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Computational Investigation of Rearrangements in Huisgen Cycloadducts of Azolium *N*-Dicyanomethanide 1,3-Dipoles with Alkynes: A Mechanistic Panoply

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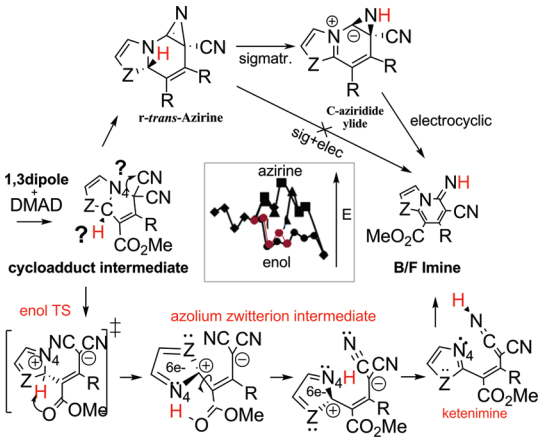

The reaction surfaces leading to rearrangements and ring expansions of azapentalene cycloadducts of imidazolo- and triazolodicyanomethanide 1,3-dipoles with alkynes are studied with the B3LYP DFT method using the 6-31G(d) and 6-311+G(2d,p) basis sets. The surprisingly complex surface involves (1) consecutive but not combined pericyclic steps, a coarctate TS, and pseudopericyclic mechanisms, (2) anchimerically assisted H-atom transfer competing effectively with concerted symmetry-allowed sigmatropic steps, and (3) azolium methanide zwitterions and ketenimines as key intermediates. The azolium methanide is identified as the intermediate detected previously in a variable-temperature NMR experiment that converted the unstable cycloadduct to product imine.

Introduction

As specific needs arise, "click chemistry"[1,2] reactions will inevitably depart from the goal of simple reactions to more complicated adaptations.[3,4] Other reactant azides or 1,3-dipoles[5] will be sought, opening up possibilities for rearrangement. Encountering unexpected rearrangements subsequent to cycloadditions, often involving multistep cascades,[6−8] is a significant feature of the synthetic versatility of the original Huisgen 1,3-dipolar cycloaddition reaction. An early example is the synthesis of diazapentalene isomers that was used to confirm calculations of aromaticity in 10π electron systems. Boekelheide and Fedoruk[9] observed an interesting variant in the synthesis of 1,3-*a* diazapentalenes by way of 1,3-dipoles and alkynes. Instead of the expected diazapentalenes (Scheme 1a), the dicyanomethanide dipole gave a rearrangement and ring expansion to an imidazo[2,3-*a*]pyridinimine (**B/F Imine**) (Scheme 1b).

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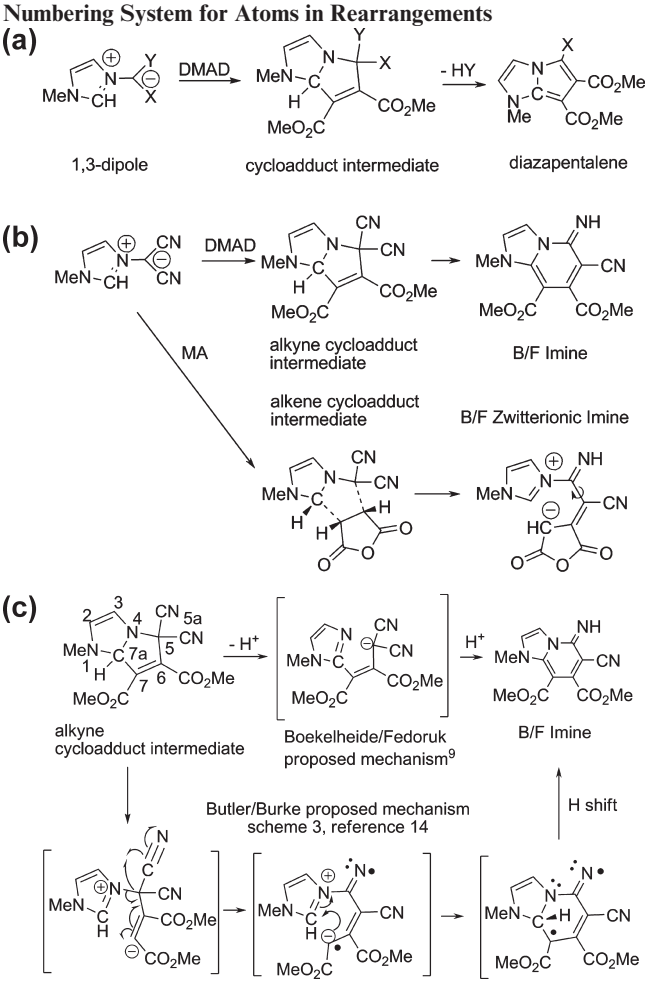
The authors proposed a mechanism (Scheme 1c) for the expansion that involved anion formation by loss of the bridgehead C(7a) proton, cleavage of the N(4)−C(5) bond, and attack by the N-(4) anion on the nitrile carbon (a conjugated E1cb-type process followed by a Baldwin 6-*exo*-*dig* ring closure). This Huisgen 1,3-dipolar cycloaddition reaction can proceed under the mild conditions required of a "click reaction", yet it results in ring-expansion rearrangements with nitrile substituents.

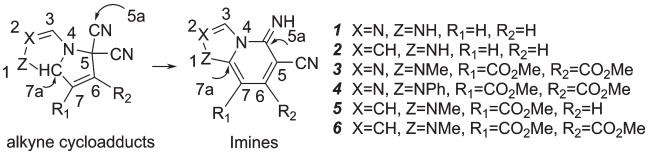
Given our interest in azinium dicyanomethanides,[10−13] we revisited the Boekelheide−Fedoruk (B/F) ring expansion and suggested another mechanism[14] based on cycloaddition results of imidazolium dicyanomethanide with maleic anhydride (**MA**). This leads to a zwitterionic product resembling the classic two-step intermediate (Scheme 1b), but interestingly, with the B/F rearranged imine product. We suggested that the rupture of the C7−C7a bond in the dimethylacetylenedicarboxylate (**DMAD**) cycloadduct would be analogous to the maleic anhydride zwitterionic intermediate[14] generating an ylide intermediate, possessing resonance stabilized termini (Scheme 1c). It was calculated that imidazolium dipoles plus **MA** give highly nonsynchronous TS structures and that the two new bonds formed in the cycloadducts are unusually long, between 1.60 and 1.63 Å (Scheme 1b), due to either the interaction of the **MA** carbonyl groups with the dipole NMe and CN groups in the *endo* configuration of the 5,5,5 tricyclic anhydride product[14] or some reflection of the reaction pathway.[15−18] Thiazolium dicyanomethanides react with alkenes to give stable saturated cycloadducts[19] without opening to the zwitterion, while with DMAD[9] they give the B/F expansion to the imine. The reaction was extended to 1,2,4-triazoles by Elguero et al.,[20] and to date, the only alkyne cycloadduct intermediate that was isolated before ring expansion occurs is the thermally unstable species from the Huisgen cycloaddition of *N*-phenyl-1,2,4-triazolium substrate with **DMAD** (series ***4***, Scheme 2).

