Mechanism of [2 + 1] Cycloadditions of Hydrogen Isocyanide to Alkynes: Molecular Orbital and Density Functional Theory Study

Loc Thanh Nguyen,[†,‡] Trung Ngoc Le,[†,§] Frank De Proft,[†] Asit K. Chandra,[⊥] Wilfried Langenaeker,[†] Minh Tho Nguyen,*[,⊥] and Paul Geerlings*[,†]

Contribution from the Eenheid Algemene Chemie, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium, Faculty of Chemical Engineering, HoChiMinh City University of Technology, HoChiMinh City, Vietnam, Faculty of Chemistry, University of Danang, Danang, Vietnam, and Department of Chemistry, University of Leuven, Celestijnenlaan, 200 F, B-3001 Leuven, Belgium

Received September 23, 1998. Revised Manuscript Received March 22, 1999

Abstract: The reactions of hydrogen isocyanide (HN≡C) with various simple alkynes (HC≡C−X, with X = H, CH_3, NH_2, F), formally [2 + 1] cycloadditions, have been studied by density functional theory (DFT) with the hybrid exchange correlation B3LYP functional and a 6-311G(d,p) basis set, as well as by MO theory with CCSD(T) calculations. For each reaction, the intrinsic reaction coordinate (IRC) pathway has been constructed. It is shown that each [2 + 1] cycloaddition is nonconcerted but proceeds in two steps: rate-determining addition of HN≡C to a carbon atom of HC≡CX, giving rise to a zwitterion intermediate, followed by a ring closure of the latter, yielding finally cyclopropenimine. In all cases, HN≡C behaves as an electrophile. The activation energies corresponding to both possible initial attacks of HN≡C are distinguishable, introducing thus a site selectivity and an asynchronism of bond formation in the initial step, for which a rationalization using DFT-based reactivity descriptors and the local HSAB principle has been proposed. Except for HC≡C−F, initial attack on the unsubstituted alkyne carbon is preferred. The hardness and polarizability profiles along the IRC reaction paths of the supersystem have also been constructed. In some cases, there are no clear-cut extrema; in other cases, there is a minimum in the hardness profile and a maximum in the polarizability profile, but these extrema do not coincide with the energy maximum and are rather shifted toward the side having the closest value, following apparently a generalized Hammond postulate. While the higher hardness−lower polarizability criterion seems to hold true, there is no obvious relationship between hardness and energy. The activation energy (E_{act}) vs hardness difference relationship recently derived by Gázquez turns out to be successful in the interpretation of the calculated E_{act} sequences.

1. Introduction

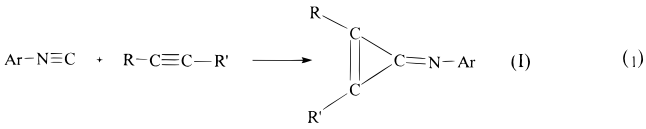
Isocyanides (RN≡C), the higher energy isomers of cyanides, are versatile building blocks in organic synthesis and interesting ligands in complexation to metals. The cyanide−isocyanide isomerization has often been employed as an initial step in numerous preparative methods.[1] Isocyanides usually react with a wide range of substrates, including nucleophiles, electrophiles, and radicals, under various experimental conditions, giving rise to different primary imine adducts.[2] The mechanism and, in particular, the stereospecificity of these addition reactions have been investigated in details.[3−6] Owing to the presence of a monocoordinated carbon atom having an electron lone pair, isocyanides are also well suited as 1,1-dipolar partners in different types of cycloaddition whose primary cycloadducts undergo further rearrangements and/or ring expansions.[7] Isocyanides have been known to add to doubly bonded dipolarophiles such as disilenes ($R_2Si{=}SiR_2$),[8] diphosphenes (RP═PR),[9,10] and silenes ($R_2C{=}SiR_2$).[11,12] Similar reactivities of isocyanides toward alkenes ($R_2C{=}CR_2$), ketones ($R_2C{=}O$), thioketones ($R_2C{=}S$), or analogous compounds are not reported yet, but the [2 + 1] cycloreversion of cyclopropanimines and other analogues of methylene-cyclopropanes, giving each an isocyanide plus a doubly bonded compound, have been well established.[13−16] In contrast, relatively little is known about the

* Authors to whom correspondence should be addressed. E-mail: pgeerlin@vub.ac.be and minh.nguyen@chem.kuleuven.ac.be.
† Vrije Universiteit Brussel.
‡ HoChiMinh City University of Technology.
§ University of Danang.
⊥ University of Leuven.

(1) Rüchardt, C.; Meier, M.; Haaf, K.; Pakusch, J.; Wolber, E. K. A.; Müller, B. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 893.
(2) Walborsky, H. M.; Periasamy, M. P. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds; John Wiley: NewYork, 1983; Suppl. C, Chapter 20, p 835.
(3) Nguyen, M. T.; Hegarty, A. F.; Sana, M.; Leroy, G. *J. Am. Chem. Soc.* **1985**, *107*, 4141.
(4) Nguyen, M. T.; Ha, T. K.; Hegarty, A. F. *J. Phys. Org. Chem.* **1990**, *3*, 697.
(5) Malone, S.; Hegarty, A. F.; Nguyen, M. T. *J. Chem. Soc., Perkin Trans. 2* **1988**, 477.
(6) Nguyen, M. T.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1675.
(7) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991,** *113*, 8975 and references therein.
(8) Yokelson, H. B.; Millevolte, A. J.; Haller, K. J.; West, R. *J. Chem. Soc., Chem. Commun.* **1987**, 1605.
(9) Baudler, A. M.; Simon, J. *Chem. Ber.* **1987**, *120*, 421.
(10) Lentz, D.; Marshall, R. *Z. Anorg. Allg. Chem.* **1992**, *617*, 53.
(11) Brook, A. G.; Kong, Y. K.; Saxena, A. K.; Sawyer, J. F. *Organometallics* **1988**, *7*, 2245.
(12) Brook, A. G.; Saxena, A. K.; Sawyer, J. F. *Organometallics* **1989**, *8*, 850.
(13) L'abbé, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 276.
(14) L'abbé, G.; Dekerk, J. P.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Angew. Chem.* **1978**, *90*, 207.
(15) Quast, H.; Fuss, A.; Heublein, A., Jacobi, H., Seiferling, B. *Chem. Ber.* **1991**, *124*, 2545.
(16) Quast, H.; Meischner, G.; Seiferling, B. *Chem. Ber.* **1987**, *217*, 225.

10.1021/ja983394r CCC: $18.00 © 1999 American Chemical Society
Published on Web 06/15/1999

addition of isocyanides to alkynes. As far as we are aware, there are actually two reports by Krebs and co-workers[17,18] on the addition of aryl isocyanides to electron-rich or strained cyclic alkynes (eq 1) in which cyclopropenimines (**I**) could be isolated or trapped.



(1)

Despite the scarcity of experimental studies, available observations appear to point toward a different behavior of alkynes, relative to doubly bonded systems, with respect to addition to isocyanides. Let us first summarize briefly the main experimental background of the isocyanide plus alkyne reactions.

(i) The most consistent result concerns perhaps the electrophilic character of isocyanides. In fact, while electron-deficient isocyanides react much faster than electron-rich counterparts, yne-diamines ($R_2N-C\equiv C-NR_2$) add about 1000 times faster than ynamines ($R_2N-C\equiv C-R'$) to isocyanides. In addition, Krebs and co-workers[17,18] have found a high ρ-value ($\rho = 2.27$) in the Hammett correlation for aryl isocyanides: electron-withdrawing substituents in the latter tend to accelerate the addition.

(ii) The question as to whether the addition is concerted or stepwise remains, however, unanswered.

(iii) The solvent effect on the addition rate is quite small.

