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AM1 Calculations of Parts of the Enthalpy Surfaces for Additions of Active Methylene Nitriles to α,β-Unsaturated Nitriles

S. El-Taher* and M. H. Elnagdi

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

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ABSTRACT

The nucleophilic additions of active methylene nitriles (MNs), $R_1R_2CH^-$, where $R_1=CN$ and $R_2=CN$, and $CSNH_2$, to acetaldehyde and to the resultant α,β-unsaturated nitriles have been studied theoretically by the AM1 semiempirical MO method. The additions of MNs anions to acetaldehyde are found to be endothermic with late productlike transition states (TSs) on the reaction coordinate. Their additions to α,β-unsaturated nitriles may conceivably proceed via two pathways: addition to the C=C double bond and addition to the C≡N triple bond. It has been found that the nucleophilic attack at the α,β-unsaturated linkage is exothermic, while that at the nitrile group is endothermic and has a relatively high enthalpy barrier. Both additions have late productlike transition states. The reactivity of the nucleophilic attack has been discussed in the light of the frontier molecular orbital theory and in terms of the HOMO–LUMO two-electron interaction. The calculations have been compared with experimental results.

INTRODUCTION

Pyridinethiones constitute an important class of heterocyclic compounds of considerable interest due to their utility as excellent starting materials for the synthesis of biologically active heterocyclic systems [1].

The reaction of active methylene nitriles (MNs) **1** with *α,β*-unsaturated nitriles **2** is one of the most extensively utilized routes to pyridinethiones [2–13]. The reaction mechanism of such a synthetic route has been a point of debate during the 1980s. One of us (M.H.E.) and his coworkers previously reported [14–17] that the reaction of *α,β*-unsaturated nitriles with cyanothioacetamide proceeds via the addition of the latter to one of the nitrile groups. Others believe that the addition of cyanothioacetamide to the *α,β*-unsaturated linkage prevails over the addition to the nitrile group [4,6,9].

Another point of debate has been concerned with the relative nucleophilic reactivities of MNs with respect to the addition to *α,β*-unsaturated nitriles. It has been reported [18] that, in mixtures of cyanothioacetamide, aldehydes, and MNs, cyanothioacetamide adds to aldehydes and then to the resultant ylidenes in spite of the relative reactivities of the other MNs present in the mixtures.

Recent experimental work [12,13] has demonstrated that mixtures of aldehydes, malononitrile, and cyanothioacetamide react to yield thiopyrans that rearrange to pyridinethiones. These results encouraged us to reinspect the previous reports [14–17] by investigating the reaction products of a mixture of acetaldehyde, malononitrile, and cyanothioacetamide in ethanolic piperidine at room temperature [19]. A product of the formula $C_8H_8N_4S$ was obtained. This formula is consistent with the acyclic

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*To whom correspondence should be addressed.

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structure **3**, the thiopyran **4**, or the pyridinethione **5**. It has been assumed that product **4** is formed via the intermediacy of the Michael adduct **3**. Moreover, compound **5** could also be formed on refluxing the starting mixture (Scheme 1b).

In order to shed light on the reaction course for mixtures of aldehydes, malononitrile, and cyanothioacetamide, we have now carried out a comparative theoretical study for the nucleophilic additions of active methylene nitriles to aldehydes as well as to the resultant α,β-unsaturated nitriles. The calculations have been used to clarify the experimental points of debate and to support the available experimental results. It is important to mention that the aim of the present work is directed at the theoretical estimation of trends in activation enthalpies of the title additions using semiempirical quantum mechanical methods and not to determine individually accurate activation enthalpies.

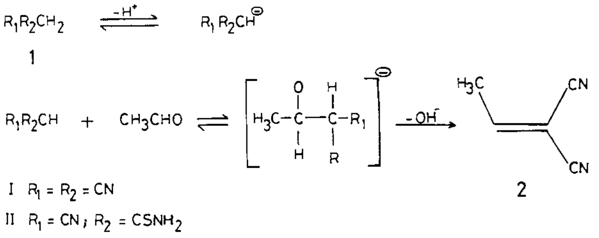
METHODS OF CALCULATION

The calculations of the equilibrium geometries of reactants, intermediates, transition states (TSs), and product structures of the studied reactions were all performed with the AM1 [20] Hamiltonian implemented in the MOPAC6 [21] program package. The geometries were fully optimized at the SCF level using internal coordinates and refined by using the PRECISE option. The geometries were further refined by minimizing the gradient norm [22] to 0.1 by using the GNORM option. The reaction coordinate method [23] was used to calculate the enthalpy surfaces and to locate the corresponding transition structures. The transition states of the studied additions were then calculated by using the SADDLE option. The geometries were refined by the gradient norm minimization and characterized by confirming only one negative eigenvalue in the Hessian matrix [24].