The present research is a theoretical comparison of bond breaking at C7−C7a and N4−C5 in the cycloadducts in order to find possible pathways to the imines. Six reaction series are considered (Scheme 2). Although the choice of mechanism for ring expansion looks at first to be a simple proton transfer and bond rearrangement, when carefully dissected it reveals a rich panoply of nearly *20* pericyclic and anchimeric reaction mechanisms. The energetics from the *endo* additions[10,13] of the dipole + dipolarophile partners to cycloadducts are also reported. We reported[14] on transient NMR signals when the series ***4*** cycloadduct[20] was heated, giving the product B/F imine. We report here the calculated NMR chemical shifts for various intermediates found for series ***4***.

SCHEME 1. (a) Diazapentalenes Found with 1,3-Dipolar Cycloaddition of Imidazolium Methanides with Alkynes Followed by Elimination, (b) Ring Expansion to Imine Found with Dicyano 1,3-Dipoles and Alkynes and Ring-Opening to Zwitterionic Imine with Maleic Anhydride (MA), and (c) Mechanisms for Ring Expansion and Rearrangement of the Alkyne Cycloadduct and Numbering System for Atoms in Rearrangements



SCHEME 2. Six Reaction Series Numbered According to Substitutions (Bold, Italics) and Numbering System for Atoms in Rearrangements



Computational Procedure

This procedure includes the use of the Gaussian03 and GaussView3[21] suite of programs, choice of unrestricted (where appropriate) B3LYP[22,23] method, 6-31G(d) basis set, geometry optimization using analytical gradients, visual inspection of the

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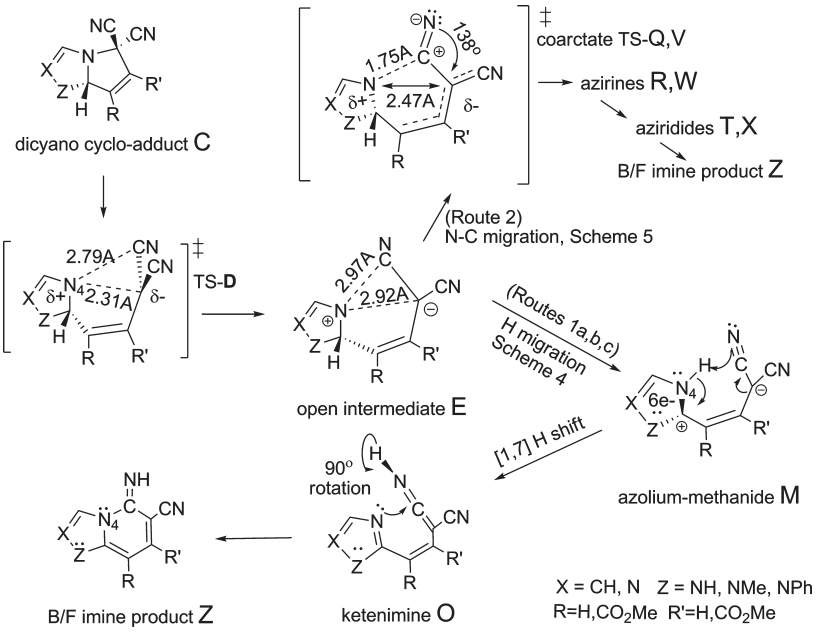
SCHEME 3. Two Reaction Pathways for Rearrangement of the Alkynyl Cycloadduct C to the B/F Imine Product Z through an "Open Intermediate" E Formed by Cleavage at the N4−C5 Bond: (Route 1) Involving Three Intramolecular Shifts of the C(7a) H Atom (Routes 1a,b,c) Followed by Bond Formation at N4−C(5a) (Detailed in Scheme 4) or (Route 2) First Bond Formation at N4−C(5a) to Azirines and then Shifts of the C(7a) H Atom to Aziridides and Rearrangement to Product (cf. Scheme 5)



single imaginary frequency in the TS for expected bond formation/breaking transition moments, and at each step of the pathway the use of the same corresponding rotational conformations for all substituents. NMR chemical shifts were calculated using the GIAO method[24] using single-point B3LYP/6-311+G(2d,p) calculations and chemical shift references in the GaussView03 visualization program.[21] In this study, intrinsic reaction coordinate (**IRC**)[25,26] calculations were performed on the model series ***1***, ***3***, and ***5*** for route 1c (vide infra) to authenticate the connection of a TS to reactant and product. More than 175 equilibrium and TS structures have been calculated in this study. Refinements such as reoptimization results of the series ***1***, ***2***, and ***5*** with the 6-311+G(2d,p) basis set, free energies for all series, and indications of the solvation effect obtained by the use of a polarization continuum model[27,28] (solvent = acetonitrile, "sphereonh" for H atom in intramolecular transfers) on series ***1*** are available in the Supporting Information. Key points for series ***1*** were also reoptimized with one MeCN molecule near the active site in order to have an indication if solvent molecules would change a class of mechanism (pericyclic, etc.). No significant structural or energetic changes were found with these refinements. The coordinates for all structures calculated in this study are available in PDB format in the Supporting Information.

Results and Discussion

The pathways from the cycloadducts to the imine product involve ca. 26 similar equilibrium and transition-state structures that are labeled **A**−**Z** in the schemes and figures. Thus, for 1,2,4-triazolium-4-dicyanomethide and ethyne (series ***1***, Scheme 2), the sum of their energies is designated ***1*****A**, their cycloaddition TS is ***1*** TS-**B**, their cycloadduct ***1*****C**, and so forth until the product imine ***1*****Z**.

1. The Two N4−C5 Routes. First, the N4−C5 bond-breaking pathway in the cycloadduct is examined, followed by C7−C(7A) (section 2.). The N4−C5 bond-breaking pathway diverges into two "routes" involving *several* mechanistic steps. They both start from an "open intermediate", **E**, which is formed from a simple breaking of the N4−C5 bond and is *key* to the subsequent energetics (routes 1 and 2, Scheme 3). The specifics of route 1 are discussed in section 1.1 and route 2 in section 1.2.

The two routes depend on whether the C(7a) H atom is shifted first (route 1) or if the N4−C(5a) bond is formed first (route 2). With route 1, there are three possible paths for the H shift to take place, each rejoining in an azolium methanide zwitterion, **M** (routes 1a−c, Scheme 4). Transfer of the azolium N(4)H to one of the nitriles then gives a ketenimine, **O**, and subsequent bond formation at N4−C(5a) gives the imine product **Z**.

While we consider only intramolecular H-transfer mechanisms in the computations for series ***2***−***6***, we acknowledge that some suprafacial transfers, which require high temperatures in the gas phase, occur readily in solution by solvent-assisted intermolecular processes[29] (e.g., the 1,3-H-transfer of 1,3-cyclohexadien-5-ylidene systems to give toluenes). Other examples include the catalytic effect of trace amounts of water in proton transfers[30−32] and the participation of methanol in proton transfer from C to O atoms.[33] The MeCN solvent used in these reactions could possibly assist the necessary proton transfer from C(7a) to N4. However, the PCM calculations and reoptimization of geometries including placing an individual