In an attempt to tackle questions (i) and (ii) posed by experimental results and in relation with our recent theoretical studies[19−23] on reactions of hydrogen isocyanide with doubly bonded dipolarophiles, we have carried out quantum chemical calculations on some simple model systems, HN≡C + HC≡C−X with X = H, CH_3, NH_2, and F. The objective of this study is twofold: (a) first, to obtain quantitative information on various structural and energetic aspects of the additions, and (b) second, to attempt an analysis of the mechanistic aspects, in particular the stereospecificity and asynchronism, in using novel reactivity descriptors based on density functional theory (DFT), which we recently used to discuss various aspects of electrophilic and nucleophilic addition or substitution reactions.[24−27] (For reviews on conceptual aspects of DFT, see refs 28 and 29.) In an earlier work,[23,30] only the local softness of the reaction centers was employed to interpret the addition asynchronism. In this work, we extend the analysis to a wider scope by constructing the hardness and polarizability profiles along the intrinsic reaction coordinate (IRC) pathways. The correlation between these electronic properties and the position of the transition structures as well as the calculated energy barriers will be investigated.

Table 1. Frontier Orbital Energies and Related Properties of HN≡C and Alkynes Considered

structure	E(HOMO)[a] (IE)[b]	ΔE[LUMO(HNC) − HOMO(HCCX)][c]	ΔE[LUMO(HCCX) − HOMO(HNC)][c]
HN≡C	−13.0 (12.2)		
HC≡CH	−11.0 (11.4)	16.7 (14.9)	19.1 (15.5)
HC≡C−CH_3	−10.4 (10.3)	16.0 (13.8)	19.2 (15.2)
HC≡C−NH_2	−9.3 (9.0)	15.0 (12.5)	18.9 (14.7)
HC≡C−F	−11.2 (11.3)	16.9 (14.8)	19.9 (15.6)

[a] Energies of the highest occupied orbitals from HF/6-31G(d) wave functions in eV. [b] Vertical ionization energies calculated using B3LYP/6-311G(d,p) in eV are given in parentheses. [a] In parentheses are the differences using B3LYP ionization energies and electron affinities.

2. Methods of Calculation

All quantum chemical calculations were carried out with the aid of the Gaussian 94 set of programs.[31] The stationary points were initially located using Hartree−Fock (HF) wave functions with the 6-31G(d) basis set and characterized at this level by harmonic vibrational analyses.

Geometrical parameters of the relevant equilibrium and transition structure (ts) were then reoptimized using DFT with the popular hybrid B3LYP functional in conjunction with the 6-311G(d,p) basis set. Analytical harmonic vibrational wavenumbers of these stationary points have again been computed at the B3LYP level to verify further their identity and to estimate the zero-point energies (ZPEs). In the simplest HN≡C + HC≡CH case, geometry optimizations using molecular orbital second-order perturbation theory (MP2) with the 6-31G(d,p) basis set and higher-level coupled-cluster calculations, including all single and double excitations plus perturbative corrections for triple excitations, CCSD(T)/6-31G(d), have also been performed to ascertain the existence of zwitterion intermediates. To follow the variations of the reactivity descriptors along the chemical process, IRC pathways have been constructed starting from the ts's of interest at the B3LYP/6-311G(d,p) level. Once an IRC pathway was mapped out, geometries of selected points on that path were employed to calculate the electronic properties of the supersystem. In this way, profiles of various descriptors can be consistently constructed. Particular attention has been paid to the evolution of global hardness and polarizability. Throughout this paper, bond distances are given in angstroms, bond angles in degrees, total energies in hartrees, and zero-point and relative energies, unless otherwise noted, in kilojoules per mole.

3. Results and Discussion

A. Preliminary Analysis of Frontier Orbital Interactions. In this work, we have studied the reactions between hydrogen isocyanide and acetylene and three monosubstituted alkynes, HC≡C−X with X = CH_3, NH_2, and F. Let us first present a brief analysis of the frontier orbital interactions which indicates already the very nature of both reaction partners. Table 1 lists the HOMO−LUMO energy differences in which HN≡C involves either its HOMO or its LUMO. These values are further confirmed by rigorous calculations of the vertical ionization energies (IE) and electron affinities (EA) of the separated reactants.

(17) Krebs, A.; Kimling, H. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 409.
(18) Krebs, A.; Güntner, A.; Versteylen, S.; Schulz, S. *Tetrahedron Lett.* **1984**, *25*, 2333.
(19) Nguyen, M. T.; Vansweevelt, H.; Vanquickenborne, L. G. *J. Org. Chem.* **1991**, *56*, 5651.
(20) Nguyen, M. T.; Vansweevelt, H.; De Neef, A.; Vanquickenborne, L. G. *J. Org. Chem.* **1994**, *59*, 8015.
(21) Nguyen, M. T.; Van Keer, A.; Pierloot, K.; Vanquickenborne, L. G. *J. Am. Chem. Soc.* **1995**, *117*, 7535.
(22) Nguyen, M. T.; Van Keer, A.; Vanquickenborne, L. G. *Chem. Ber./Recl.* **1997**, *130*, 69; *J. Chem. Soc., Perkin Trans. 2* **1996**, 299.
(23) Chandra, A. K.; Geerlings, P.; Nguyen, M. T. *J. Org. Chem.* **1997**, *62*, 6417.
(24) Tielemans, M.; Areschka, V.; Colomer, J.; Promel, R.; Langenaeker, W.; Geerlings, P. *Tetrahedron* **1992**, *48*, 10575.
(25) Langenaeker, W.; De Proft, F.; Geerlings, P. *J. Phys. Chem. A* **1998**, *102*, 5944; *J. Phys. Chem.* **1995**, *99*, 6424.
(26) Langenaeker, W.; Demel, K.; Geerlings, P. *J. Mol. Struct. (THEOCHEM)* **1991**, *234*, 329.
(27) Roy, R. K.; Krishnamurti, S.; Pal, S.; Geerlings, P. *J. Phys. Chem. A* **1998**, *102*, 3746.
(28) Parr, R. G.; Yang, W. *Annu. Rev. Phys. Chem.* **1995**, *46*, 701.
(29) Geerlings, P.; De Proft, F.; Langenaeker, W. *Adv. Q. Chem.* **1999**, *33*, 303.
(30) Damoun, S.; Van De Woude, G.; Mendez, F.; Geerlings, P. *J. Phys. Chem.* **1997**, *101*, 886.
(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacome, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*; Gaussian Inc.; Pittsburgh, PA, 1995.

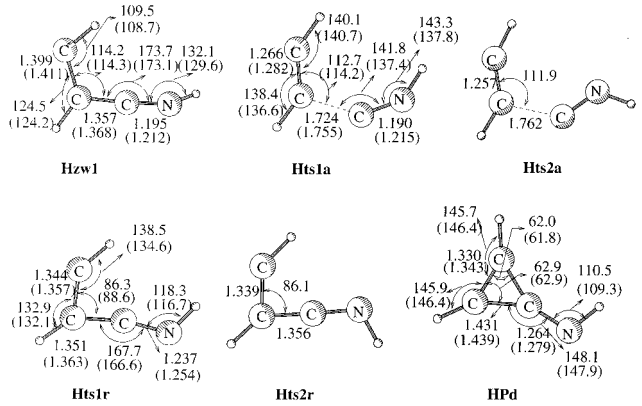


Figure 1. Selected geometrical parameters of the stationary points related to the HN≡C + HC≡CH addition. Optimized values are from B3LYP/6-311G(d,p); in parentheses are CCSD(T)/6-31G(d) values.

It is clear that, in all cases, the interaction HOMO (HC≡C−X)−LUMO (HN≡C) consistently results in a smaller orbital energy gap than the alternative HOMO (HN≡C)−LUMO (HC≡C−X). According to a simple perturbation theory treatment, the smaller the frontier orbital energy gap, the larger the stabilizing interaction energy between both partners. Thus, the isocyanide moiety behaves in this process essentially as an electrophile reagent involving its vacant π^* orbital. This is in line with the experimental observations mentioned above but in contrast with the behavior of HN≡C when adding to doubly bound dipolarophiles, where it reacts as a nucleophile using its electron pair.[22]

It is of interest to note already that attachment of an electron-donating substituent such as CH_3 and NH_2 on alkynes tends to reduce the orbital gap. In contrast, the fluorine atom shows a marginal effect on this property.