RESULTS AND DISCUSSION

Additions of MNs to Acetaldehyde

Scheme (1a) shows the possible reactions that might take place in a mixture of malononitrile, cyanothioacetamide, and acetaldehyde in ethanolic piperidine at room temperature. The reaction of either malononitrile (**I**: $R_1 = R_2 = CN$) or cyanothioacetamide (**II**: $R_1 = CN$, $R_2 = CSNH_2$) with acetaldehyde proceeds in two steps: deprotonation of the MN, followed by the addition of the resulting anion to acetaldehyde. The resultant adduct loses OH^-, in a subsequent fast step, to yield the final product, $CH_3CH = CR_1R_2$. Therefore, the importance of studying this addition originates from its being the initial step in the route generally adopted for the synthesis of pyridinethiones. Moreover, the calculations of the enthalpy surfaces for such additions would fairly determine the relative nucleophilic reactivities of the respective MNs.



SCHEME 1a

Table 1 shows selected geometrical parameters of the fully optimized geometries for the transition states and adduct structures of the studied additions. The structures of the transition states are depicted in Figure 1. The malononitrile anion has a planar structure with an H–C–CN angle of 118.48°. This is due to the π-interaction between the π-acceptor orbitals, π^*, of the cyano groups and a nonbonding orbital, n_p, on the central carbon atom. Such π-interactions stabilize the planar structure over the pyramidal one. As a result, the C–CN bond becomes shorter (1.379 Å) compared to its length in the neutral molecule (1.448 Å).

On adding to acetaldehyde, the malononitrile anion approaches the carbon atom of the carbonyl group in the molecular plane along the C–O axis. The electrostatic attraction between the anion and the carbonyl group reaches a maximum value at a $C_1 \ldots C_2$ distance of 4.135 Å and a $C_1C_2O_3$ angle of 159.18°. The geometry of the reactant complex shows little distortion from the geometries of the interacting species. At C_1C_2 distances less than 4 Å, as the orbital interactions increase, the $C_1C_2O_3$ angle decreases until it reaches 111.36° and 113.5° at C_1C_2 distances of 1.851 Å (TS **I**) and 1.658 Å (adduct **I**), respectively. Moreover, the n-HOMO of the malononitrile anion interacts with the low-lying π^*-LUMO of acetaldehyde and loses its interaction with the π^* orbitals of cyano groups. As a result, the C–CN bond loses its π-character and becomes relatively longer on going from the MN anion (1.379 Å) to the TS **I** (1.424 Å) and finally to the adduct **I** (1.442 Å). On the other hand, the CO bond becomes longer on going from acetaldehyde (1.232 Å) to the TS **I** (1.272 Å) and finally to the adduct **I** (1.292 Å). The CO bond length of the product is intermediate between the CO double bond of formaldehyde and a typical C–O single bond (1.400 Å) in a CH_3OH molecule. This elonga-

TABLE 1 Selected Geometrical Parameters of the AM1 Optimized Geometries for Transition States and Adducts of the Studied Nucleophilic Additions

	TS					*Adduct*				
	I	**II**	**III**	**V**	**VI**	**I**	**II**	**III**	**V**	**VI**
Bond length (Å)										
C1C2	1.851	1.815	2.127	2.266	2.312	1.658	1.625	1.553	1.554	1.551
C2O3(C3)	1.272	1.286	1.398	1.385	1.378	1.292	1.312	1.479	1.484	1.486
C1H4	1.115	1.114	1.107	1.100	1.103	1.126	1.124	1.135	1.137	1.135
C2H5	1.129	1.129	1.108	1.104	1.106	1.143	1.142	1.132	1.131	1.131
C2CH_3	1.524	1.522	1.483	1.481	1.476	1.540	1.535	1.514	1.515	1.516
C1R1	1.424	1.475	1.412	1.400	1.402	1.442	1.510	1.453	1.454	1.523
C1R2	1.424	1.428	1.434	1.402	1.414	1.443	1.443	1.521	1.454	1.523
C3CN	—	—	1.407	1.416	1.418	—	—	1.390	1.407	1.408
C3R3	—	—	1.409	1.458	1.459	—	—	1.392	1.398	1.401
Bond angles (deg)										
H4C1C2	102.03	104.94	91.97	88.67	88.88	106.24	107.96	106.97	107.42	107.43
H5C2C1	94.92	96.47	86.94	83.38	82.57	99.78	101.33	104.82	105.87	105.56
CH_3C2C1	99.63	101.79	102.99	98.05	101.85	103.60	105.39	111.05	110.89	110.73
R1C1C2	108.51	104.48	102.39	103.20	99.14	111.69	109.32	110.20	110.73	110.02
R2C1C2	106.12	106.97	102.88	106.64	101.38	109.40	110.49	113.79	113.04	113.47
C1C2C3(O3)	111.36	110.17	104.17	107.79	101.37	113.50	113.15	111.26	110.66	111.44
CN-C3C2	—	—	122.92	120.70	120.29	—	—	120.79	117.00	117.00
R3-C3C2	—	—	120.28					118.97		
Dihedral angles (deg)										
H4C1C2O3(C3)	187.51	−179.21	−43.53	3.94	−20.49	185.62	180.63	−48.07	−34.90	−51.62
R1C1C2O3(C3)	305.80	−61.22	−158.45	−113.72	−135.66	−56.03	298.67	−164.31	−152.77	−167.77
R2C1C2O3(C3)	70.39	61.95	76.58	120.94	99.21	68.29	61.54	70.40	83.69	67.36
R3C3C2C1	—	—	79.10	79.97	78.87	—	—	65.01	75.08	70.94
CNC3C2C1	—	—	−99.79	—	—	—	—	−123.98		

