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Why Nature Eschews the Concerted [2 + 2 + 2] Cycloaddition of a Nonconjugated Cyanodiyne. Computational Study of a Pyridine Synthesis Involving an Ene–Diels–Alder–Bimolecular Hydrogen-Transfer Mechanism

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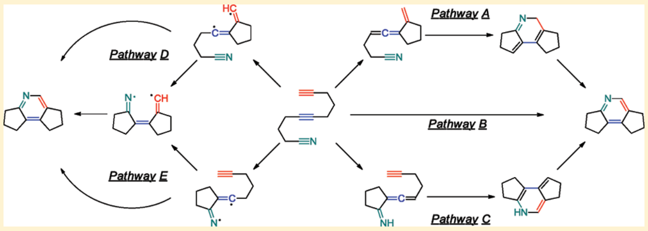
S Supporting Information

ABSTRACT: An intramolecular formal metal-free intramolecular [2 + 2 + 2] cycloaddition for the formation of pyridines has been investigated with M06-2X and B3LYP density functional methods, and compared to the experimentally established three-step mechanism that involves ene reaction–Diels–Alder reaction–hydrogen transfer. The ene reaction of two alkynes is the rate-determining step. This is considerably easier than other possible mechanisms, such as those involving an ene reaction of an alkyne with a nitrile, a one-step [2 + 2 + 2] cycloaddition, or a 1,4-diradical mechanism. The relative facilities of these processes are analyzed with the distortion-interaction model. A bimolecular hydrogen-transfer mechanism involving a radical-pair intermediate is proposed rather than a concerted intramolecular 1,5-hydrogen shift for the last step in the mechanism.



INTRODUCTION

The pyridine ring is a ubiquitous heterocycle that occurs in the structure of many natural products and pharmaceutical compounds.[1] A variety of synthetic routes to pyridines have been developed,[2] many of which involve transition-metal-catalyzed reactions such as [2 + 2 + 2] cycloadditions.[3−8] Recently, Sakai and Danheiser reported the first example of the formation of pyridines via uncatalyzed formal [2 + 2 + 2] cycloadditions. Thermolysis of cyanodiynes of general type **1** at 140−200 °C in toluene was found to produce substituted pyridines of general type **6**.[9] This work represents the first report of the uncatalyzed intramolecular construction of pyridines from cyanodiynes.

Five possible mechanistic pathways were discussed to account for the course of the formal [2 + 2 + 2] cycloaddition (Scheme 1). In pathway B, thermal [2 + 2 + 2] cycloaddition directly generates pyridine **6c** via a one-setp process. Alternative pathways A and C each involve stepwise mechanisms. Pathway A begins with a propargylic ene reaction,[10] followed by an intramolecular Diels–Alder reaction involving the vinylallene and the cyano group. After a 1,5-hydrogen shift, the substituted pyridine **6c** is generated. In this paper we describe how this unlikely 1,5-shift could occur. Alternative pathway C begins with an intramolecular propargylic ene reaction in which the cyano group serves as the enophile.[11] After hetero-Diels–Alder reaction[12] and tautomerization (via 1,5-hydrogen shift or via a series of proton transfers), the same pyridine product **6c** is formed. Finally, diradical pathways can also be envisioned proceeding via diradical intermediates of type **dr1** or **dr2**. The alkyne or cyano group reacting with the radical carbon forms diradical intermediate **dr3**. The product **6c** generates by the coupling of **dr3**. The product **6c** also can be generated by the directed intramolecular cycloaddition from **dr1** or **dr2**. In the case of related "all-carbon" formal [2 + 2 + 2] cycloadditions involving triynes, diradical mechanisms have been proposed,[13] but recently evidence was reported supporting the operation of a mechanism analogous to pathway A for these reactions.[10f] For the case of cyano diyne **1c**, experimental studies consistent with the operation of pathway A have also been reported.[9]