B. Addition of the Unsubstituted System HN≡C + HC≡CH (Reaction H). Figure 1 displays geometrical parameters of the equilibrium and transition structures for the addition of HN≡C to HC≡CH, optimized at both B3LYP/6-311G(d,p) and CCSD(T)/6-31G(d) levels of theory. The structures shown include **Hts1a**, **Hts2a**, **Hzw1**, **Hts1r**, **Hts2r**, and **HPd**. The separated system **HRe** is omitted for the sake of simplicity. In general, the structures are labeled by a combination of letters and numbers, in which **H** stands for unsubstituted acetylene (X = H), **ts** for transition structure, **a** for addition, **zw** for zwitterion intermediate, **r** for ring closure, and **Pd** for the cyclopropenimine product. Figure 2 summarizes the relative energies computed using two different levels, namely B3LYP and CCSD(T) with the basis set mentioned above. Approach of the partners to each other could, in principle, result in four distinct ts's, depending on the relative position of both moieties as well as the bending of isocyanide. Nevertheless, only two distinguishable ts's, **Hts1a** and **Hts2a,** have been located following geometry optimization. Both structures are characterized by a inward attack of HN≡C; both moieties are situated in a cis configuration with respect to the forming C···C bond. The **Hts2a** lies a few kilojoules per mole higher in energy than **Hts1a**. Such a difference is the result of a stereoelectronic effect which has been analyzed in detail in previous work.[21,22] Briefly, **Hts1a** is preferred owing to a harmonious migration of the electron flow in the same direction. The C−C intermolecular distance in **Hts1a** amounts to 1.75 Å. It is, however, shorter than the usual distance by about 2.0 Å for carbon−carbon bond formation or breaking. This is presumably due to the presence of the isocyanide moiety. In fact, the C−C≡N bond in cyanides is consistently shorter than the C−C bond in alkanes.

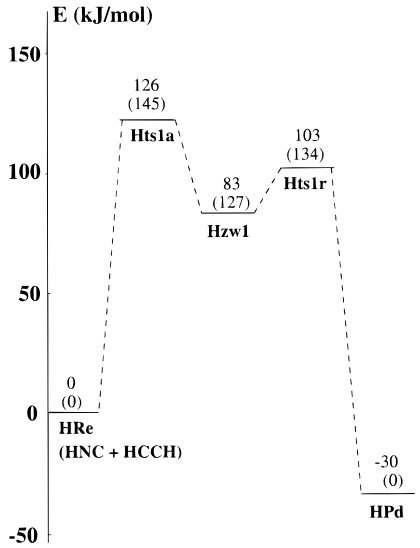


Figure 2. Schematic potential energy profile showing the two-step addition of HN≡C to HC≡CH. Relative energies obtained at B3LYP/6-311G(d,p) and CCSD(T)/6-311G(d,p) (values in parentheses) using B3LYP/6-311G(d,p)-optimized geometries and corrected for zero-point contributions.

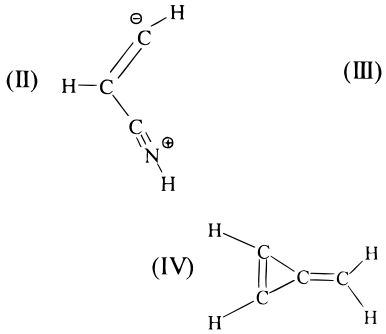
Intrinsic reaction coordinate calculations starting from **Hts1a** unambiguously show that this ts is connecting the separated reactants **HRe** with the intermediate **Hzw1**. The latter is characterized by a short C−C bond (1.36 Å) and a quite open C−C−C angle (114°). The C═C bond distance, originally from acetylene, is stretched from 1.19 Å in **HRe** to 1.34 Å in **Hzw1**, indicative of a double bond character. For its part, the **Hts1r** is identified by IRC calculations as the ts linking **Hrw1** and the three-membered product **HPd**.

Figure 2 indicates that the addition is a two-step process in which the initial addition step is rate-determining. While coupled-cluster calculations confirm the existence of **Hzw1** as a genuine local minimum, they tend to increase the energy barrier to addition and reduce, in the meantime, the relative stability of the zwitterion intermediate. The latter appears in any case to lie in a rather shallow potential well. We note that many difficulties were encountered in locating **Hzw1** and **Hts1r** using MP2 calculations**.**

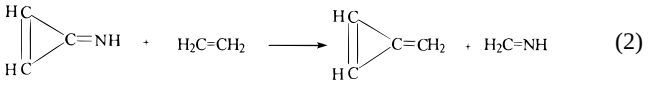
As mentioned above, **Hts2a** is calculated to be 3 kJ/mol higher in energy than **Hts1a**. Starting from **Hts2a**, we were, however, not able to locate a zwitterion having a corresponding conformation around the NCH moiety. All energy minimizations from **Hts2a** invariably lead to **Hzw1**. An alternative ts for cyclization from the zwitterion, namely **Hts2r**, has also been located, the latter lying 3 kJ/mol higher than **Hts1r**. Similarly, IRC following or energy minimization from **Hts2r** also gives rise to **Hzw1**. Consistent with the electrophilic character of HN≡C emphasized above, there is actually in **Hts1a** a charge transfer from HC≡CH to HN≡C. The amount is small but noticeable (dependent on the method for population analysis, being 0.1 e with the Mulliken population analysis). Nevertheless, in the equilibrium structure **Hzw1**, there is clearly a larger concentration of negative charge on the acetylene moiety, which is, as a group, negatively charged, whereas the HNC group is positively charged. As such, the intermediate can better be described as a zwitterion than as a biradical. Moreover, it turned out that both the transition state and the intermediate structures were stable singlet wave functions and that the stabilization energy due to solvatation in a highly polar continuum is larger for **Hzw1** than

for **Hts1a**. The latter was concluded from test calculations using the continuum treatments available in the Gaussian 94 program.[31]

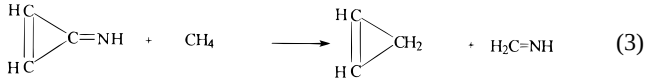
The existence of the zwitterion intermediate, irrespective of its real relative stability, appears to be a strong manifestation of the asynchronism in the formation of the two novel C···C bonds. In the addition of HN≡C to doubly bonded systems (X = Y),[19−23] even though there is consistently a high asynchronism in the formation of both C···X and C···Y bonds, each addition has been found to be energetically concerted, having only one transition structure leading directly to the three-membered cycloadduct. The existence of the extra π system on the acetylene moiety induces presumably an additional resonance stabilization of the negatively charge terminal carbon (see structure **II**), relative to the hypothetical structure **III** (in the case of addition to ethylene), allowing finally **II** to exist as an energy minimum.



It is also interesting to note that the cyclopropenimine **HPd** is a nitrogen analogue of triafulvene (**IV**), which is formally a 2π aromatic system. In particular, interaction between the π electrons of the ring and exocyclic double bond tends to reinforce the stability of the combined system. It is worth examining the stability of cyclopropenimine via the two representative isodesmic reactions 2 and 3:



(2)



(3)

Using B3YP/6-311G(d,p) geometries and energies, the heats of the reactions 2 and 3 amount to 34 and 63 kJ/mol, respectively. Both reactions 2 and 3 are thus endothermic, indicating a higher stability of the right-hand side. In other words, the cyclopropenimine exhibits a stability at least comparable to that of triafulvene, and the coupling between a cyclopropene and an exocyclic imine functional is energetically beneficial for the ring.

Addition of HN≡C to HC≡C−CH$_3$ (Reaction M). We now consider the effect of a methyl group attached to the acetylene moiety. For this system, only B3LYP/6-311G(d,p) calculations have been performed. Calculated results are recorded in both Figures 3 and 4. The structures are now labeled with an **M**, which stands for methyl. Again, the addition has been found to be a two-step process. Due to the presence of the methyl group, the two acetylene carbon centers are no longer equivalent, and this induces, as a consequence, a site selectivity in the attack of HN≡C. Overall, the number of stationary points are doubled relative to the unsubstituted case.