tion may be explained in terms of the conversion of the sp^2 hybridized carbon atom of the CO group to a tetrahedrally coordinated one.

In the addition depicted by **TS II**, the steric hindrance caused by the bulky $CSNH_2$ group decreases the $C_1C_2O_3$ angle of the reactant complex to 151.51° at a $C_1 \ldots C_2$ distance of 4.024 Å. Moreover, the electron-donating $CSNH_2$ group stabilizes the *n*-HOMO of cyanothioacetamide by 0.63 eV over that of malononitrile ($E_{\mathrm{HOMO}} = 2.84$ eV) and consequently decreases the extent of its interaction with the low-lying π-LUMO ($E_{\mathrm{LUMO}} = 0.7$ eV) of acetaldehyde. This may explain the 0.036 Å shortening in the C_1C_2 bond (1.815 Å) of **TS II** as compared to that of **TS I** (1.851 Å). In other words, the addition of the more active malononitrile anion has a relatively early transition state along the reaction coordinate as against that of the relatively less active cyanothioacetamide anion. This is true as long as the steric effect is minor.

The stereochemistry of the nucleophilic addition of the MNs to a carbonyl compound is greatly controlled by the nature of the substituents on both the MNs and the carbonyl compound. The dihedral angles $H_4C_1C_2O_3$, $R_1C_1C_2O_3$, and $R_2C_1C_2O_3$ measure the orientation of the malononitrile and cyanothioacetamide anions in both transition states and adducts with respect to the CO group. The value of $H_4C_1C_2O_3$ in **TS I** is 187.51°, while that in **TS II** is 180.79° (Table 1). It seems that the distortion from the Cs symmetry caused by the steric effect of the methyl group of acetaldehyde has been compensated for by the replacement of the CN group by the bulky $CSNH_2$ one in the MN anion. That orientation is mostly preserved in the corresponding adducts of additions **I** (185.38°) and **II** (180.63°).

Figure 2 shows the enthalpy profiles for additions **I** and **II**. Upon going from the reactant, $MN^- + CH_3CHO$, to the final product, two stationary points are found for each addition: a reactant complex, $MN^- \,..\, CH_3CHO$, and a transition state (TS). As the MN^- approaches the CH_3CHO molecule along the reaction coordinate, the electrostatic attraction between them lowers the energy so that the reactant complex is formed without an enthalpy barrier. A point to notice here is that the enthalpy barriers are estimated as the difference between the heats of formation at 298 K of the reactant complexes and the transition states. Reactant complexes are usually formed in reactions of ions with closed shell species