During the course of the study reported herein, a theoretical investigation of the mechanism of the all-carbon intramolecular propargylic ene/Diels–Alder reaction was published by Li and Xu.[14] They calculated the cascade pathway involving the 1,6,11-triyne analogous to **1c** at B3LYP level; the reactions examined include an ene reaction, Diels–Alder reaction, and hydrogen shift analogous to those depicted in pathways A and C in Scheme 1. In their Supporting Information, these workers also disclosed calculations on the cyano diyne reaction reported by Sakai and Danheiser. However, the system they examined involved an oxygen atom in the tether linking the two alkyne units, a structural feature that significantly lowers the barrier for intramolecular processes. In this paper, we present detailed calculations on the cyano diyne reaction for a substrate with all-carbon tethers, exploring why the direct [2 + 2 + 2]

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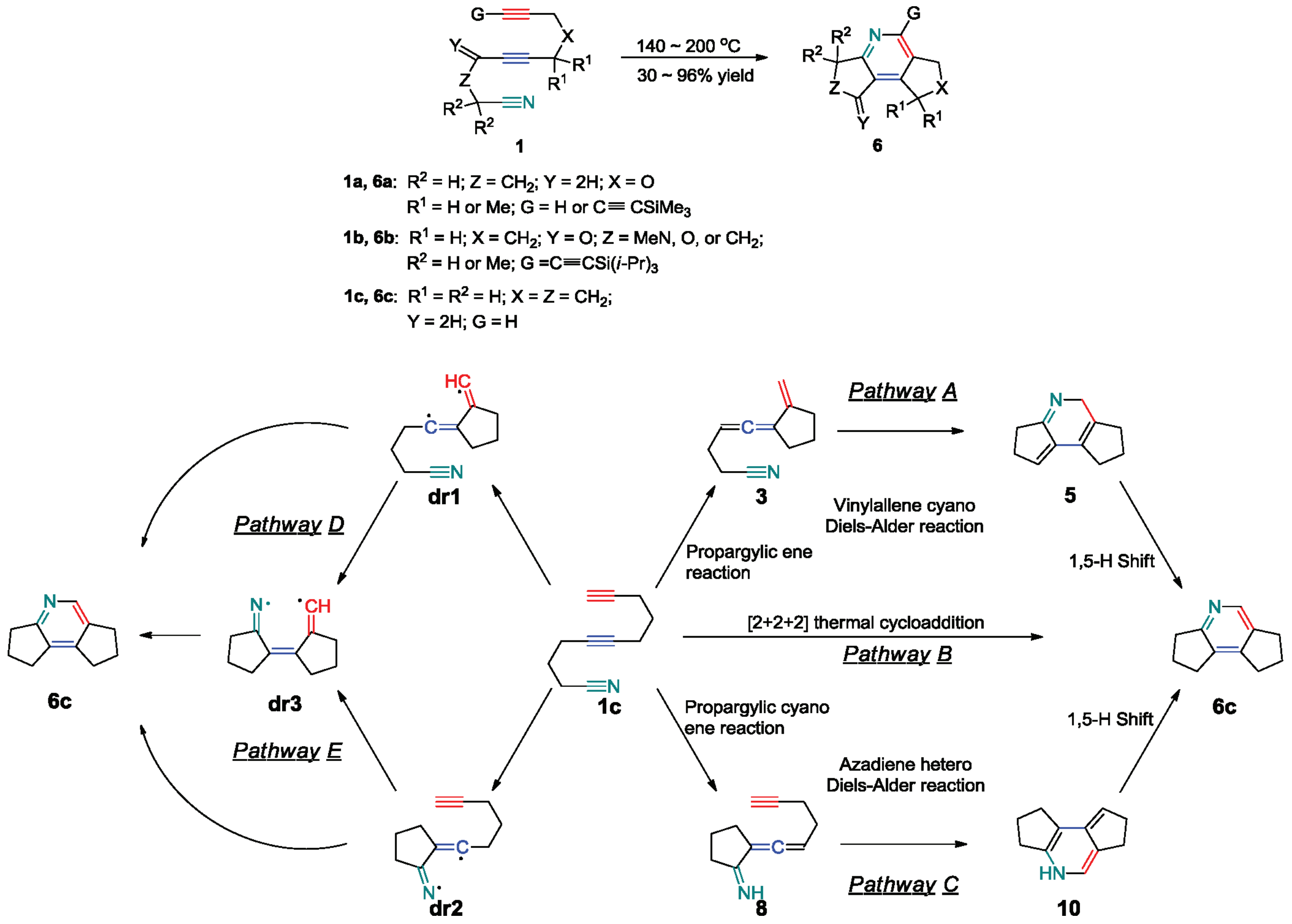
Scheme 1. Five Alternative Pathways for the [2 + 2 + 2] Cycloaddition



cycloaddition does not occur, and providing calculations of the barriers for pathways A, B, and C. We also provide energetics using MO6-2X, a method known to give better energetics for such reactions.