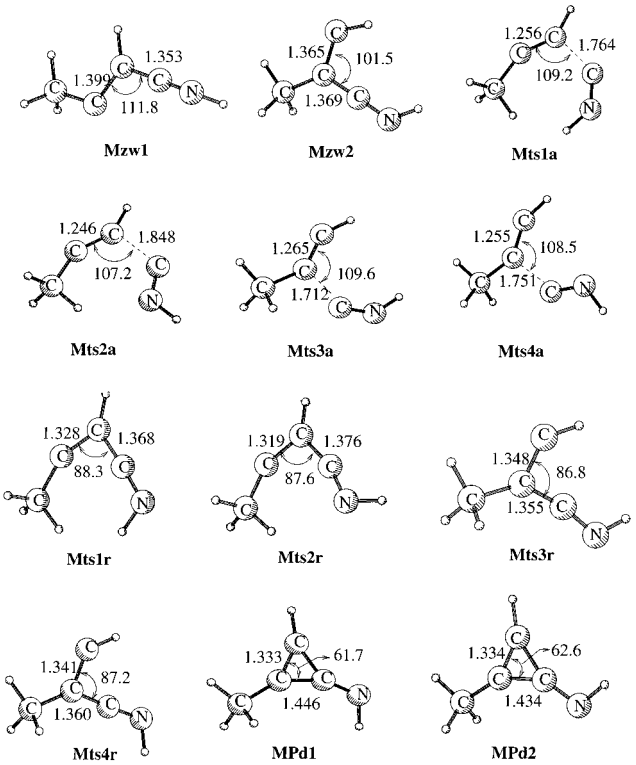


Figure 3. Selected geometrical parameters of the points on the HN≡C + HC≡C−CH$_3$ pathway (reaction M) using B3LYP/6-311G(d,p).

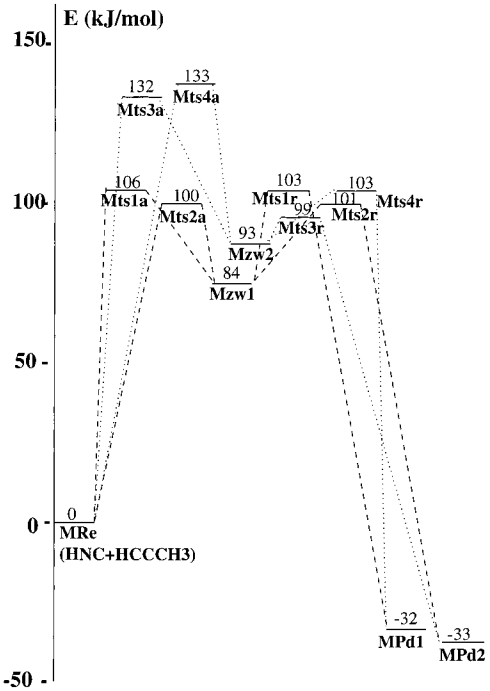


Figure 4. Schematic potential energy profile for the HN≡C + HC≡C−CH$_3$ reaction (M). Energies obtained from B3LYP/6-311G(d,p) + ZPE.

As can be seen in Figure 4, attack of HN≡C to the unsubstituted carbon (C^1) via **Mts1a** and **Mts2a** is consistently preferred over that to the substituted center via **Mts3a** and **Mts4a**. The former are about 30 kJ/mol lower in energy than the latter. Contrary to the unsubstituted case, **Mts1a** lies about 1 kJ/mol higher than **Mts2a**, which is no doubt due to the steric repulsion between terminal H and CH$_3$ groups. Thus, in this case, the determining factor is the steric repulsion rather than

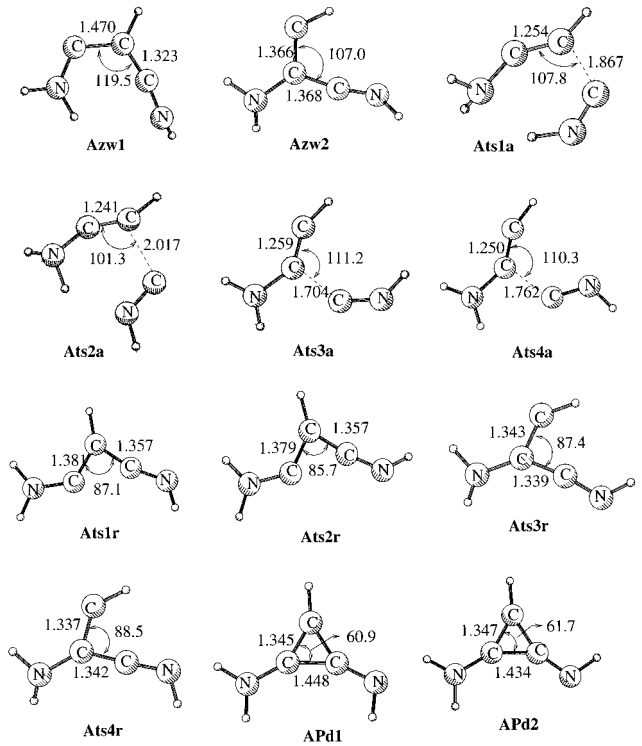


Figure 5. Selected B3LYP/6-311G(d,p) geometrical parameters for the various points on the HN≡C + HC≡C−NH_2 pathway (reaction A).

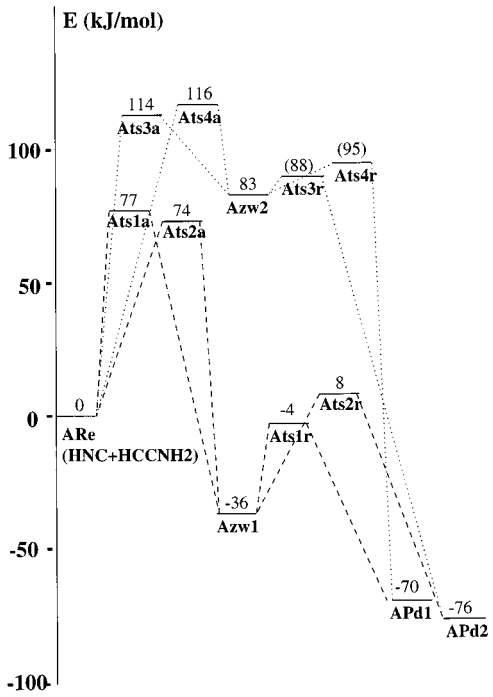


Figure 6. Schematic profile illustrating the potential energy of the HN≡C + HC≡C−NH_2 reaction (A). Values are from B3LYP/6-311G-(d,p) + ZPE calculations. In parentheses are B3LYP/6-311G(d,p) values using HF/6-31G(d)-optimized geometries and corrected for zero-point contributions.

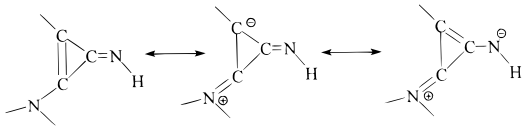
the stereoelectronic effect. The attack via **Mts2a** thus forms the most favored addition path, characterized by a markedly long intermolecular $C^1\cdots C$ distance (1.84 Å). The latter is by far longer than those in the remaining ts's and in **Hts1a** and **Hts2a**. Relative to the unsubstituted case, the energy barrier for addition is found to be reduced by about 25 kJ/mol. Again, only two zwitterion intermediates, **Mzw1** and **Mzw2**, instead of four, have been located either from IRC paths or from separate energy minimizations. The intermediates, as well as the cyclic products, have relative stabilities comparable to those of the unsubstituted system. Similarly, the energies of the ts's for ring closure of the second step are not significantly modified. The initial addition remains the rate-determining step of the entire process.