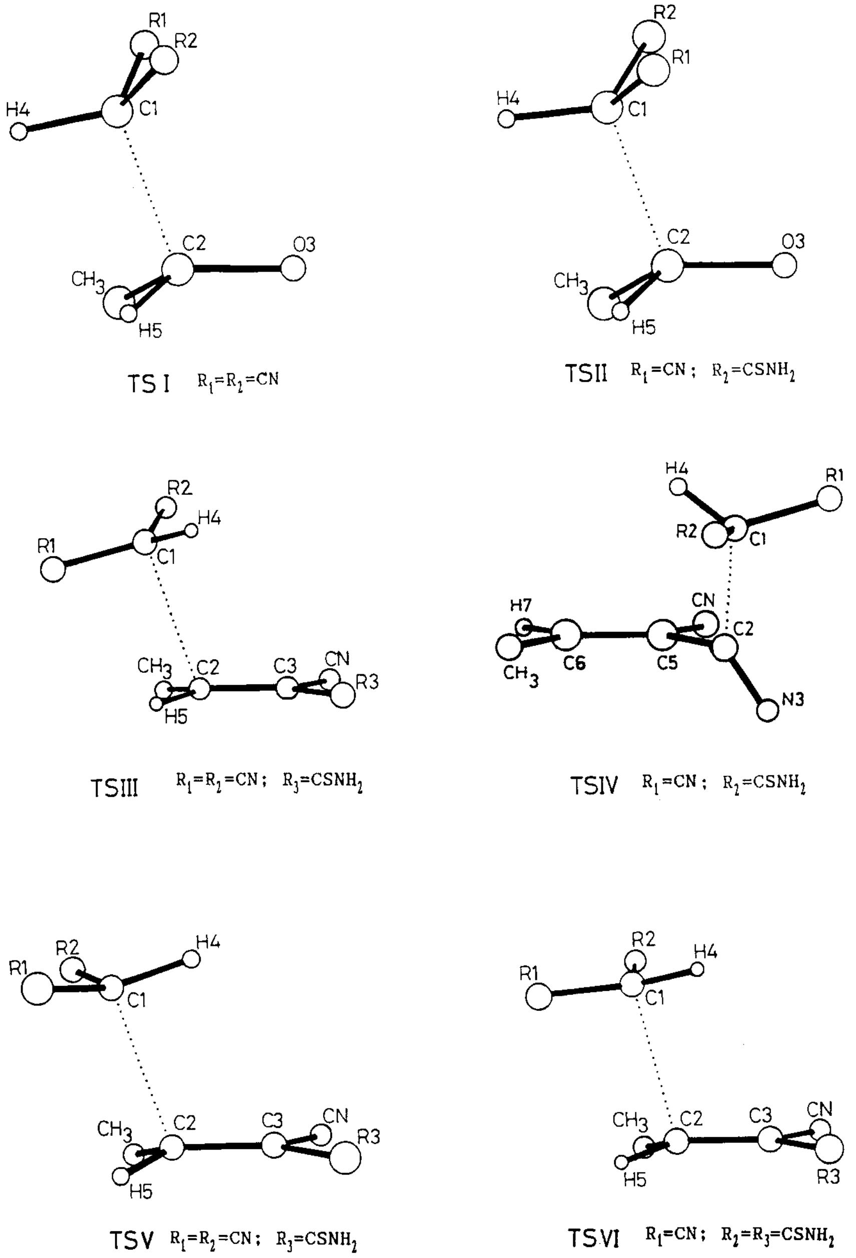


FIGURE 1 Computer plot of transition states structures of the studied nucleophilic additions.

in the gas phase [25]. The reactant complexes have to pass over enthalpy barriers of 14.35 and 21.68 kcal/mol for additions **I** and **II**, respectively, in order to complete the reaction. This may be explained in terms of the two-electron interaction between the frontier orbitals: the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbitals. The HOMO–LUMO interaction for addition **I** is relatively larger than that for addition **II** since the HOMO–LUMO energy gap is found to be 3.44 eV for addition **I** and 3.98 eV for **II**. Although they both have late transition states along the reaction coordinates, TS **I** lies earlier by 0.036 Å than TS **II**. Both TS **I** and TS **II** resemble closely the final products in structures and energies. This is in agreement with the Hammond postulate [26].

In conclusion, malononitrile is much more reactive than cyanothioacetamide toward the addition to acetaldehyde. Therefore, malononitrile will add first to acetaldehyde to finally yield ethylidenemalononitrile **2** (Scheme 1a). In the absence of malononitrile, cyanothioacetamide will add to **2** (Scheme 1b).

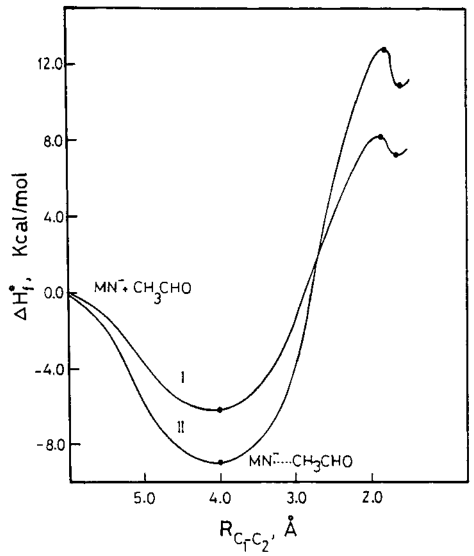
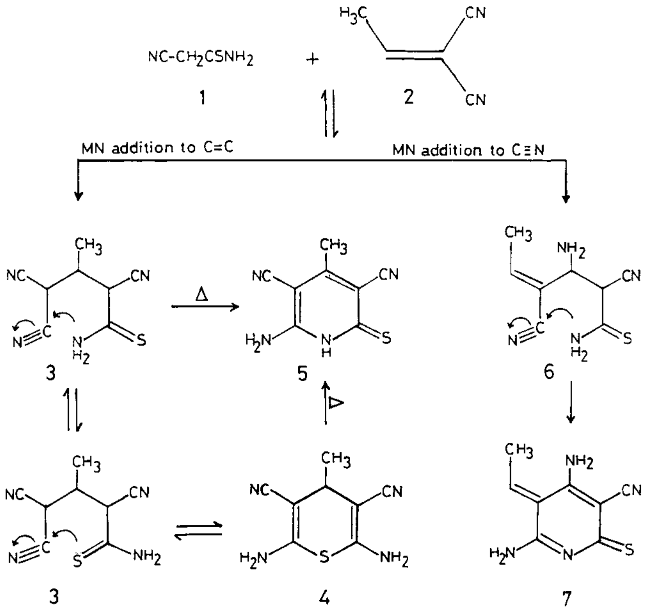