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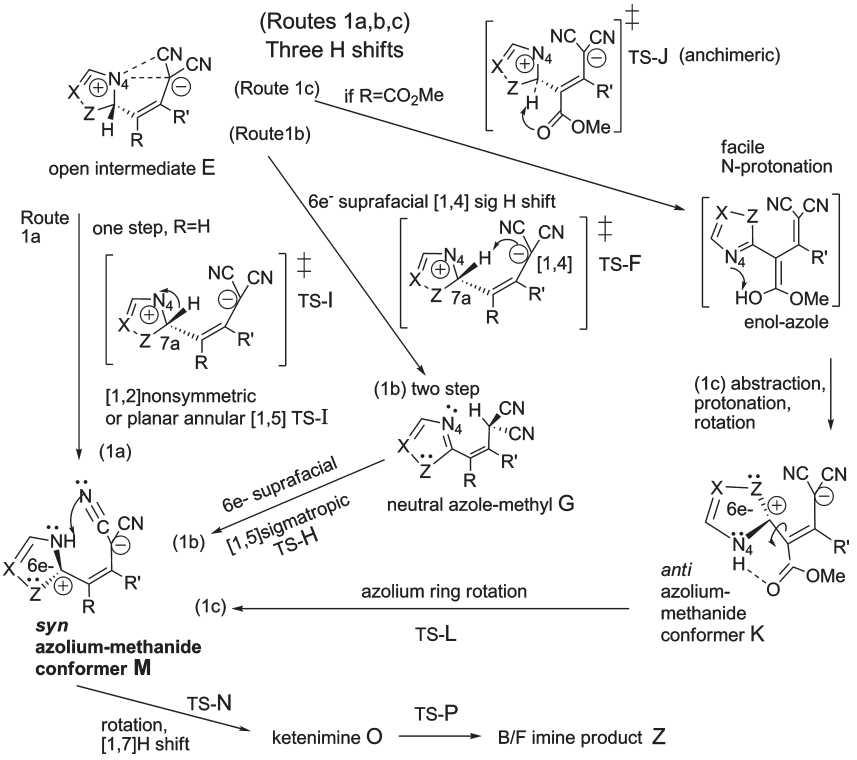
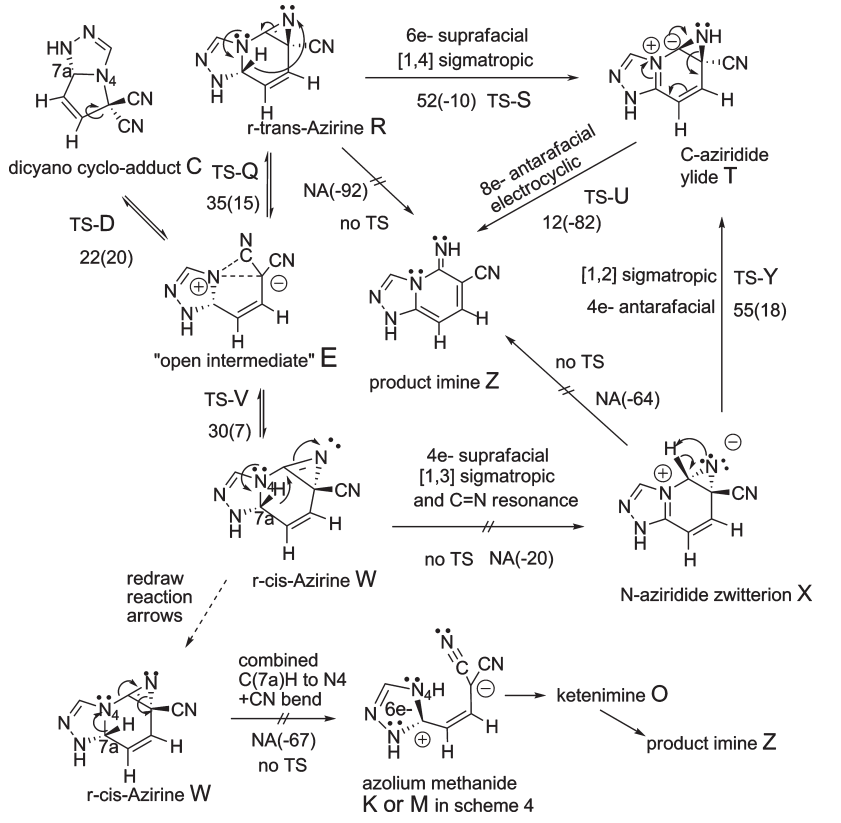
SCHEME 4. Three Possible Shifts of the C(7a) H Atom (Routes 1a−c) (E−M) and then Bond Formation at N4−C(5a) (M−Z)



SCHEME 5. Reaction Pathways for Rearrangement of the Cycloadduct to the B/F Imine First through Migration of the N4−C5 bond to N4−C(5a) then Transfer of the H on C(7a) for Series *1*[a]



[a]Numbers on arrows give E_a and reaction energies (kcal/mol) for that step (NA, not applicable, no TS found). Last line gives possible link between routes 1 and 2 through *r-cis*-azirine, but no combined TS was found.

MeCN molecule near the active sites for bond breaking and H transfer in series ***1*** (cf. the Supporting Information) showed no covalent interactions between the solvent molecule and the TS structures, thus no change in mechanism. Our results indicate that the reaction in solution involves an intramolecular proton transfer by one or all three separate allowed paths and there is no necessity for an intermolecular solvent intervention.

With Route 2, N4−C(5a) bond formation occurs before the H shift, forming a *trans* or *cis* 2R-azirine intermediate, then an aziridide ylide and B/F ring expansion to the imine product (Scheme 5). The relative energy diagrams for the different pathways are given in Figures 1 and 2 for series ***1*** and ***4***. The TS mechanisms for each step are discussed in the following sections. Table 1 gives a summary of the mechanisms for each step in series ***1*** through ***6*** and their E_a and ΔE.

1.1. N4−C5 Break, H Shifts (by Routes 1a−c), then N4−C (5a) Closure. The TS-**D** for N4−C5 bond breaking from the cycloadduct **C** is nearly equal to the open intermediate **E** in structure, where the N4−C5 and N4−C(5a) distances were both nearly 3.0 Å (Figure 3, Scheme 3). There are several conformers of the open intermediate **E** depending on the orientation of the azole ring around the conjugated anionic system. We choose the conformer represented in Scheme 3 as the reference in reporting energies within the series ***1***−***6***. The energies for the open intermediate **E** in the substituted imidazolium series ***5*** and ***6*** lie below those for the cycloadduct **C** (Table 1, step C−(D)−E). Formation of **E** is key to the H atom migration from the bridgehead C(7a). In the zwitterionic **E**, the positive charge is delocalized over only four atoms of the C protonated azolium ring. After migration to the adjacent N4, the charge is delocalized over the whole azolium ring and the resulting aromaticity accounts for the approximate 40 kcal/mol difference between **E** and **M** isomers.

Route 1a. The simplest step leading from the "open intermediate" **E** involves a [1,2] H shift through TS-**I**. Alternatively, when taking the whole ring π system into consideration, this is a $6e^-$ system, and the H shift to N4 can be described as a [1,5] sigmatropic shift analogous to that in 1,3-cyclopentadiene, followed by a planarization of the nitrogen terminus or a planar annular [1,5] shift. **IRC** calculations show a connection from the structure **E** shown in Figure 3 (shifting H is at upper right of **E**) through TS-**I** to the planar structure **M** (shifted H is