Overall, the most significant effect induced by the methyl group is a noticeable reduction of the energy barrier.

D. Addition of HN≡C to HC≡C−NH_2 (Reaction A). Krebs and co-workers[17,18] observed that ynamines (−C≡C−N<) and, in particular, yne-diamines (>N−C≡C−N<) react efficiently with aryl isocyanides. Here we have chosen amino-acetylene as a model system. Again, only B3LYP/6-311G(d,p) calculations have been performed. While Figure 5 displays related geometrical parameters of the points along the HN≡C + HC≡C−NH_2 pathway, Figure 6 records schematically the energy profiles. The structures are labeled with the letter **A**, which stands for amino.

As in the methyl case, **Ats2a** is found to be the lowest-lying ts for addition among the four possible structures. **Ats2a** effectively corresponds to an attack to the unsubstituted carbon (C^1) and an outward bending of isocyanide. The intermolecular $C^1\cdots C$ distance becomes now remarkably long in **Ats2a**, being longer than 2 Å. Proceeding in the addition direction, the ts can be regarded as occurring earlier than the corresponding ts, such as in **Hts1a** (1.75 Å). As a consequence, the energy barrier is substantially reduced to 74 kJ/mol, as compared with 126 kJ/mol in **Hts1a** and 100 kJ/mol in **Mts2a**. This trend is consistent with the variation of the HOMO−LUMO energy gaps, which are successively reduced on going from HC≡CH to HC≡C−CH_3 to HC≡C−NH_2 (Table 1).

Of particular interest is perhaps the higher stability of the amino-zwitterion **Azw1**, which is now −36 kJ/mol below the separated reactants. Proceeding in the fragmentation direction, from zwitterion intermediate to separated fragments, the **Ats2a**, having a C−C distance of more than 2 Å, could be regarded as occurring later than other ts's, such as **Hts1a** (1.75 Å). From the simple view of the Hammond postulate, a later ts is expected to induce a higher barrier energy. Because **Ats2a** is also determined by the addition, the zwitterion **Azw1** should be strongly stabilized in such a way that the energy barrier for fragmentation is increased on going from **Hzw1** to **Azw1**.



(4)

In the same vein, both amino-cyclopropenimines **APd1** and **APd2** are also stabilized appreciably. The many possible resonance structures, as written in eq 4, contribute a great deal to the stabilization of the cycloadduct. The ring closure from the intermediates is energetically less demanding. Overall, the initial addition remains by far rate-controlling.

E. Addition of HN≡C to HC≡C−F (Reaction F). In the last reaction considered in this work, fluorine has been taken as the acetylene substituent. F is well known as the most electronegative element, but its electronic effect is not completely electron-withdrawing. In many cases, the latter effect is tempered by an electron back-donation. The calculated results derived from B3LYP/6-311G(d,p) computations are illustrated in Figures 7 (related geometries) and 8 (energy profiles). For this system, the structures are labeled obviously by the letter **F**.

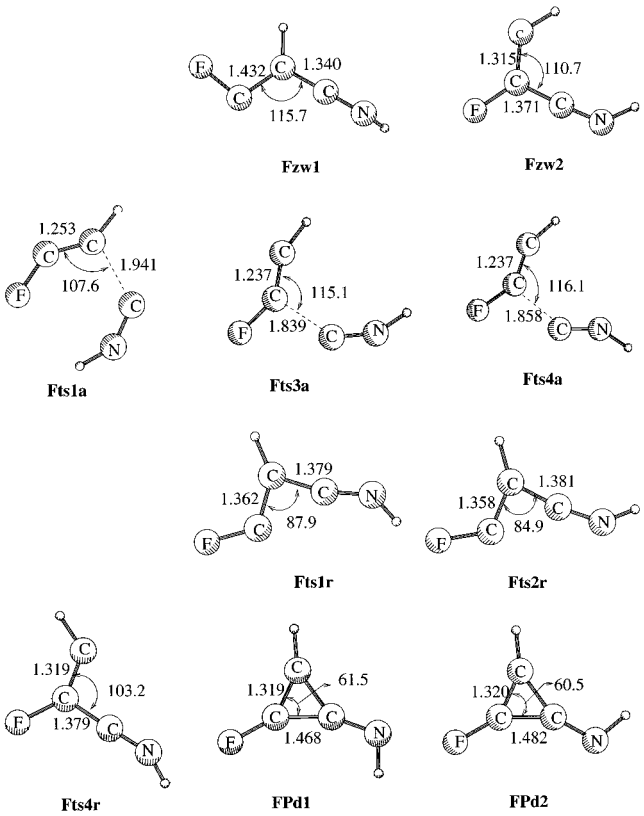


Figure 7. Selected B3LYP/6-311G(d,p) geometrical parameters for the points on the HN≡C + HC≡C−F pathway (reaction F).

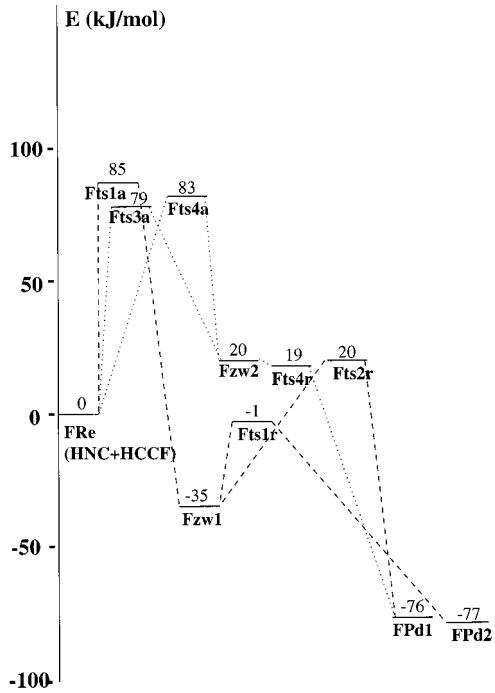


Figure 8. Schematic potential energy profile related to the HN≡C + HC≡C−F reaction (F). Values are from B3LYP/6-311G(d,p) + ZPE.

The addition of the fluorinated system presents some similarities but also marked differences with respect to the previous cases. Briefly, a few interesting points can be noted.

(i) The initial attack occurs preferentially at the substituted carbon site; **Fts3a** turns out to be the lowest-lying ts for addition, even though it exhibits a shorter C···C intersystem distance (1.84 Å) versus that (1.94 Å) in **Fts1a**. Note that we were not able to locate the **Fts2a**.

(ii) The associated energy barrier via **Fts3a** is also reduced to 79 kJ/mol, being thus at a similar magnitude than that in the amino case. It is remarkable that such a reduction is not manifested at all in the HOMO−LUMO energy gap (Table 1). The latter in the F-system is, in fact, comparable with that of acetylene. The overall result comes presumably from the peculiar properties of F as mentioned above.

(iii) The zwitterions, as well as fluoro-cyclopropenimines, are stabilized quantitatively relative to the reactants. **Fzw1** is more stable than **Fzw2**; the former possesses, however, an *E*-configuration. A *Z*-counterpart which would result directly from the relaxation of **Fts1a** was not found.

(iv) Similar to the previous cases, the rate-determining character of the addition step still persists.

In summary, a number of chemically significant results emerge from the analysis presented in this paragraph.

(i) The addition of isocyanide to alkynes is stepwise, in which the initial addition step is rate-controlling. In this step, isocyanide exerts the role of an electrophile.

(ii) The barriers to addition are not particularly high, being 130 kJ/mol in acetylene and decreasing in the order H > CH_3 > NH_2 ∼ F, to about 75 kJ/mol in amino-acetylene. The energy barrier seems also to be foreshadowed by the stability of the zwitterion intermediate. The latter is quite stabilized in the amino-substituted system and induces thus a substantial decrease of the addition barrier.

(iii) There is a site selectivity in the initial attack of isocyanide; except for fluoro-acetylene, the unsubstituted alkyne carbon is preferred.