FIGURE 2 Enthalpy profiles for the additions of $(CN)_2CH^-$ (**I**) and $NH_2CS(CN)CH^-$ (**II**) anions to CH_3CHO.



SCHEME 1b

Addition of Cyanothioacetamide to Ethylidenemalononitrile

Scheme (1b) shows the nucleophilic additions of cyanothioacetamide **1** to ethylidenemalononitrile **2**. There are two different pathways to be investigated: an addition to the activated CC double bond (as depicted in TS **III**) and the other an addition to one of the two nitrile groups (TS **IV**) of **2**. The optimized geometries of TS **III** and its adduct are given in Table 1, while those of TS **IV** are given in Table 2.

It is well known that a nucleophilic addition to a CC double bond is energetically difficult unless the bond is activated by a suitable substituent. In our studies, the CN groups attached to C_3 strongly activate the CC double bond and play an important role in stabilizing the resultant adduct. This is due to the resonative electron-withdrawing ability of the CN group.

The addition of **1** to the electrophilic carbon, C2, of the activated CC double bond of **2** initially forms a reactant complex at a $C_1 \ldots C_2$ distance of 5.033 Å and with a $C_3C_2C_1$ angle of 162.63°. As the nucleophilic addition progresses, the geometries of both the nucleophile and the attacked molecule are markedly distorted. The $C_3C_2C_1$ angle decreases to 104.17° (TS **III**) and then to 111.26° (adduct **III**) at C_1C_2 bond distances of 2.127 Å and 1.553 Å, respectively (Table 1). The C_2C_3 double bond is elongated on going from the reactant (1.350 Å) to the TS (1.398 Å), and finally to the adducts (1.479 Å). As the electrophilic center C_2 becomes tetrahedrally coordinated, the C_2H_5 and C_2–CH_3 bond lengths are elongated by 0.026 and 0.042 Å (adducts **III**), compared to their lengths in the reactant (1.106 and 1.472 Å). In contrast, the developing anionic center, C_3, is almost planar, with the $R_3C_3C_2C_1$ and CN-$C_3C_2C_1$ dihedral angles of 79.10° and −99.79° (TS **III**) and 65.01° and −123.98° (adduct **III**), respectively. Moreover, the C_3–CN bond is shortened by 0.017 Å (TS **III**) and 0.034 Å (adduct **III**), compared to their lengths in the reactant (1.424 Å). This may be attributed to the π-bonding interaction between the low-lying π-LUMO of the CN groups and the n-HOMO of the developing anionic center, which stabilizes the resultant carbanion.

For the addition, depicted in TS **IV**, the cyanothioacetamide anion approaches the carbon atom of one of the nitrile groups of **2** in the molecular plane forming a reactant complex with a C1C2N3 angle of 102.27° and a CN-C5C2C1 dihedral angle of 136.01° at a C1 . . . C2 distance of 5.483 Å. The geometry of the reactant complex shows very little distortion when compared to that of the constituent reagents. As the reagents get closer, within the bonding distance, the C1C2N3 angle approaches 119.22° at a C1C2 distance of 1.8002 Å (TS **IV**) and 124.63° at 1.597 Å (adduct **IV**), and the central (*sp* hybridized) carbon atom becomes trigonally coordinated (Table 2). Moreover, the CN-C5C2C1 dihedral angles become 96.27° (TS **IV**) and 102.35° (adduct **IV**).