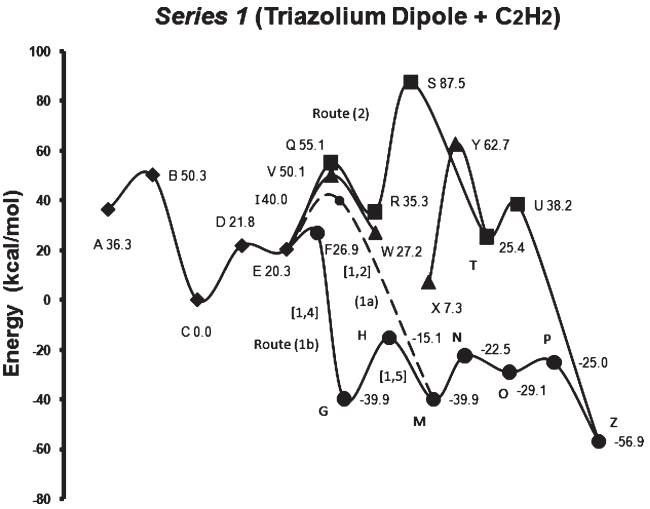


FIGURE 1. Energies (kcal/mol) relative to the cycloadduct (point **C**) of 1,2,4-triazolium-4-dicyanomethanide dipole and ethyne (point **A**) to the imine product (point **Z**), series ***1***. The cycloadduct **C** opens at N4−C5 to an "open intermediate" **E**, from which the product imine **Z** might be formed through two principle routes. The lower energy route involves first H shifts along either (route 1a, **E** directly to **M**) a [1,2] H shift from C(7a) to N4 (circle, dashed line) or (route 1b, **E** to **G** to **M**) a [1,4] H shift from C(7a) to C5 and then a [1,5] shift from C5 to N4. The H shift continues to the CN to form ketenimine **O**, which cyclizes at N4−C5a to give **Z**. With route 2, the open intermediate **E** first recombines at N4−C(5a) forming azirines in the *r-cis* (triangles) and *trans* (squares) configurations, followed by H shift to aziridides **T** and **X**. No TS structure was found between *r-cis*-azirine **W** and *N*-aziridide **X**.

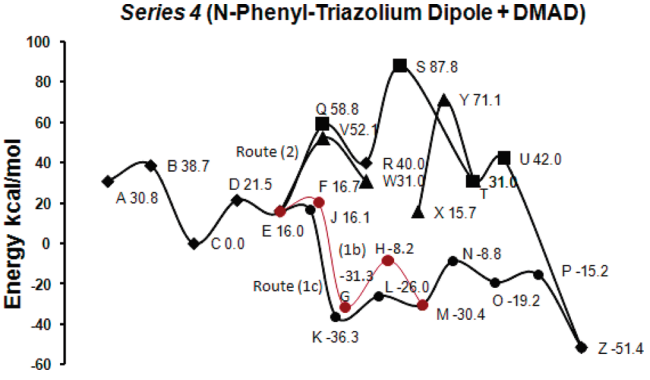


FIGURE 2. Energies (kcal/mol) relative to the *N*-Ph-triazolium dipole plus **DMAD** cycloadduct, **C**, series ***4***, for routes 1b (brown circles), 1c (black circles), and 2 (*cis*, triangles; *trans*, squares).

innermost). The mechanisms considered here are pericyclic, coarctate,[34−36] nonpericyclic,[37,38] pseudopericyclic,[39−52] or a compromise between pericyclic and pseudopericyclic.[53,54] (Since 1976, we have avoided using the term pericyclic for a

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TABLE 1. Activation Energies E_a and Reaction Energies ΔE (kcal/mol, B3LYP/6-31G*) for Each Step in Series *1*−*6*

step	mechanism	*1*E_a	ΔE	*2*E_a	ΔE	*3*E_a	ΔE	*4*E_a	ΔE	*5*E_a	ΔE	*6*E_a	ΔE
A−(B)−C	cycloaddition	13.9	**−36.3**	16.0	**−32.3**	7.6	**−28.4**	7.8	**−30.8**	8.7	**−29.0**	7.2	**−24.0**
C−(D)−E	coarctate C(7A) to N4 H	21.8	**20.3**	12.4	**5.5**	18.3	**11.6**	21.5	**16.1**	8.6	**−6.8**	8.8	**−5.2**
1a) E−(I)−M	[1,5]sigmatropic	19.7	**−60.2**	28.3	**−46.5**	18.6	**−48.9**	X		X		X	
1b) E−(F)−G	[1,4]sigmatropic	6.6	**−60.2**	12.2	**−44.9**	7.0	**−48.0**	4.2	**−47.4**	15.5	**−29.8**	13.6	**−32.1**
G−(H)−M	[1,5]sigmatropic	24.7	**−0.1**	21.8	**−1.6**	24.0	**−0.9**	23.0	**0.9**	19.5	**−6.7**	22.4	**−3.7**
1c) E−(J)−K	enol	X		X		0.8	**−52.7**	0.6	**−52.4**	3.7	**−40.6**	6.5	**−38.6**
K−(L)−M	rotation ketenimine to imine	X		X		8.9	**3.9**	10.3	**5.9**	5.5	**4.1**	6.2	**2.6**
M−(N)−O	[1,7]sigmatropic	17.5	**10.8**	18.9	**13.8**	23.2	**13.7**	21.5	**11.2**	25.2	**16.0**	26.7	**18.3**
O−(P)−Z	pseudopericyclic azirine to imine	4.1	**−27.8**	2.7	**−31.9**	2.6	**−34.4**	3.9	**−32.2**	2.7	**−35.1**	2.1	**−38.2**
trans E−(Q)−R	dbl coarctate	34.8	**15.0**	46.4	**28.8**	42.1	**27.1**	42.7	**23.8**	48.2	**41.1**	51.1	**43.2**
R−(S)−T	[1,4]sigmatropic	52.2	**−9.9**	50.6	**−10.6**	45.9	**−11.8**	47.8	**−9.0**	46.2	**−12.0**	42.5	**−13.1**
T−(U)−Z	8e,ant,electrocyc	12.8	**−82.3**	13.9	**−82.9**	10.6	**−85.0**	11.1	**−82.4**	11.1	**−84.8**	11.5	**−86.0**
cis E−(V)−W	dbl coarctate	29.7	**6.8**	41.3	**20.2**	35.0	**21.4**	36.0	**14.9**	44.8	**40.7**	46.6	**30.0**
X−(Y)−T	4e,ant.[1,2]sig	55.4	**18.1**	55.4	**18.6**	55.1	**16.2**	55.4	**15.2**	55.0	**16.8**	55.5	**17.0**
T−(U)−Z	same as above	12.8	**−82.3**	13.9	**−82.9**	10.6	**−85.0**	11.1	**−82.4**	11.1	**−84.8**	11.5	**−86.0**

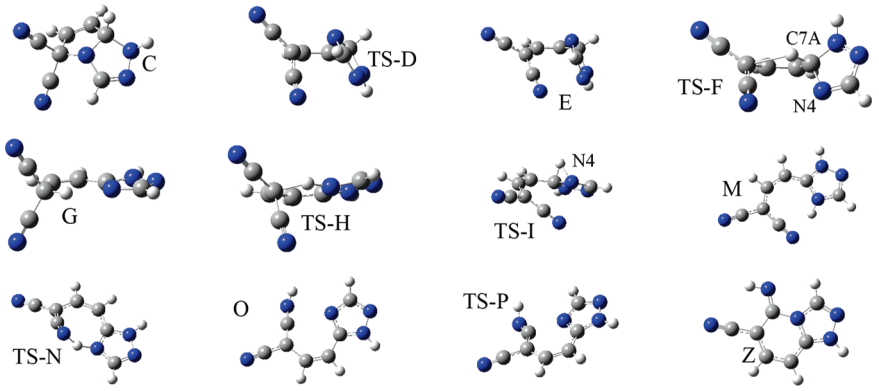


FIGURE 3. Structures for series *I* from cycloadduct **C** through "open intermediate" **E** and routes 1a (**F**−**H**) and 1b (**I**) to common point **M** and on to ketenimine and product imine **Z**. The N4 and CN atoms in TS-**N** and **O** are ca. 30^o out of plane.