(iv) The zwitterion intermediate does exist within a rather shallow potential well. It is, however, stabilized upon substitution of H by NH_2 and F. Conversion of these reactive intermediates to the more stable cyclopropenimines is a quite facile step. In this sense, these zwitterions are not expected to induce any important effect on the course of the cycloaddition. In fact, various experiments[17,18] suggested that the reaction is almost solvent-independent.

F. Asynchronism in Addition. It has been observed from our discussion in the previous section that addition of HNC to the alkynes, leading to a three-membered ring compound, proceeds through two steps: an asynchronous initial attack of HNC on one of the triply bonded carbon atoms of the alkyne, followed by a step for ring closure. For substituted acetylenes (X−C≡C−H), the two carbon atoms are not equivalent, and this introduces site selectivity in the initial HNC attack, resulting in a significant difference in activation energy between the two transition structures, corresponding to an initial attack on the two nonequivalent carbon atoms. It has been observed from our calculations that initial attack on the unsubstituted carbon atom, C^1, of acetylene is associated with a lower energy barrier, except in the case of fluoro-acetylene, where initial attack is favorable at the substituent-bearing carbon atom, C^2. To explain this observed site selectivity, an analysis has been carried out using DFT-based reactivity descriptors such as Fukui functions and local softness. These descriptors have recently been successfully used for explaining the observed site selectivity in [2 + 1] addition reactions between HNC and various doubly bonded dipolarophiles,[23] for explaining the site selectivity of radical attack on substituted ethylenes,[32] and for interpreting the regioselectivity of Diels−Alder reactions.[30] A detailed discussion about these reactivity parameters and their role in concep-

(32) Chandra, A. K.; Nguyen, M. T. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1415.

tual DFT can be found elsewhere;[28,29,33] only the relevant expressions used for the evaluation of the various quantities are given below. The global hardness (η) and softness (S) are calculated from the operational formulas given by Pearson and Parr,[34]

$$\eta = 1/2(\mathrm{IE} - \mathrm{EA}) \tag{5}$$

and

$$S = 1/(\mathrm{IE} - \mathrm{EA}) \tag{6}$$

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

The Fukui function is defined as

$$\mathrm{f}(\boldsymbol{r}) = [\partial\rho(\boldsymbol{r})/\partial N]_{\mathrm{v}} \tag{7}$$

Combined with the total softness S, $f(\boldsymbol{r})$ yields the local softness function,[35]

$$\mathrm{s}(\boldsymbol{r}) = S\,\mathrm{f}(\boldsymbol{r}) \tag{8}$$

It has been argued that the greater the Fukui function value, the greater the reactivity of a site.[35] Yang and Mortier[36] later proposed a condensed-to-atom form of the Fukui function. The condensed Fukui functions of an atom, k, in a molecule with N electrons are expressed as

$$\begin{aligned} \mathrm{f}_k^{+} &= [q_k(N+1) - q_k(N)] && \text{for nucleophilic attack} \\ \mathrm{f}_k^{-} &= [q_k(N) - q_k(N-1)] && \text{for electrophilic attack} \\ \mathrm{f}_k^{0} &= [q_k(N+1) - q_k(N-1)]/2 && \text{for radical attack} \end{aligned} \tag{9}$$

where q_k is the electronic population of atom k in a molecule. The condensed softness parameters can easily be calculated from the condensed Fukui function and global softness by using eqs 8 and 9. In the present work, the atomic charges are evaluated by following various procedures, such as Mulliken charges, electrostatic potential driven charges (ESP), and natural population analysis (NPA). ESP and NPA charges were chosen as they were found to be less basis set sensitive than the more conventional Mulliken population analysis[37] and were calculated by using MK and NPA options in the Gaussian program.

In view of the local HSAB principle of Gázquez and Mendez,[38] which states that the interaction between two molecules, A and B, is favored when it occurs through those atoms having equal softness values, it is expected that the initial attack of the carbon atom of HNC will be at that center of substituted acetylene, which is closer in softness to the HNC carbon atom. However, to apply this HSAB principle, one first needs to classify the two reactants as nucleophilic or electrophilic (cf. eq 9). As discussed in section A on the basis of HOMO, LUMO energies and IE and EA, substituted acetylenes act as a nucleophile and HNC as an electrophile in the reactions of our present interest. Table 2 shows the softness value for nucleophilic attack for the carbon atom of HNC and softness for electrophilic attack for the two carbon atoms of substituted acetylene. It is clear that the unsubstituted carbon atom, C^1, of the substituted acetylenes has larger softness for electrophilic attack than the substituted carbon atom, C^2. Table 3 presents the activation energies and the softness differences between the carbon atom of HNC and the two carbon atoms of the substituted acetylenes. The difference is lower for the C^1 atom of acetylene, and thus initial attack should be on this carbon atom. This explains why the attack on C^1 is associated with a lower energy barrier. However, the present analysis fails to explain why, in the case of an F-substituent, the initial attack is favorable at the C^2 atom although the softness difference is smaller for the C^1 atom. The present analysis is based solely on the properties of isolated reactants, and thus it is not unexpected that, in some extreme cases, some other stronger interaction can overwhelm the predictions made from softness alone. It is also interesting to note from Tables 1 and 3 that the activation barrier decreases with increasing softness of the acetylenic systems (H → CH_3 → NH_2). Once again, the fluorine substituent is the exception. This is no doubt due to the fact that an increase in softness enhances the ease of electron transfer from the acetylene to the HNC. The hardness and polarizability values for the two major transition structures associated with the initial HNC attack on the two distinct sp^1 carbon atoms of substituted acetylenes are listed in Table 4. In the case of CH_3 and NH_2 substituents, the lower energy ts has higher hardness and lower polarizability. Once again, fluoro-acetylene is the exception. Nevertheless, this observation corroborates well with the observation made by Chandra and Nguyen[39] in the context of 1,3-dipolar cycload-

Table 2. Local and Global Softness of HN≡C and Alkynes Considered (in au)

compound	local softness[a] C*	local softness[b] C^1	local softness[b] C^2	global softness
HN≡C*	1.383 (1.215)			1.731
H−C^1≡C^2−H		0.866 (0.825)	0.866 (0.825)	1.856
H−C^1≡C^2−CH3		1.096 (0.846)	0.460 (0.674)	2.048
H−C^1≡C^2−NH2		1.403 (1.075)	−0.216 (0.191)	2.353
H−C^1≡C^2−F		1.042 (0.951)	0.489 (0.512)	1.857

[a,b] Local softness values using electrostatic potential driven charges (ESP); in parentheses are values obtained from natural population analysis (NPA) charges. [a] Local softness for nucleophilic attack (s_k^+) of carbon atom C*. [b] Local softness for electrophilic attack (s_k^-) of carbon atoms C^1 and C^2.

Table 3. Activation Energies (kJ/mol) and Values Δ of Softness Differences (in au)

reactant with HN≡C*	Δ[a] **Ts2a**	Δ[a] **Ts3a**	E_{act} **Ts2a**	E_{act} **Ts3a**
H−C^1≡C^2−H	0.517 (0.390)	0.517 (0.390)	129	
H−C^1≡C^2−CH3	0.287 (0.369)	0.923 (0.541)	100	132
H−C^1≡C^2−NH2	−0.020 (0.140)	1.599 (1.024)	74	114
H−C^1≡C^2−F	0.341 (0.264)	0.894 (0.703)	85[b]	79

[a] Δ represents the softness differences between C* of HN≡C* and C^1,C^2 of alkynes using electrostatic potential driven charges (ESP); in parentheses are values obtained from natural population analysis (NPA) charges. [b] Activation energy of **Fts1a**.

Table 4. Hardness and Polarizability (in au) of the Transition State of HN≡C + (substituted) Acetylene Reactions

reactant with HN≡C*	hardness **ts2a**	hardness **ts3a**	polarizability **ts2a**	polarizability **ts3a**
H−C^1≡C^2−H	0.156		45.128	
H−C^1≡C^2−CH3	0.166	0.153	55.689	57.241
H−C^1≡C^2−NH2	0.174	0.155	50.264	53.929
H−C^1≡C^2−F	0.173*	0.170	43.071[a]	43.755

[a] Values of **Fts1a**.