■ COMPUTATIONAL METHOD

The B3LYP/6-31G* method[15] was employed to calculate the geometries and energies. M06-2X/6-311+G(d) calculations[16] were also employed, since this method has been found to give better reaction energies.[17] The MO6-2X values are discussed in the text, but the two methods agree on the mechanism and both lead to single explanation of why the multistep mechanism is more favorable than the one-step process. All calculations were performed with Gaussian 09.[18]

■ RESULTS AND DISCUSSION

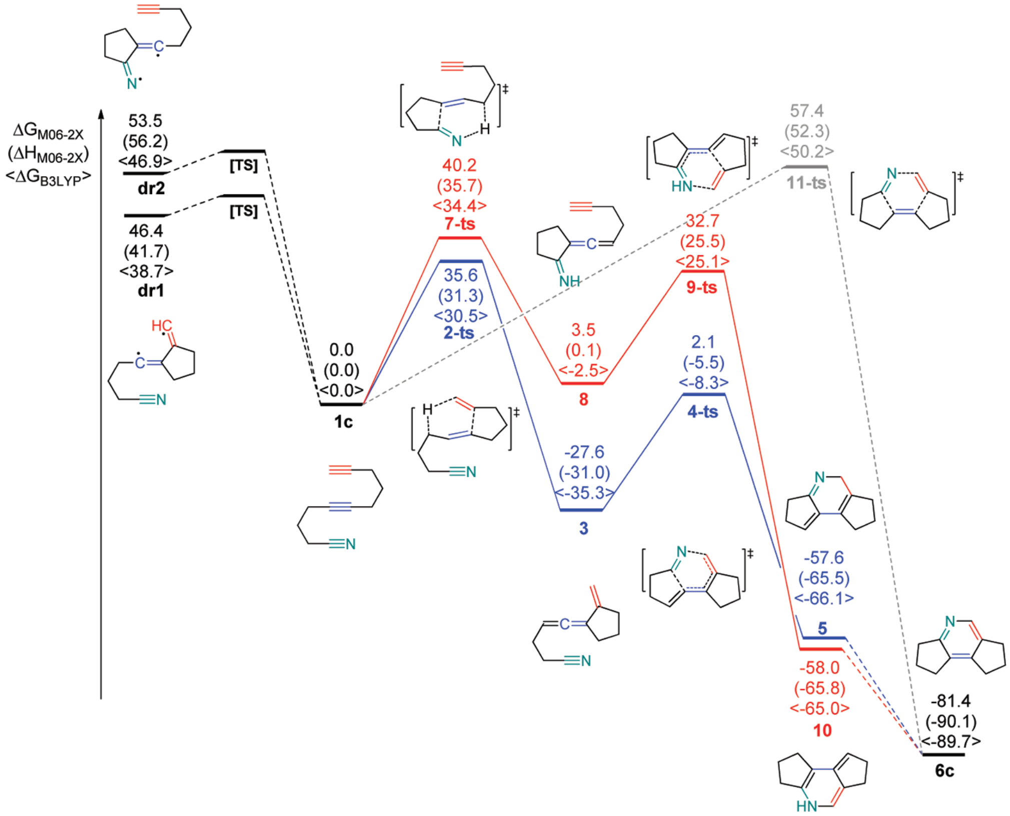
Scheme 2 gives the relative free energies and enthalpies for the five proposed pathways for the reaction of the intramolecular system. Beginning with cyano diyne **1c**, in pathway A the intramolecular Alder ene reaction involving the two alkynes occurs via transition state **2-ts** with an activation free energy of 35.6 kcal/mol. The generation of allene **3** is exergonic by 27.6 kcal/mol. The subsequent intramolecular Diels—Alder reaction of the vinylallene with the cyano group as dienophile occurs via transition state **4-ts** with a 29.7 kcal/mol barrier to form the cross-conjugated dienyl imine intermediate **5**. A 1,5-hydrogen shift is needed to form the final pyridine product **6c**.