Figure 3 shows the enthalpy profiles for additions depicted in TS **III** and **IV**. The estimated enthalpy barriers are 9.85 and 34.20 kcal/mol for **III**

TABLE 2 AM1 Optimized Geometries of Both Transition State and Adduct for the Nucleophilic Addition of Cyanothioacetamide anion to One of the Nitrile Groups of Ethylidenemalononitrile

Bond Length (*Å*)	*TS*	*Adduct*	*Bond Angle* (*deg*)	*TS*	*Adduct*	*Dihedral Angle* (*deg*)	*TS*	*Adduct*
C1C2	1.799	1.597	N3C2C1	119.22	124.63	H4C1C2N3	191.62	193.78
C2N3	1.205	1.228	H4C1C2	105.97	109.48	C5C2C1N3	180.52	180.38
C1H4	1.113	1.125	C5C2C1	101.31	106.28	C6C5C2C1	273.19	278.69
C2C5	1.470	1.500	C6C5C2	124.17	124.59	CNC5C2C1	96.27	102.35
C5C6	1.347	1.345	H7C6C5	119.91	120.24	H7C6C5C2	182.47	183.67
C6H7	1.103	1.103	CNC5C2	115.63	115.19	$CH_3C6C5C2$	2.77	3.17
C1R1	1.427	1.445	CH_3C6C5	124.09	124.59	R1C1C2N3	73.18	74.60
C1R2	1.466	1.505	R1C1C2	103.68	108.78	R2C1C2N3	310.41	312.26
CNC5	1.426	1.426	R2C1C2	104.90	108.72			
CH_3C6	1.473	1.474						

and **IV**, respectively. Moreover, addition **III** is exothermic by 19.19 kcal/mol, which is consistent with the lowering in its enthalpy barrier, while addition **IV** is endothermic by 20.23 kcal/mol. Therefore, it is obvious that the nucleophilic addition to an activated CC double bond prevails energetically over the addition to a nitrile group. This may be explained within the framework of the frontier orbital (FMO) theory [27]. The most important factors that control the reactivity of a nucleophilic addition are the energy gap, $\Delta\varepsilon$, between the interacting FMOs (HOMO of the nucleophile and LUMO of the electrophile) and the extent of overlap. As shown in Figure 4, the LUMO of **2** has the largest coefficient at the CC double bond (74%), while only 11.1% of the LUMO is possessed by the C≡N group. Moreover, it has a $\Delta\varepsilon$ value of 2.63 eV with the *n*-HOMO of the cyanothioacetamide anion. This means that the addition to the CC double bond is much more stabilized by the large extent of overlap and the relatively small $\Delta\varepsilon$. On the other hand, the LUMO of **2**, which has the largest coefficient at the C≡N group, is 4.95 eV higher than that at the *n*-HOMO. This explains why the addition to the nitrile group is endothermic and has a relatively high enthalpy barrier.

The available experimental results [19] confirm that the thiopyran **4** is the product that is formed by the addition of **1** to the C=C double bond of **2**, and its structure was established based on its ^{13}C NMR spectrum. The spectrum indicates that the product has a plane of symmetry, as only five carbon signals appear in addition to the fact that C2, C3, C5, and C6 are identical and the two CN groups are magnetically identical. If the product had been that formed by the addition to the nitrile group, to give **7** (Scheme 1b), eight signals for magnetically different carbons would have been observed. ^{1}H NMR spectra support the proposed structure, **4**, since they reveal a doublet for the CH_3 group at $\delta = 1.18$ and a multiplet at $\delta = 3.07$ of the thiopyran H-4 as well as a four-proton D_2O exchangeable signal at $\delta = 6.75$ for the NH_2 protons. Therefore, the theoretical results that have been discussed above not only clarify the reaction mechanism of the addition of an MN to α,β-unsaturated nitriles, from a theoretical point of view, but also strongly support the experimental findings as well.

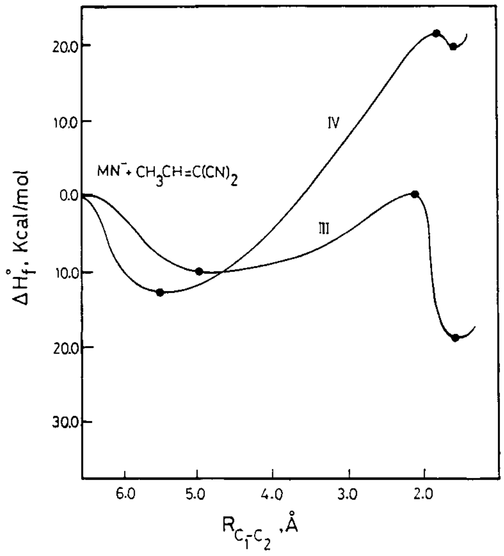


FIGURE 3 Enthalpy profiles for the additions of $H_2NCS(CN)CH^-$ anion to the α,β-unsaturated linkage (**III**) and to the nitrile group (**IV**) of $CH_3CH=C(CN)_2$.