(33) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
(34) Pearson, R. G.; Parr, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.
(35) Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049.
(36) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.
(37) De Proft, F.; Martin, J. M. L.; Geerlings, P. *Chem. Phys. Lett.* **1996**, *256*, 400.
(38) Gázquez, J. L.; Mendez, F. *J. Phys. Chem.* **1994**, *98*, 4591.

ditions and by others[40] in a different context that a higher hardness ts in general shows lower polarizability.

The possibility for defining a hardness profile in analogy with an energy profile has been discussed many times in the recent past.[40−44] In some cases, hardness has been found to go through a minimum near the transition state along the reaction coordinate. However, this is not the general behavior, and in many other cases no minimum has been found near the transition state. The maximum hardness principle (MHP),[45] originally formulated by Pearson,[46] states that molecules tend to rearrange themselves so as to achieve maximum hardness and suggests that hardness will be minimum when the energy of a system is maximum under constant chemical potential (μ) and external potential [$v(r)$]. For a chemical reaction, neither μ nor $v(r)$ can be kept constant, and thus it is not likely that an extremum will be found in the hardness profile. However, it has been observed on many occasions that the MHP is satisfied even if the conditions of constant μ and $v(r)$ are relaxed to some extent.[46] It has been pointed out by Parr and Gázquez[47] that hardness should reach an extremum at a point where both the electronic energy and the nuclear repulsion energy of a molecule reach their own respective extrema. Later, Gázquez et al.[48] showed that, under constant chemical potential, the hardness of a system will be maximized where the electronic energy is a minimum and vice versa. However, the conditions for which one can expect a smooth hardness profile similar to an energy profile, along a reaction path for a general chemical reaction, are still not well understood.

We have constructed the hardness, polarizability, and energy profiles for all the reactions studied here. We feel that this will help in further understanding the conditions for getting a hardness profile along a reaction coordinate. Moreover, the hardness and polarizability profiles will be helpful in the understanding the relationship between them in a wider context. The profiles are constructed for the two minimum energy ts's associated with the attack of HNC on two distinct carbon atoms of the substituted acetylenes. In all the cases, the profiles were constructed near the ts, because of the obvious technical difficulty in calculating hardness from the finite difference formula when the two reactants are far apart but still interacting. The polarizability (α) has been calculated as an arithmetic average of the three diagonal elements of the polarizability tensor [$\alpha = 1/3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$] using the finite field method.[49]

Figure 9 presents the hardness, polarizability, and energy profiles for the HN≡C + HC≡CH reaction. It is interesting to notice that η goes through a shallow minimum and α shows a maximum along the profile. These two extrema, however, do not coincide with the maximum in energy profile. The extrema in the η and α profiles appear more toward the product side compared to the maximum in energy profile. The variations of η and α along the reaction coordinate are opposite to each other. This shows that the observation of higher hardness, implying lower polarizability, made from the η and α values of the transition structures, holds well in a much wider context. Figures 10−12 display the various reaction profiles corresponding to the two minimum energy transition states (**ts2a** and **ts3a**) associated with the two possible initial HNC attacks on the sp^1 carbon atoms of the substituted acetylenes H−C≡C−CH_3, H−C≡C−NH_2, and H−C≡C−F. While for both cases the

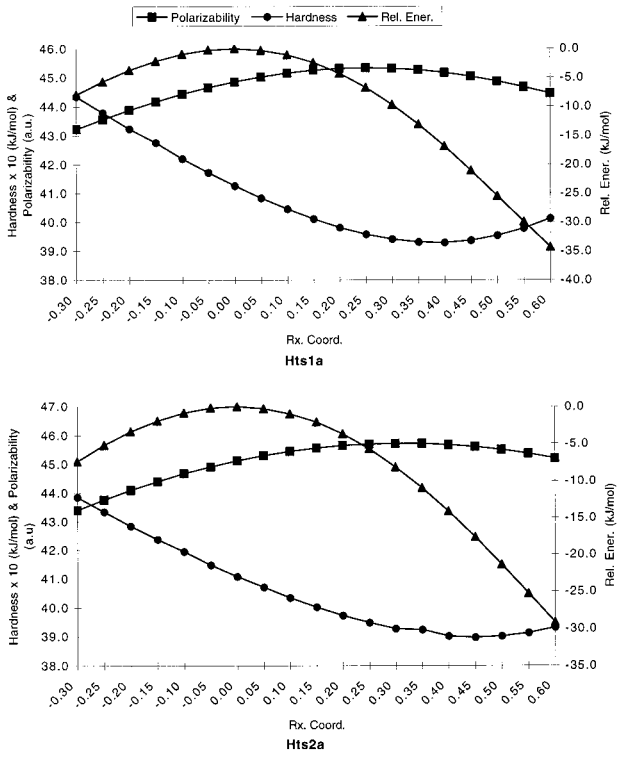


Figure 9. Profiles of hardness (η in kJ/mol) and polarizability (α in au) along the IRC pathway of the HN≡C + HC≡CH reaction.

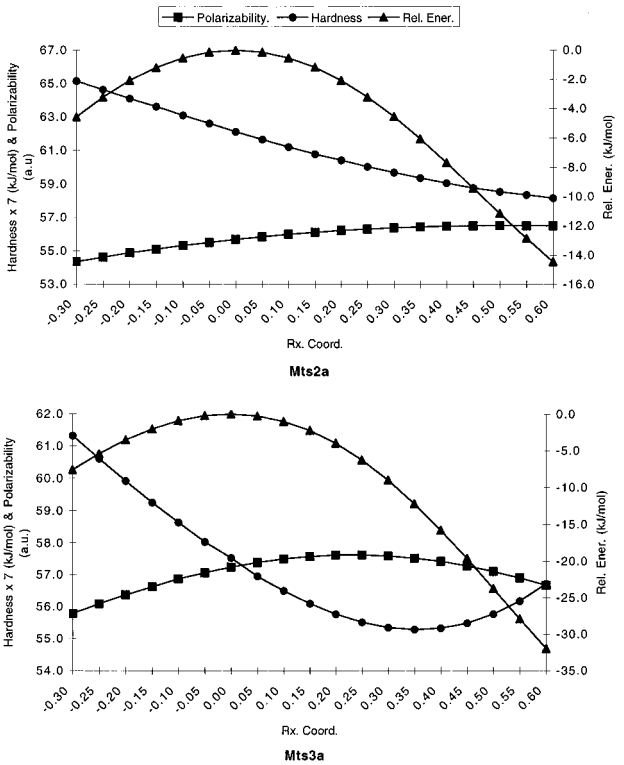


Figure 10. Profiles of hardness (η in kJ/mol) and polarizability (α in au) along the IRC pathway of the HN≡C + HC≡C−CH_3 reaction.

(39) Chandra, A. K.; Nguyen, M. T. *J. Comput. Chem.* **1998**, *19*, 195; *J. Phys. Chem. A* **1998**, *102*, 6181.
(40) Ghanty, T. K.; Ghosh, S. K. *J. Phys. Chem.* **1996**, *100*, 12295.
(41) Chattaraj, P. K.; Nath, S.; Sannigrahi, A. B. *J. Phys. Chem.* **1994**, *98*, 9143.
(42) Chandra, A. K. *J. Mol. Struct. (THEOCHEM)* **1994**, *312*, 297.
(43) Kar, T.; Scheiner, S. *J. Phys. Chem.* **1995**, *99*, 8121.
(44) Cárdenas-Jirón, G. I.; Gutiérrez-Oliva, S.; Melin, J.; Toro-Lablé, A. *J. Phys. Chem. A* **1997**, *101*, 4621.
(45) Parr, R. G.; Chattaraj, P. K. *J. Am. Chem. Soc.* **1991**, *113*, 1854.
(46) Pearson, R. G. *Acc. Chem. Res.* **1993**, *26*, 250.
(47) Parr, R. G.; Gázquez, J. L. *J. Phys. Chem.* **1993**, *97*, 3939.
(48) Gázquez, J. L.; Martinez, A.; Mendez, F. *J. Phys. Chem.* **1993**, *97*, 4059.
(49) Cohen, H. D.; Roothaan, C. C. J. *J. Chem. Phys.* **1965**, *43*, S34.