The final product **6c** is 81.4 kcal/mol lower in energy than the reactant. In this pathway, the rate-determining step is the initial Alder ene reaction, and the activation free energy of this pathway is 35.6 kcal/mol. The relative free energies calculated by the B3LYP method are 5—10 kcal/mol lower than those by the M06-2X method. The differences between the free energies and the enthalpies in Scheme 2 reflect the relatively minor influence of entropies on these intramolecular processes. The $-T\Delta S$ quantities are 4—7 kcal/mol for the various transition states and contribute to all the activation free energies in a similar way.

Pathway C involves the intramolecular Alder ene reaction involving the central alkyne and the cyano group. The free energy of transition state **7-ts** is 4.6 kcal/mol higher than **2-ts**. The formation of allenylimine **8** is endergonic. The activation free energy for the hetero-Diels—Alder reaction leading to **10** is 29.2 kcal/mol via transition state **9-ts**. A 1,5-hydrogen atom transfer in intermediate **10** gives the final pyridine product **6c**. The initial ene reaction is the rate-determining step in pathway C.

Pathway B involves the one-step [2 + 2 + 2] cycloaddition. While an aromatic product is formed in this process, and the reaction is exergonic by a huge 90 kcal/mol, this pathway has an extremely high barrier of 57.4 kcal/mol via transition state **11-ts**. Comparing the three pathways, pathway A consequently is most favorable. As has been shown experimentally,[9a] if the initial propargylic ene step is blocked (e.g., as in compound **1b**), pathway C is then followed. The one-step [2 + 2 + 2]

Scheme 2. M06-2X/6-311+G(d) Free Energies Profile for the Five Alternative Pathways for the [2 + 2 + 2] Cycloaddition[a]



[a]The values in parentheses are the enthalpies relative to **1c**. The values in brackets are the relative free energies calculated by B3LYP/6-31G(d) method.

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cycloaddition is highly unfavorable, as has been observed experimentally.

The diradical pathways were also computed by the unrestricted M06-2X and B3LYP methods. As shown in Scheme 2, two pathways proceeding via singlet 1,4-diradical intermediates can be envisioned to account for the pyridine synthesis. The diradical **dr1** is formed from intramolecular coupling of the two alkyne units. The relative free energy of **dr1** is 46.4 kcal/mol, which is about 10 kcal/mol higher than the transition state of the Alder ene reaction (**2-ts**) involved in pathway A. Another diradical **dr2** is formed by the coupling of the central alkyne and cyano groups; this diradical is 7.1 kcal/mol higher in energy than **dr1**. The computed $<S^2>$ of **dr1** and **dr2** are 1.06 and 1.04, respectively, by the UM06-2X method. The geometries of **dr1** and **dr2** are shown in Scheme 3. The computed atomic spin densities show the singlet 1,4-diradical characters. The transition states for the generation of **dr1** and **dr2** are not found by these DFT methods. We also tried to localize the singlet intermediate **dr3**, but the product **6c** is formed directly.

The geometries of all the ene reaction and cycloaddition transition structures are shown in Scheme 3. The ene reactions and cycloadditions have similar characteristics, with forming C−C and C−N bond lengths of 1.9−2.4 Å and forming and breaking C−H bond lengths of 1.3−1.5 Å. In the transition structure **11-ts** for the concerted [2 + 2 + 2] cycloaddiion, all partial forming bond lengths are 2.14−2.34 Å, which is similar to our previous theoretical calculation of the concerted [2 + 2 + 2] cycloaddition transition structure of alkenes (2.22 Å) and alkynes (2.21 Å).[19]