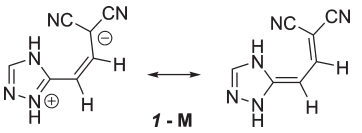
TABLE 2. Selected Calculated NMR H Chemical Shifts for Series *4* (Atom Positions Correspond to Scheme 1c, Experimental Values in Parentheses)[14]

entries	series *4* NMR-*d*	**7a**	**3**	**7**-OMe	**6**-OMe	N4-H
1	cycloadduct **C**	6.63 (6.59)	7.07 (7.30)	3.90 (3.66)	4.01 (3.84)	
2	imine **Z**		9.13 (9.14)	3.42 (2.96)	3.93 (3.86)	
3	**E**	9.16	8.71	3.80	3.90	
4	[1,4] **G**	8.28[a]	8.25	3.22	3.97	
5	*anti* **K**		8.03	3.27	3.87	8.84
6	*syn* **M**		7.83	3.78	3.80	13.18
7	obsd intermediate[14]		(7.53)	(3.47)	(3.39)	(8.55, up)[b]
8	ketenimine **O**		8.17	3.21	3.93	8.31

[a]On C5. [b]Drifts upfield.

reaction that can be described simply as an attack of a lone pair within the plane of a π system[37] and use the normal pericyclic nomenclature for a similar reaction where there is extensive disruption of the π system.[38] Using centroids of charge of localized MOs, we noted in an ab initio study of the cyclization of azidoazomethine to tetrazole that in the TS region there was only movement of the in-plane LMO centroids during bending of the azide and that the in-plane NH lone pair was extended. There was no significant change in the 5 membered π system. The mechanism was thus considered to be not electrocyclic since only in-plane LMOs were involved in the TS. The barrier to cyclization was noted to be low (12 kcal/mol), especially when later compared to the protonated methine cyclization (43 kcal/mol), where the terminal NH_2 group rotates in the region of the TS. In a contemporaneous study,[39] planar reactions similar to neutral azidoazomethine were named "pseudopericyclic" and the reaction was later generalized.[40−52] The low barriers were noted; and since there is little involvement of the π system, the number of electrons involved is not a factor as with pericyclic reactions. Recent studies[53,54] have shown a mechanistic continuum between the extremes of "pseudopericyclic" (90°, orthogonal interacting π systems) and *classic* pericyclic reactions in which there is usually some involvement of the σ system with nearly planar π systems. Since none of the reactions found in this study are exactly in-plane, we use the pericyclic designations but will also note nearly planar mechanisms with relatively small barrier heights as being pseudopericyclic.) The H shift in route 1a from **E** brings the proton around the C3═N4 bond to the in-plane hybrid orbital on N4 that is perpendicular to the azolium

SCHEME 6. Zwitterion Aromatic and Covalent Nonaromatic Resonance Forms of *1*-M



π system (Figure 3). Thus, the reactant and product have nearly orthogonal symmetry elements. However, in TS-**I** the shifting H atom is still over the C(7a)−N4═C3 plane and only ca. 10° out of the azole π system. The barrier of ca. 20 kcal/mol is comparable to those found in [1,5] sigmatropic H shifts in cyclopentadienes.[55−58] The mechanism can be considered as a sigmatropic shift combined with a nonpericyclic pyramidalization at N4.

A large negative energy is obtained with the H shift (−60 kcal/mol) **E** to **M**. The charge that developed in **E** is localized over the three atoms involved in bond breaking and formation, N4, C5, and C(5a). The charges in the zwitterionic product **M** are delocalized and account for the ca. 60 kcal/mol lower energy. NBO charges confirm that the negative charge of the methanide is delocalized over the dicyanopropenyl moiety and the positive charge is contained in the $6\pi e^-$ aromatic azolium ring. NICS(0) and (1)[59,60] calculations on ***1*-M** gave values of (0) = −9.9, (1) = −6.3 indicating an aromatic character of the triazolium ring. (H-triazolium cation values were calculated to be NICS(0) = −13.7, (1) = −10.4.) Thus, the zwitterionic character is maintained for structures ***1*-** and ***2*-M**, which are planar (Scheme 6), and the covalent but nonaromatic resonance structures are minor. In ***4*-M**, where the triazolium ring is 38^o out of plane, NICS(0) = −9.9, (1) = −6.9.

Route 1a represents the first part of the most direct route to the B/F imine product **Z**, i.e., transfer of the C(7a) H atom ultimately to the nitrile N atom and shift of the N4 bond from C5 to C(5a). The E_a of 20 kcal/mol for the initial [1,2] H shift will be seen to be competitive with azirine formation (Figure 1, dashed line), but not with other pathways.

Route 1b. When the **E** azole ring rotates perpendicular to the C═C system, there is the possibility for abstraction of the C(7a) H atom by the anionic C(5a) atom (TS-**F**, Figure 3). When the CH bond is ca. 10° out of plane, a symmetry-allowed $6e^-$ suprafacial [1,4]sigmatropic H shift occurs. The structure and energy content of TS-**F** resemble the open intermediate **E** due to the much lower relative energy (−60 to −30 kcal/mol) of the product **G**, which is a neutral azole−dicyanomethyl system. The E_a are lower for the more acidic triazoles ***1***, ***3***, ***4*** (5−7 kcal/mol, Table 1) than for the imidazoles ***2***, ***5***, ***6*** (12−15 kcal/mol). Although this is a [1,4] shift, for which values for experimental barriers are not known, comparison to [1,5]sigmatropic shift[55−57] show these [1,4] values of ca. 10 kcal/mol to be very low. This is a hallmark of pseudopericyclic[39−50,52] reactions or reactions involving the attack of an in-plane lone pair before extensive rearrangement of the out-of-plane π system occurs.[37]

The H atom is subsequently transferred from the neutral azole **G** in a [1,5] shift through TS-**H** to give the azolium zwitterion **M**. The CH of the $CH(CN)_2$ group and the triazole ring are coplanar in the neutral azole intermediate **G**, possibly permitting a pseudopericyclic in-plane H transfer mechanism. However, the ring and the $CH(CN)_2$ rotate out of the C═C π system in TS-**I** during the H shift by ca. 15^o. The mechanism can thus be described as symmetry-allowed $6e^-$ suprafacial [1,5]sigmatropic shift. The E_a for this step (25 kcal/mol) is in the usual range for this mechanism,[55−57] with the triazolium species having a slightly higher E_a than the imidazolium, reflecting the lesser basicity of the triazolium N lone pairs that abstract the H from $CH(CN)_2$. Interestingly, the zwitterionic azolium product **M** has nearly the same energy content as the neutral azole **G** for both the imidazole series ***2*** and triazole series ***1*** (Table 1, line G−(H)−M).

Route 1b initially involves a carbanion lone pair as the bond transfer catalyst rather than a carbonyl lone pair, which is more normally considered in anchimerically assisted paths. The initial barrier from **E** is ca. 6 kcal/mol (triazoles), compared to the 20 kcal/mol barrier to the [1,2] H shift in route 1a. The 25 kcal/mol barrier involved in the [1,5] sigmatropic H shift between the neutral azole−methane and zwitterionic azolium−methanide might, however, provide a potential well for an intermediate (Figures 1,2).