Additions of MNs to Ethylidenecyanothioacetamide

In mixtures of ylidenecyanothioacetamides, cyanothioacetamide, and MNs, the nucleophilic reactivity

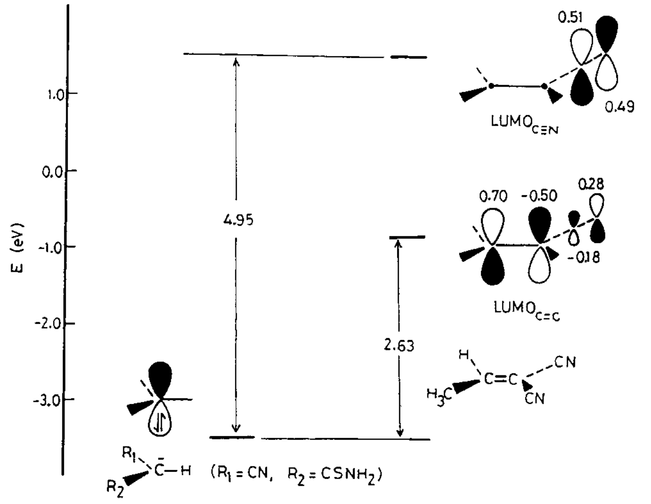


FIGURE 4 HOMO–LUMO energy gaps between the *n*-HOMO of cyanothioacetamide anion and the LUMOs of ethylidenemalononitrile. The atomic orbital coefficients are given for the LUMOs.

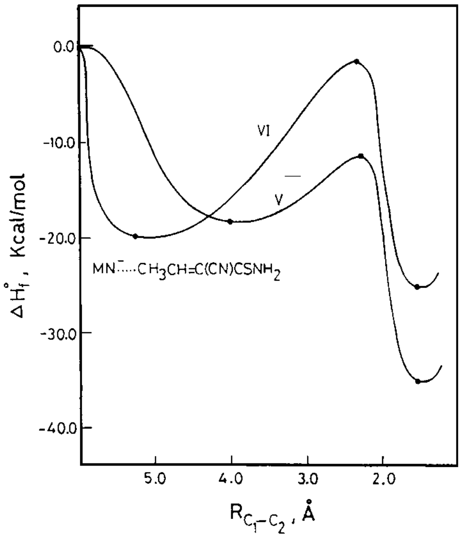


FIGURE 5 Enthalpy profiles for additions of $(CCN)_2CH^-$ (**III**) and $NH_2CS(CN)CH^-$ anions to $CH_3CH=C(CN)CSNH_2$.

of each MN toward the addition to the *α,β*-unsaturated linkage plays the most important role in the prevailing of the addition of one MN over another. Both electronic and steric factors control the reactivity of a nucleophile. It is important, therefore, to estimate theoretically the relative reactivities of a series of MNs and to clarify the experimental point of debate in this respect.

The additions of malononitrile **V** and cyanothioacetamide **VI** to the activated CC double bond of ethylidenecyanothioacetamide initially form reactant complexes with a C3C2C1 angle of 92.65° at 3.998 Å and 104.92° at 5.250 Å, respectively. As the reaction progresses, the C3C2C1 angle increases to 107.79° (TS **V**) and then to 110.66° (adduct **V**) at C1C2 bond distance of 2.266 Å and 1.554 Å, respectively (Table 1). The C2C3 bond is elongated on going from reactant (1.350 Å) to TSs (1.385 Å, 1.378 Å), and finally to adducts (1.484 Å, 1.486 Å) for additions **V** and **VI**, respectively. This may be attributed to the conversion of the electrophilic center C2 (sp^2 hybridized) atom to a tetrahedrally coordinated one. On the other hand, the developing anionic center, C3, becomes planar with CN-C3C2C1 and R3C3C2C1 dihedral angles of −101.14° and 79.97° (TS **V**) and −102.48° and 78.87° (TS **VI**), respectively. Moreover, the C3–CN bond becomes shorter by 0.01 Å (TS **V**) and 0.02 Å (adduct **V**), compared to its length in the reactant (1.426 Å). This may be explained in terms of the *π*-interaction between the low-lying *π*-LUMO of the nitrile group and the *n*-HOMO on the anionic center, which stabilizes the resultant carbanion.

Figure 5 shows enthalpy profiles for additions **V** and **VI**. The reactant complexes are 18.23 kcal/mol (**V**) and 20.19 kcal/mol lower in energy than those of their reactants. Enthalpy barriers of 6.86 kcal/mol (**V**) and 18.67 kcal/mol (**VI**) must be passed by the reactant complexes to complete the reactions. The 11.81 kcal/mol difference between the two barriers confirms that malononitrile is more reactive than cyanothioacetamide in adding to an *α,β*-unsaturated bond. Both additions are exothermic by 34.96 kcal/mol (**V**) and 25.06 kcal/mol (**VI**).