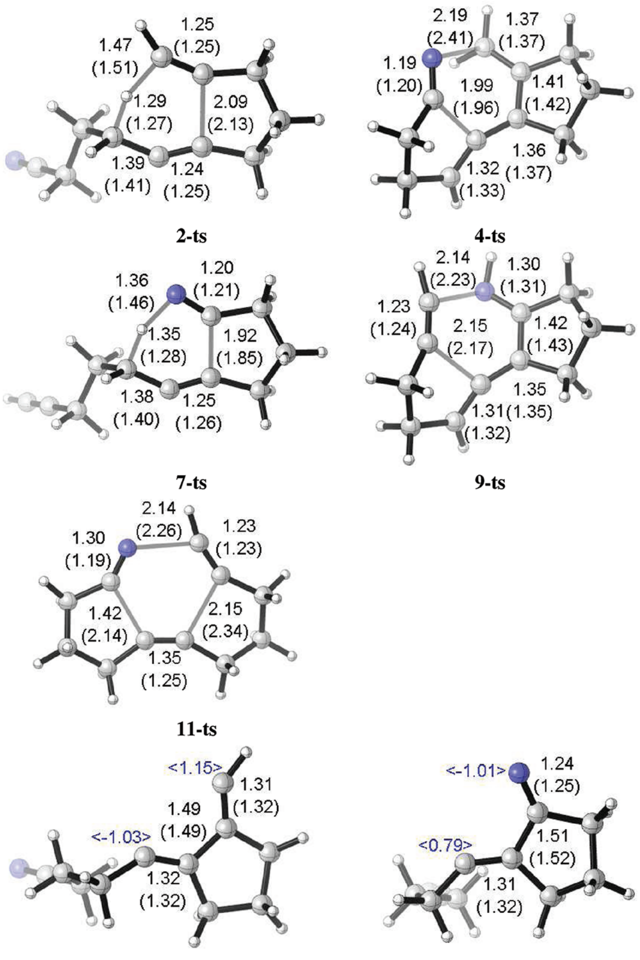
The intramolecular Alder ene reaction involving the two alkyne groups in pathway A is 31.1 kcal/mol more exothermic than that between the central alkyne and cyano groups in pathway B. The lower barrier of pathway A parallels this difference. The enthalpy of hydrogenation for the C≡N triple bond is 35.4 kcal/mol less favorable than of the C≡C triple bond (Figure 1). The relative weakness of the alkyne π bond relative to the nitrile π bond explains why the rate-determining step in pathway A is lower in energy as compared to that in pathway C.

Intermolecular propargylic ene reactions and the direct [2 + 2 + 2] cycloaddition have been studied to understand the difference in reactivities between these two processes. The difference between the activation energies can be explained by the distortion-interaction theory.[20] This involves calculation of the energy to distort reactants into their transition state geometries, and then their interaction energies: $\Delta E^{\ddagger} = E^{\ddagger}_{\text{dist}} + E^{\ddagger}_{\text{int}}$. We have computed the energetics of the intermolecular ene reactions and the transition state, activation energies, distortion, and interaction energies are shown in Scheme 4.

The activation energy of the butyne−propyne ene reaction is 2.3 kcal/mol lower than that of the butyne−acetonitrile reaction. It is more difficult to distort the nitrile than propyne, and consequently the transition state is later. The later transition state causes the 2-butyne to be more distorted and to have a high distortion energy.

Butyne, propyne, and acetonitrile were also examined to model the direct intermolecular [2 + 2 + 2] cycloaddition. The activation energy was found to be 60.7 kcal/mol via **14-ts** which is 21.6 kcal/mol higher than **12-ts**. The distortion-interaction

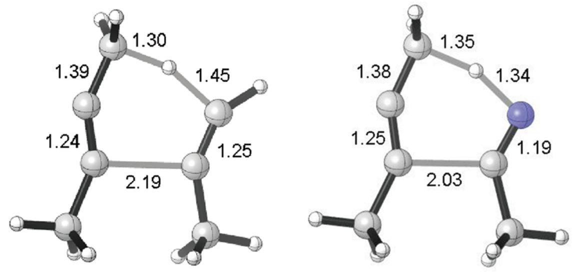
Scheme 3. M06-2X Geometries of the Transition Structures and Intermediates of the Proposed Pathways[a]



2-ts **4-ts** **7-ts** **9-ts** **11-ts** **dr1** **dr2**

[a] The values in parentheses are the B3LYP bond lengths. The values in brackets are the computed atomic spin densities.