Route 1c. In series ***3*−*6***, the open intermediate **E** has a CO_2Me oxygen atom in position for abstraction of the C(7a) H atom to form an enol−azole (through TS-**J**, Scheme 4, Figure 4). The barrier to this anchimeric abstraction is remarkably low, ca. 0.7 kcal/mol for the triazoles and higher, ca. 6 kcal/mol, for the imidazoles. An optimized structure for the enol could not be found. Transfer of the enol OH proton to N4 could arguably be an in-plane, nearly barrierless, pseudopericyclic proton transfer. Indeed, the flexibility of substituents and the highly negative reaction energy (ca. −50 kcal/mol for triazoles ***3*** and ***4*** and −40 for imidazoles ***5*** and ***6***) lead directly to the protonation of the nearby N4 during the geometry optimization in Gaussian03 to produce the structure **K**. This is a zwitterionic azolium−methanide that is the 180° conformer of **M**, that was found in routes 1a and 1b and is labeled as the *anti* zwitterionic azolium−methanide structure **K** in Scheme 4 and Figure 4. Rotation through TS-**L** gives the *syn* conformer **M,** in which the H on N4 can be shifted to one of the CN to form the ketenimine. In each series **3** to **6,** the 180° conformer **K** is lower in energy due to the H-bonding between the N4−H and the carbonyl lone pair (Figure 4). The energy profile for the Ph−triazolium dipole plus **DMAD**, series ***4***, is given in Figure 2. Route 1a is not displayed in Figure 2 as the anchimeric abstraction in TS-**J** very effectively competes with the [1,2] migration in TS-**I** in series ***4***, ***5***, and ***6***.

Ketenimine Continuation. There is a ca. 16 kcal/mol barrier for the H shift in series ***1*** and ***2*** (Figure 1, Scheme 4, Table 1) from the N4-protonated zwitterion **M** through TS-**N** to the ketenimine **O** in the route 1a−c pathways. This barrier increases in the series ***3*−*6*** to ca. 24 kcal/mol due to the steric hindrance of carbomethoxy and *N*-azole substituents that push the ring out of plane (Figure 4, *syn*) with the CC π bond in series ***3*−*6***. This barrier TS-**N** also provides a potential well

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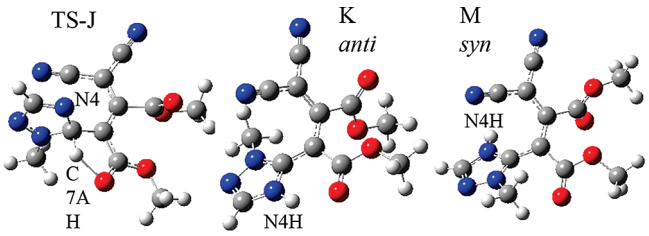

FIGURE 4. Route 1c, anchimeric assistance (TS-**J**) for transfer of C(7A) H atom to N4 (**K,** *anti*) and then rotation to (**M**, *syn*), from which the H atom can be transferred to CN for ketenimine formation. (Drawn here: series ***3***).

for an intermediate in the anchimeric pathways in ***1***−***6***. The mechanism can be described as a symmetry-allowed, 8-electron, antarafacial [1,7] sigmatropic H shift. For unsubstituted ***1*** and ***2***, which are nearly planar in **M**, the distortion of N4 and CN becomes ca. 30^{o} out of plane in TS-**N** and ca. 45^{o} for series ***3***−***6***, thus permitting the antarafacial passage.

The ketenimine **O**, which is twisted ca. 30° out of plane at bond C5−C6 in series ***1***−***6***, undergoes a closing through TS-**P**, in which the π system is nearly planar (within 8°) in series ***1***−***6*** from the ketenimine C(5a) through the azole N4 (Figure 3). The isomer of imine product **Z** is formed, where the H atom is *trans* to the CN. **IRC** calculations and the transition vectors of the imaginary frequency in TS-**P** point to two major motions, which are orthogonal, i.e., (1) the rotation of the out-of-plane =NH group toward the N4 lone pair and (2) the formation of the N4−C(5a) bond. The rotation of the NH group out of plane, as measured by the dihedral angle between *C*=NH and *N*=C=C(CN) in **O** is 95°, while in TS-**P** it is 135°. There is only one rotational direction or rotational isomer in the TS; i.e., geometry optimizations of TS-**P** starting at 45° return the NH to 135°. The two π bonds at the ketenimine C(5a) atom are broken in structure **O**, and two bonds are formed in TS-**P**, the new ring N4−C(5a) single bond and a new imine double bond during NH rotation. The mechanism is considered pseudopericyclic due to the planarity that occurs in TS-**P**, the bending at the ketenimine central C(5a) atom, and the relatively low barrier, ca. 4 kcal/mol.

1.2. N4−C5 to N4−C5a Bond Shift, then H Shift (Routes 2). 2*R*-Azirines[61] are usually generated in situ from species such as vinyl azides or *N*-sulfonyloxaziridines.[62] It is suggested that loss of a labile species generates a nitrene intermediate, which then cycles to an azirine. In our previous study,[14] we proposed a nitrene intermediate that is stabilized by an extensive π system (Scheme 1c, (Scheme 3 in ref 12)). Although that pathway and that for the formation of an azirine involve barriers of ca. 30 kcal/mol from **E**, exploration of these higher energy surfaces was pursued as an example for those 1,3-dipolar cycloadditions that might not have the possibility for anchimeric assistance or H transfer to the methanide group. The azirines are generally 20−30 kcal/mol higher in energy than the dipole + dipolarophile reactants but the reaction energy to the imines is ca. −80 kcal/mol (Figures 1 and 2).

1.2.a. Azirine. IRC calculations confirmed that the *trans* and *cis* TS-**Q** and TS-**V** leading to azirine formation are directly linked to the **E** structure, depending on rotation of the C(CN)$_2$ group. The azirine *cis* configuration **W** is lower in energy than the *trans* **R** by ca. 8 kcal/mol in ***1***−***6***. The azirine C=N bond in the *cis* configuration is more in conjugation with N4 and the azole C=N π system than the *trans* configuration. There is a slight lengthening of the azirine C=N bond in the *cis* configurations due to better conjugation with N4. Correspondingly, the E_a for *cis* formation, 29.7 kcal/mol is lower than the *trans*, E_a = 34.8 kcal/mol, and the *cis*-TS-**V** structure is earlier (series ***1***, new N−C bond 1.7874 Å) than the *trans*-TS-**Q** (new bond 1.7490 Å).

Inspection of the nuclear displacements and transition moment vectors for the imaginary vibrational frequency shows two movements for the azirine ^{1}TS-**Q**. One is for the expected vibration along the new N−C bond, and the other is a strong angle bending of the former nitrile N atom toward formation of the new azirine N−C bond (132^{o}). Breaking of the five membered ring in N(4)−C(5) has already occurred in the TS as well as rotation about the C(5) center (Figure 5). The electronic rearrangement is similar to the cyclization reaction of a cyanoketene-formaldimine complex to an azirine studied by Sordo et al.[63,64] Our TS-**Q,V** structures have almost identical transition vectors to their "**TS$_{zw}$**"[63] and our **E** "open intermediates" are structurally similar to their cyanoketene−formaldimine complex. As noted by Sordo et al.,[63] the "**TS$_{zw}$** could be considered as an example of a *coarctate* TS for the lone pair−five membered ring terminators processes."[34,35]