According to the FMO theory [27], only the frontier orbitals (HOMO of the donor and LUMO of the acceptor) are important in a charge transfer reaction between a donor and an acceptor. Those orbitals are the key factors in controlling the stability of the transition state and hence the reactivity of the donor–acceptor interaction. The stabilization gained by electron transfer (ΔE_{ct}) from a filled orbital (i) of a donor to an empty orbital (j) of an acceptor can be approximated by the following equation:

$$\Delta E_{ct} = (H_{ij})^2/\Delta\varepsilon \qquad (1)$$

where $\Delta\varepsilon$ is the energy gap ($E_j - E_i$) and H_{ij} is the interaction matrix element, which is almost linear with the overlap (S_{ij}) between the two orbitals [27]. Therefore, according to Equation 1, the HOMO–LUMO energy gap, $\Delta\varepsilon$, provides a good measure for the nucleophilic reactivity. In other words, as $\Delta\varepsilon$ decreases, the electron-transfer stabilization, ΔE_{ct}, increases, and that leads to a lowering in the enthalpy barrier and, consequently, to an increase in the reactivity.

Figure 6 shows the FMO energies of a number

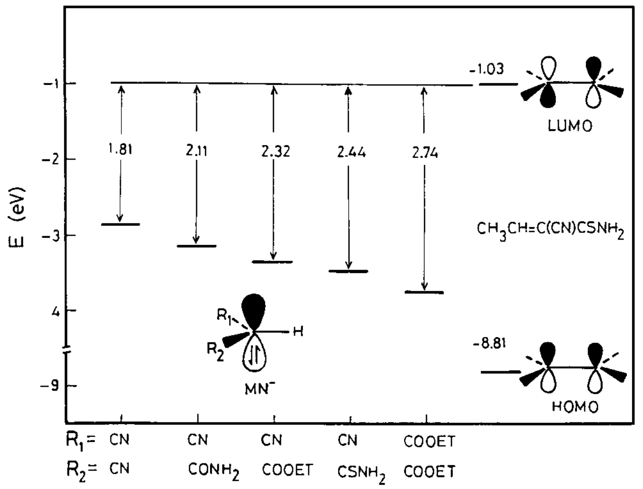


FIGURE 6 HOMO–LUMO energy gaps between *n*-HOMOs of some active methylene nitriles and the LUMO of $CH_3CH=C(CN)CSNH_2$.

of active methylene anions (donors) and ethylidenecyanothioacetamide (acceptor) and the corresponding HOMO–LUMO energy gaps. An important point to notice in Figure 6 is the substituent effect on $\Delta\varepsilon$ and consequently on the reactivity of each nucleophile. The $\Delta\varepsilon$ value is the smallest for $R_1 = R_2 = CN$ (1.81 eV) and the largest for $R_1 = R_2 = COOEt$ (2.74 eV). It is obvious that the nucleophilic reactivity increases in the direction of increasing of the electron-withdrawing ability of R_1 and/or R_2 and vice versa. This trend in the nucleophilic reactivity supports the experimental results in that cyanothioacetamide does not add to its ylidene in the presence of more reactive MNs (e.g., malononitrile, cyanoacetamide, or ethyl cyanoacetate) as was erroneously claimed [18]. As additional confirmation, no H_2S gas has been detected during the course of the reaction.

CONCLUSIONS

We conclude that (1) the nucleophilic attack reactivity of an active methylene nitrile (MN) toward either a carbonyl compound or an α,β-unsaturated nitrile may best be discussed in terms of the HOMO–LUMO two-electron interaction. In such a case, the HOMO–LUMO energy gap can be used as a good measure for such reactivity. (2) For all studied additions, reactant complexes are formed and detected on the enthalpy surfaces as minima that are lower in energy than those of the corresponding reactants. (3) The nucleophilic addition of an MN to acetaldehyde is endothermic and proceeds via a single-step mechanism with a late transition state of a productlike geometry. On the other hand, the addition to an α,β-unsaturated nitrile may conceivably proceed via two pathways: addition to the α,β-unsaturated linkage, which is exothermic, and addition to the nitrile group, which is endothermic. Both additions have late transition states of a productlike geometry. The latter has a relatively high enthalpy barrier when compared with the addition to the CC double bond, which is in agreement with the experimental findings. (4) The prevalence of one MN over another in the addition to either $C=O$ or $C=C$ double bonds strongly depends on their nucleophilic reactivities. Based on the present calculations, it has been confirmed that cyanothioacetamide does not add to its ylidene in the presence of more reactive methylene nitriles in the mixture (e.g., malononitrile, cyanoacetamide, or ethyl cyanoacetate), which is in accord with the experimental results.

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