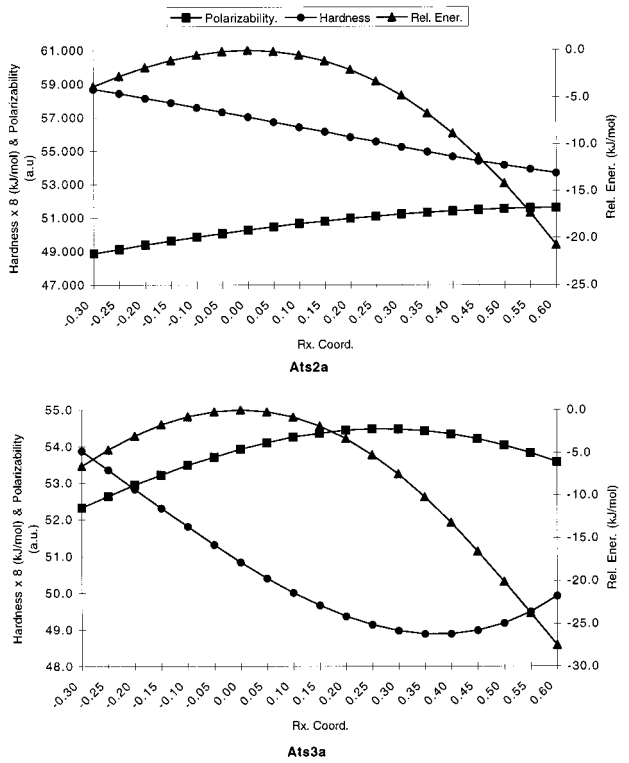


Figure 11. Profiles of hardness (η in kJ/mol) and polarizability (α in au) along the IRC pathway of the HN≡C + HC≡C−NH_2 reaction.

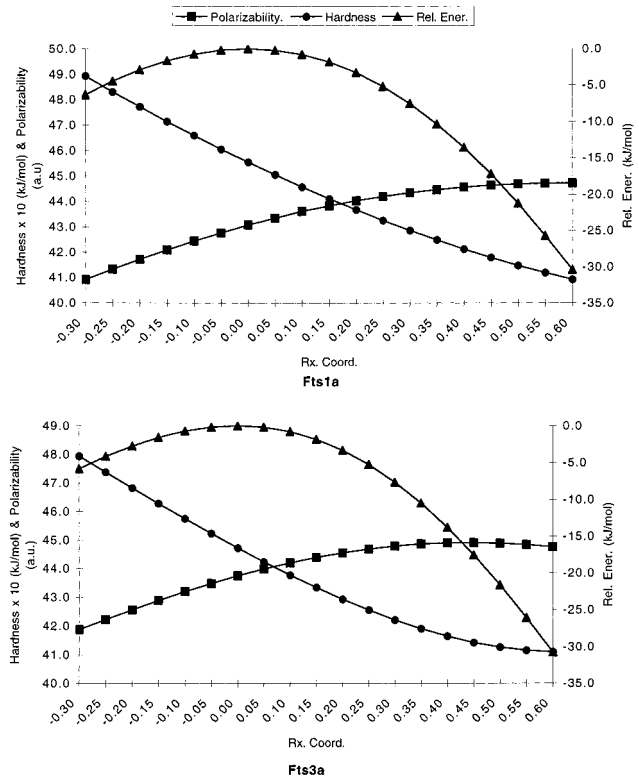


Figure 12. Profiles of hardness (η in kJ/mol) and polarizability (α in au) along the IRC pathway of the HN≡C + HC≡C−F reaction.

profiles corresponding to **ts3a** are almost the same as in the case of the HNC + C_2H_2 reaction and exhibit a minimum in the hardness profile, those associated with **ts2a** are different and do not show any extremum both in η and α profiles. We do not find any obvious explanation for this difference. Nevertheless, it is clear from the figures that changes in hardness and polarizability are opposite to each other. It thus seems, at least in the present context, that higher hardness−lower polarizability criterion holds well even when constraints of constant μ and $v(r)$ are relaxed, whereas the relationship between hardness and energy becomes more complex and does not follow any general pattern.

Table 5. Ab Initio-Calculated Activation Energies (E_{act}, kJ/mol), as Compared to the Right-Hand Side of Eq 10 (in au)

reactant with HN≡C	eq 10	E_{act}
H−C≡C−H	0.246	129
H−C≡C−CH3	0.197	100
H−C≡C−NH2	0.142	74
H−C≡C−F	0.211	85

It is interesting to relate this discussion to a DFT-based treatment along the line recently set out by Gázquez.[50] Assuming a constant chemical potential, Gázquez arrived in an approximated scheme, also used by some of the present authors in studies on the regioselectivity of Diels−Alder reaction,[30] at an expression in which the activation energy, E_{act}, is proportional to the difference in hardness between the transition state and the reactants. Assuming, as Gázquez did,[50] additivity of the softnesses of the reactants, S_i, with a proportionality constant, α, which is unknown but whose value is smaller than 1 for obvious reasons, one can assume that

$$E_{act} \sim \frac{1}{\alpha \sum_i S_i} - \frac{1}{S_{ts}} \qquad (10)$$

To test this relationship, we have correlated our ab initio-calculated activation energies (Table 3) with the values obtained using eq 10. It was found that, as can be seen from Table 5, for a reasonable choice of α (in our case arbitrarily set to 0.5), the right-hand side of eq 10 yields a H > Me > NH_2 sequence, the same sequence as for the activation energies. When going to the fluorine compound, the prediced activation energy increases again, as is confirmed from the calculations, to about the same value as the Me compound.

4. Conclusions

In the present theoretical study using both MO and DFT methods, it has been demonstrated that the formal [2 + 1] cycloaddition of hydrogen isocyanide to an alkyne is a stepwise process in which initial addition of HN≡C to an alkyne carbon atom is rate-determining. The conversion of the zwitterion intermediate to the cyclopropenimine adduct is rather facile. Therefore, the zwitterion does not play any important role in the cycloaddition. Isocyanide behaves consistently as an electrophile, in agreement with experimental observations. The energy barriers decrease in the sequence H > CH_3 > NH_2 ∼ F. There is a site selectivity and asynchronism in the initial attack of HN≡C to alkynes. Except for the fluorine case, initial attack on the unsubstituted alkyne carbon atom is favored. The site selectivity has been rationalized in terms of local softness and Fukui functions.

The hardness and polarizability profiles have also been constructed along the IRC pathway. In some cases, the extrema exist, while in other cases, they do not. When a minimum on the hardness profile and a maximum on the polarizability profile appear, they do not coincide with the position of energy maximum and are consistently displaced toward the product side. While the higher hardness−lower polarizability criterion

(50) Gázquez, J. L. *J. Phys. Chem.* **1997**, *A101*, 8967.

for the preference of one transition structure over the other seems to hold true, there is no clear-cut relationship between hardness and activation energy.

Gázquez's recently proposed E_{act}−hardness difference correlation sheds further light on the origin of the calculated E_{act} sequence.

Acknowledgment. We are grateful to the Flemish Government (Ministerie van Onderwijs) for financially supporting an "Interuniversity Program for Education in Computational Chemistry in Vietnam". P.G. and M.T.N. are indebted to the FWO-Vlaanderen. W.L. and F.D.P. thank the FWO-Vlaanderen for a postdoctoral fellowship. A.K.C. thanks the KULeuven Research Fund for a postdoctoral fellowship. We also thank Adolf Krebs from Hamburg University for bringing this problem to our attention.

JA983394R