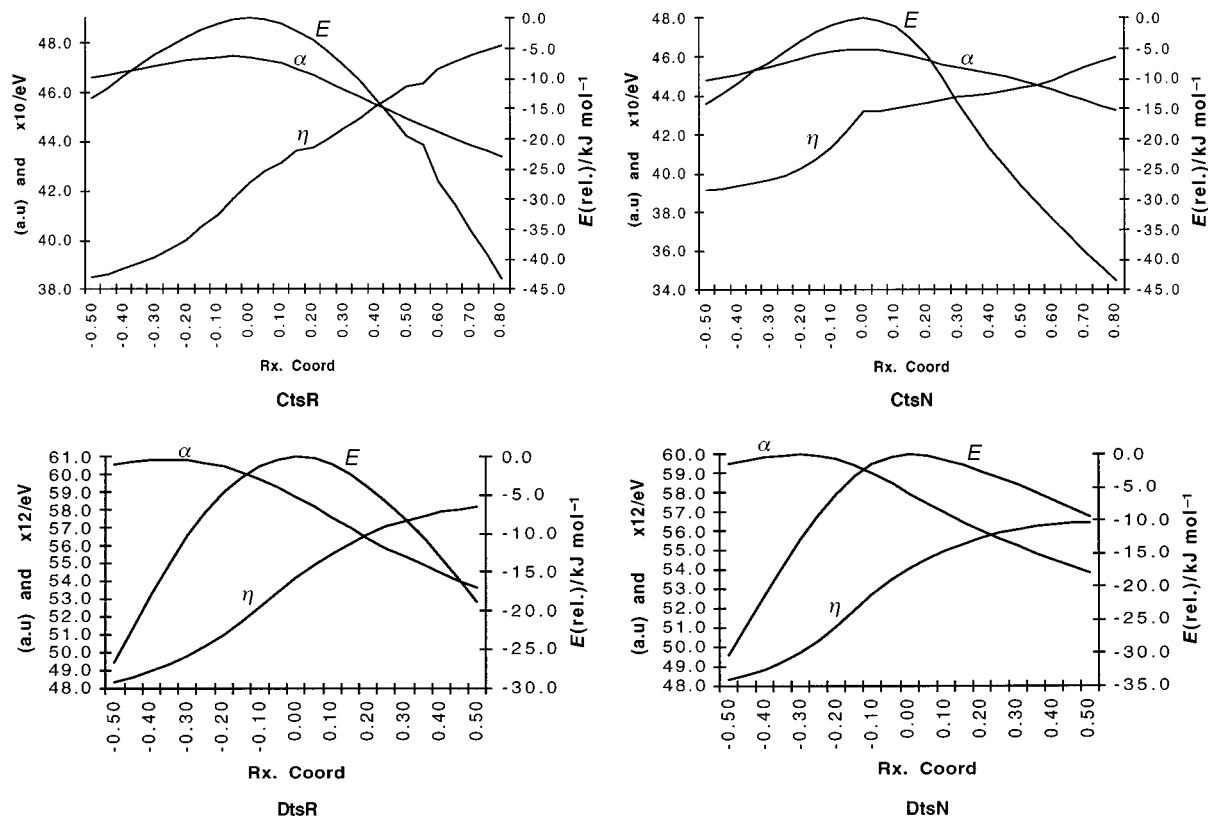


Fig. 5 Hardness (η), polarizability (α) and energy (E) profiles of HNNN + RN=S ($R = H, NH_2$) both for normal and reverse reactions. Abscissa represents IRC values in atomic units.

around the transition state, because of the obvious technical difficulty of estimating hardness from the finite difference formula when the two reactants are far away. The demand for constant external potential can be expected to be roughly fulfilled in reactions involving a cyclic transition state in view of the smaller displacement of the nuclei in the ts neighbourhood as compared to *e.g.* a displacement reaction. In view of the inverse relationship between hardness and polarizability at the transition state for a 13DC, we have also studied the variation of polarizability along the IRC to figure out whether this inverse relationship holds over a wider range near the transition state along the reaction path. Fig. 5 presents the hardness, polarizability and energy profiles for the HNNN + RNS reaction. The general behaviour of the profiles is more or less similar for $R = H$ and $R = NH_2$. Contrary to normal expectations, there is no minimum in the hardness profile near the transition state. Hardness increases continuously along the IRC, although it slows as the two reactants approach nearer to the product from the transition state. However, it is interesting to note that polarizability goes through a maximum near the transition state in both **tsN** and **tsR** for both reactions. In the case of HNNN + HNS, the maxima in energy and polarizability profile almost coincide at the same point of the IRC, but for the HNNN + H_2 -NS reaction, the polarizability maximum appears more towards the reactant side compared to the maximum in the energy profile. It is also clear from Fig. 5 that the inverse relationship between hardness and polarizability does not exist throughout the IRC path. The reaction profiles for the HCNO + RNS ($R = H$ and NH_2) reactions (not shown†) are analogous, the maximum being shifted more towards the product side for the HCNO + HNS reaction, and more towards the reactant side for the HCNO + H_2 N-NS reaction. Thus although in many 13DCs, it has been observed that hardness goes through a minimum near the transition state, this cannot

be generalized. In the present case, polarizability profiles have been found to be smoother and more promising.

4. Concluding remarks

The additions of thionitroso compounds to 1,3-dipoles are mainly characterized by their rather low energy barriers. In the cases of azides the reaction is not stereospecific. In all cases, they show a certain regioselectivity favouring the formation of a cycloadduct. Using density functional theory based reactivity descriptors and a local version of the HSAB principle, the reason for the preference of a normal approach over a reverse can be understood. The differences in the atomic Fukui functions and the softnesses of interacting atoms have been taken as a measure of satisfaction of the HSAB principle. Thus, the smaller the difference, the lower the activation energy. On the other hand, a more favoured transition structure having a lower energy appears to be associated with greater hardness and a smaller polarizability. Hardness profiles do not yield an extremum, and are opposed to polarizability. When they exist, the hardness maximum and/or minimum polarizability do not coincide with the maximum energy. It seems that the position of an extremum in each profile is conditioned by the corresponding values of the initial and final rather than by the position of total energy, following thus a kind of general Hammond postulate. The addition of solvent effects was not considered in this study and could be an important issue. However, in a recent study, Rastelli *et al.* concluded that, in general, solvent effects tend to reinforce the prediction of the regioselectivity obtained in the gas phase.³⁸

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