1.2.b. Nitrenes. No singlet nitrene-like structures were found[64] for series ***1*** and the more resonance stabilized ***3***. The triplet nitrene structure (Figure 5) is 12.9 kcal/mol lower (UB3LYP/6-31G*) than the singlet *r-trans*-azirine (13.7 for ***3***, more substituents). The singlet *r-cis*-azirine is 4.8 kcal/mol above the ^{3}nitrene (7.9 for ***3***). Although the ^{3}nitrene is nearly planar, there are two TS leading to it from **E**, similar to the *cis* and *trans* ^{1}TS-**Q,V** to azirines. The singlet ^{1}TS-**Q** leading to the r-*trans*-azirine for series ***1*** was found to be higher in energy than the triplet nitrene ^{3}TS$_{1t}$ by 12.1 kcal/mol (11.2 for ***1*** ^{1}TS$_{1c}$−^{3}TS$_{1c}$, and for ***4*** *trans* 13.9, *cis* 7.2). Attempts to find triplet *cis*- and *trans*-azirines led to a structure where the C−C bond completely opens to form a seven-membered ring described as a triplet carbene imine, as seen in other theoretical studies.[65−67] A triplet ^{3}TS$_2$ structure was found for the conversion of the ^{3}nitrene to the ^{3}carbene imine (***1*** E_a = 59.9 kcal/mol, ΔE(carbene, nitrene) = 10.7 kcal/mol). All triplet structures are available in the Supporting Information. It must be noted also that if reaction conditions were to

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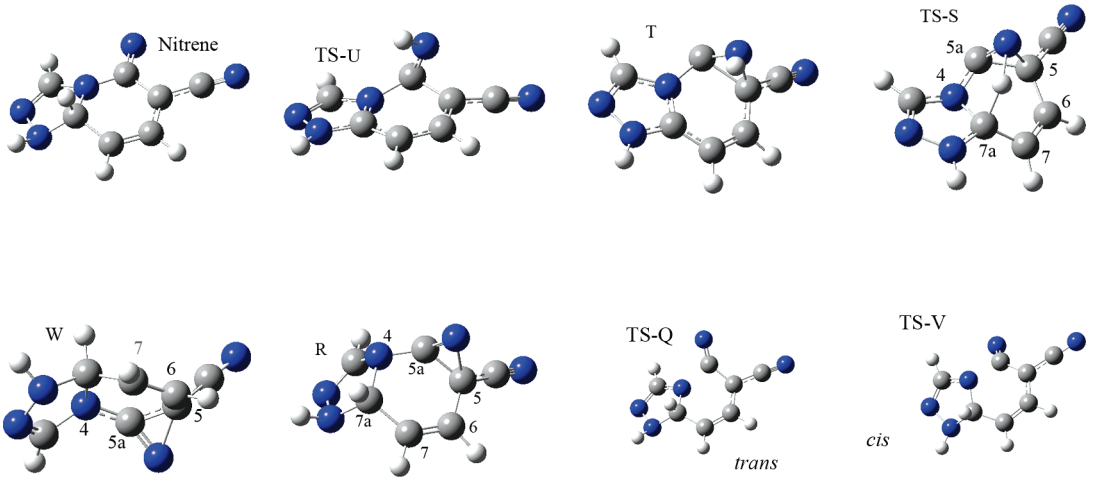

FIGURE 5. Structures for series ***1*** along route 2: *trans* **R** and *cis* **W** azirines, C-aziridide **T**, as well as TS **Q**, **S**, **U**, **V** and the triplet nitrene structure.

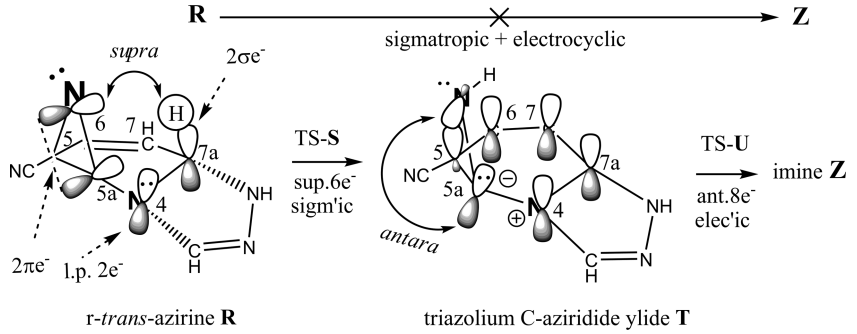

FIGURE 6. Orbital diagrams for two-step mechanism for H shift and C(5)−N opening, TS-**S** suprafacial 6e⁻ [1,4]sigmatropic shift between the azirine **R** and C-aziridide ylide **T**, and TS-**U** antarafacial 8e⁻ electrocyclic opening to imine **Z**. (Orbitals are pictured for reactants only; H shift and new C=N pictured using double headed curved arrows.) Atom numbers correspond to those in Scheme 1c and Figure 5. TS structures are given in Figure 5. No TS from **R** to **Z** for a combined sigmatropic shift plus electrocyclic ring-opening was found.

favor triplet formation, intermolecular transfer of the H atom from C(7a) to the nitrene N atom would give the B/F imine directly.

1.2.c. (*Trans* Route 2) (E, R, T, Z, Scheme 5). Only the *trans* configuration has the C(7a)−H bond in position for an H shift to the azirine N atom, which leads to the bicyclic B/F imine exothermically. The *cis* configuration **W** must await an unfavorable intermolecular H shift as the CH bond and the azirine N atom are on opposite sides of the six-membered ring. The [1,3]sigmatropic shift to the azirine C(5a) in either the *cis* or *trans* configuration is symmetry forbidden (vide infra), as is the shift to C(6) (numbering in Figure 6).

The most direct route from the *trans*-azirine to the imine product would be a synchronous H shift to the N atom combined with an opening of the azirine N−C(5) bond. This could be considered a combined pericyclic mechanism that includes an H sigmatropic shift and electrocyclic opening (Figure 6). Azirine ring distortion should favor this combination. Despite the reaction energy being −92 kcal/mol from the azirine **R** to product **Z**, and the relatively long azirine C−N bond length within a three-membered ring, no single TS combining the two motions was found. Two consecutive TS-**S** and TS-**U** separated by intermediate **T** were found (Figures 5 and 6, Scheme 5); thus, route **R**−**S**−**T**−**U**−**Z** (Figures 1 and 2). The first step, **R**−**S**−**T**, is designated a [1,4] sigmatropic shift since the bond distances radically change between the four atoms C7a, N4, and azirine C and N. The bond distances between atoms C7a, C7, C6, C5, N(azirine) (Figure 6) keep their single- and double-bond orders between the *trans*-azirine intermediate and the H-shifted product. The [1,4] shift from the azirine involves three electron pairs, i.e., the C−H bond pair, the N4 lone pair, and the azirine C=N double bond pair. The transition-state structure, TS-**S**, obtained for the suprafacial 6e⁻ [1,4]sigmatropic shift, is given in Figure 5 and Scheme 5. The E_a for this step is ca. 50 kcal/mol for series ***1*−*6***. A preliminary report[12] on the calculated [1,4] H shift between the 1,3-dipole, 4,5-dihydropyrazol-2-ium-1-ide and its imine−amine counterpart, 4,5-dihydro-1*H*-pyrazole, gave $E_a = 34.4$ and $\Delta E = -27.7$ kcal/mol. This is in the range for the theoretical E_a calculated for [1,5] H shifts in cyclic 1,3 dienes,[56,57] in which ring strain was found to play a role. The B3LYP/6-31G(d) E_a for cyclohexatriene is 41.9 kcal/mol compared to the experimental estimate of 41 kcal/mol.[68] The reason for the higher barrier in this [1,4] shift may be the π distortion of the middle N and C atoms. The TS CH bond lengths in the [1,5] shift are both 1.427 Å, while in the [1,4] TS-**U** shift CH = 1.409 Å and