Scheme 4. Transition Structures of the Intermolecular Propargylic Ene Reactions[a]



12-ts

$\Delta H^{\ddagger} = 36.7$
$\Delta E^{\ddagger} = 39.1$
$E^{\ddagger}_{dist}(\text{butyne}) = 32.5$
$E^{\ddagger}_{dist}(\text{propyne}) = 22.2$
$E^{\ddagger}_{int} = -15.6$

13-ts

$\Delta H^{\ddagger} = 39.5$
$\Delta E^{\ddagger} = 41.4$
$E^{\ddagger}_{dist}(\text{butyne}) = 41.0$
$E^{\ddagger}_{dist}(\text{acetonitrile}) = 17.7$
$E^{\ddagger}_{int} = -17.3$

[a] The values are the activation enthalpies, activation energies, the distortion energies of each component, and interaction energies. The geometries and energies are computed by the M06-2X/6-311+G(d) method; energies are given in kcal/mol.

$$HC{\equiv}CH + H_2 \xrightarrow{\Delta H = -47.1 \text{ kcal/mol}} H_2C{=}CH_2$$

$$HC{\equiv}N + H_2 \xrightarrow{\Delta H = -11.7 \text{ kcal/mol}} H_2C{=}NH$$

Figure 1. Calculated hydrogenation energies of acetylene and hydrogen cyanide.

analysis of **14-ts** is shown in Scheme 5. The distortion energies of butyne, propyne, and acetonitrile are 32.0, 10.3, and 13.9 kcal/mol, respectively. The overall distortion energy of **14-ts** is 56.2 kcal/mol, which is slightly higher than the distortion energy of **12-ts** (54.7 kcal/mol). The transition structure can be separated into individual interactions. The interaction energy of butyne and propyne is destabilizing, at 13.2 kcal/mol. This is mainly due to closed-shell repulsion that contrasts sharply with the 15.6 kcal/mol stabilizing interaction in **12-ts**, the result of the favorable cyclic interaction. The interaction energy of **15** and distorted acetonitrile is −8.7 kcal/mol, and the overall interaction energy is 4.5 kcal/mol. The high repulsive interaction energy of the two alkynes leads to the relatively high activation energy of **14-ts**. In the previous theoretical calculation for the [2 + 2 + 2] cycloaddition of three acetylenes, the MINDO/3 calculated activation energy is 72.7 kcal/mol,[19c] which is similar to that for the cycloaddition of two alkynes and one acetonitrile.

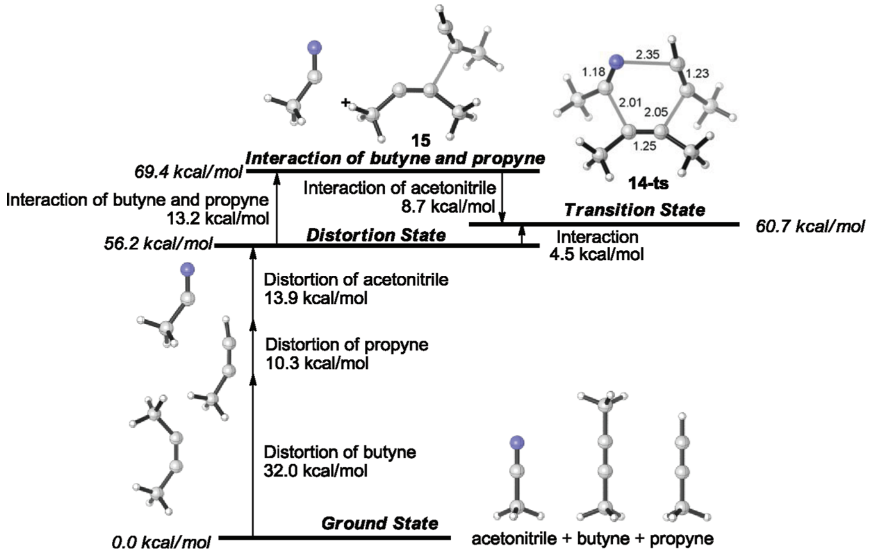
The aromatic pyridine product **6c** is formed from complex **5** via a formal 1,5-hydrogen shift. The mechanism of this 1,5-hydrogen shift is unclear. As shown in Scheme 6, the activation free energy of a concerted 1,5-hydrogen migration is computed to be 80.2 kcal/mol. In transition state **16-ts**, the bond lengths of the forming C1−H bond and the broken C4−H bond are 1.61 and 1.69 Å, respectively. The strain of the skeleton is highly unfavorable for this one-step transition state.

An alternative pathway involves an intermolecular 1,5-hydrogen shift mechanism. Such a mechanism was recently shown to be involved in the formal 1,5-hydrogen shift involved in the conversion of 6-methylpentacene and 6-methylene-6,13-dihydropentacene.[21] As shown in Scheme 6, one hydrogen transfers from C1 of one molecule **5** to C4 of another molecule **5** and forms two radical intermediates **17** and **18**. Hydrogen transfers from C4 of radical **18** to C1 of **17** then generates two molecules of the pyridine product. The free energy of **17** plus **18** is only 7.0 kcal/mol higher than complex **5**. The geometries of **17** and **18** are shown in Scheme 6. In radical **17**, the spin density is localized on C1, and the conjugation with pyridine stabilizes the radical. In radical **18**, the C2, C5, and N atoms share the spin density. Conjugation stabilizes this radical as well.[22]

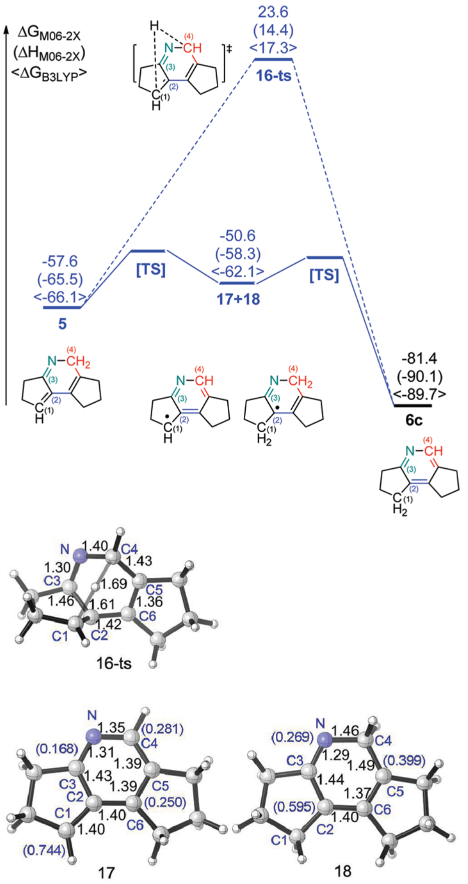
■ CONCLUSION

The intramolecular Alder ene reaction between two alkynes groups, followed by an intramolecular Diels−Alder reaction between the resultant vinylallene and a cyano group, is the most favorable pathway in the formal [2 + 2 + 2] pyridine synthesis. The stability and difficulty of distortion of the cyano group, and the high distortion energy of the [2 + 2 + 2] transition state, make ene reaction of the nitrile or the direct [2 + 2 + 2] cycloaddition more difficult than the mechanism followed (pathway A). The 1,4-diradical mechanism is also unfavorable. We propose a bimolecular radical process for the

Scheme 5. Distortion−interaction Energy Analysis of the [2 + 2 + 2] Cycloaddition Transition State, 14-ts



Scheme 6. M06-2X/6-311+G(d) Free Energy Profile of Concerted and Bimolecular Mechanisms of the 1,5-Hydrogen Shift Step[a]



[a] The values in parentheses are the enthalpies relative to **1c**. The values in brackets are the relative free energies calculated by the B3LYP/6-31G(d) method. The values in parentheses of geometry information are the calculated spin densities.

final 1,5-hydrogen shift, which is more favorable than the intramolecular concerted proton transfer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates and energies of all reported structures and full authorship of Gaussian 09. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Another possibility that the requisite formal 1,5-hydrogen shift occurs by an acid-catalyzed pathway due to adventitious acid cannot be discounted.