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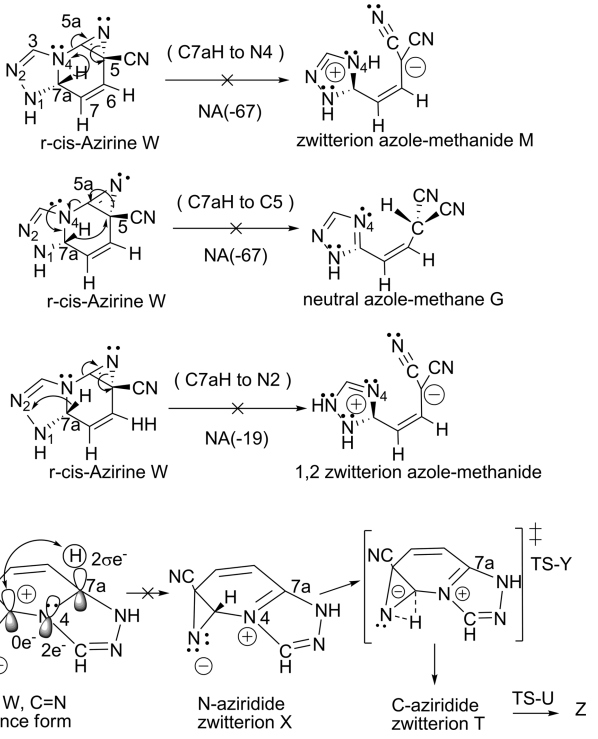

FIGURE 7. Mechanistic and orbital diagrams for the shift of the C (7a) H. The top three involve breaking the N4−C(5a) bond to give precursors of the ketenimine series ***1***. The bottom orbital diagram is for route 2, without involving C−N rupture. It involves first a symmetry-forbidden $4e^-$ suprafacial [1,3]sigmatropic shift from *r-cis* azirine **W** to *N*-aziridide ylide **X** (no TS structure found), and then to C-aziridide zwitterion **T** through a 90^o nonsymmetric $4e^-$ [1,2] H shift, TS-**Y**.

NH = 1.468 Å. Huisgen has pointed out that [1,4] shifts should be an accompanying feature of many 1,3-dipolar cycloadditions,[69] yet few theoretical studies have yet appeared. Sordo and Ardura[70] have recently shown the [1,4] H shift to be a bottleneck in the catalyzed ring expansion of cyclopropanols and that solvent assistance is needed, as is the case here.

The product of the [1,4] shift, **T** is a protonated three membered heterocycle that has a different structure than the neutral azirine. In the protonated case, both C−N bonds have similar single bond lengths (1.4 Å), whereas the ring C (5)−C(5a) bond is elongated to over 1.6 Å. The C(5a) atom of the former azirine ring assumes a pyramidal structure indicative of an anion structure (Figure 5). Thus, when the former azirine ring is protonated, it is transformed to an aziridine anionic terminus of a triazolium−aziridide ylide (designated as C-aziridide ylide, **T** in Scheme 5).

The transition-state structure, TS-**U**, leading to the B/F imine **Z** (Figure 3) resembles the C-aziridide ylide with lengthening of the HN−C(5) bond and concomitant shortening of the other aziridine HN−C(5a) bond to give the imine (5a)C=NH bond. This process can be described as a symmetry allowed, $8e^-$ antarafacial electrocyclic reaction. One can also consider the aziridide as analogous to a cyclopropyl anion, in which case the ring-opening is an allowed, $4e^-$ electrocyclic mechanism with disrotatory movement of the NH and lone pair. The barrier for ***1*** is 12.8 kcal/mol, which reflects the large negative reaction energy of −82.3 kcal/mol for opening the three-membered ring to the *exocyclic* imine product.

The question remains as to why the azirine does not transform directly to the imine during the [1,4] shift combined with the electrocyclic opening. Inspection of TS-**S** (Figure 5) shows that a preliminary lengthening of the C (5a)−N bond is all that is needed.

1.2.d. (*Cis* Route 2). Due to its configuration, the *r-cis*-azirine **W** must await intermolecular transfer of the C(7a) H atom. Extensive exploration of the energy surface involving transfer of the H atom from C(7a) toward the azirine C(5 and 5a) atoms or the N_4 and N_2 atoms revealed no TS structures that could be traced back by IRC to the azirine. The exploration used two types of starting geometries, (i) those with the tricyclic azirine bond lengths but with the H between atoms and (ii) those with an extended N4−C(5a) bond so that routes to the ketenimine path might be found. The most direct route, transfer of C(7a)H to C(5a), can be described as a symmetry-forbidden $4e^-$ suprafacial [1,3]sigmatropic reaction (Figure 7, last line) if one takes into account the normal ionic resonance structure involving an imine double bond. All other direct transformations in Figure 7 are combinations of symmetry-allowed mechanisms that include the azirine electrocyclic ring-opening. (Bifurcations[71] on energy surfaces for organic reactions and differing linkages of pericyclic reactions[72] have recently been reviewed, and sequential TS structures without an intervening intermediate have been noted.[73])

Although no TS was found, the product of an intermolecular or assisted H shift from C(7a) to C(5a) (last line, Figure 7) can be described as an azolium *N*-aziridide zwitterion, which is of nearly the same energy as the azirine. The direct step from the *N*-aziridide to the B/F imine would involve a simultaneous $4e^-$ antarafacial [1,2]sigmatropic H shift along with an electrocyclic opening of the N−C(5) bond, but again, a two-step process was found for these motions. Inspection of the atom displacements of the single imaginary frequency of the TS-**Y** structure shows a simple H atom shift between the C and N atoms, without opening of the N−C(5) bond. The **IRC** joins an antarafacial shift of the H atom from the CH to NH and explains the high activation energy for a [1,2] shift (55.4 kcal/mol). Once the H is transferred, a C-aziridide identical to that on the *r-trans*-azirine pathway is formed, with an inverted NH center. The B/F imine **Z** is then formed through the TS-**U** structure.

Thus far, there are five cases where a single TS has not been found that combines a sigmatropic H shift and a highly exergonic electrocyclic ring-opening. At this point, *it is posited that transformations consisting of two pericyclic mechanisms are not combined but pass through two consecutive steps, i.e., two distinct TS*. We note that in the anchimerically assisted transformation, **E**−TS-**J**−**K**, (Figure 4), the first step is a sigmatropic H transfer. The enol intermediate could not be found, and the positioning of the enol OH for passage to the azolium N4 could arguably be an in-plane, nearly

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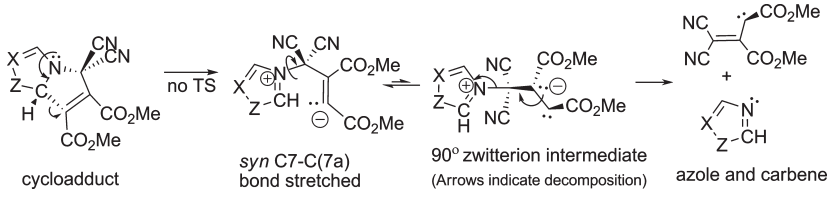
SCHEME 7. Cycloadduct Decomposition through C(7a)−C7 Bond Breaking and N4−C5 Rotation



barrierless, *pseudo*pericyclic proton transfer, as generalized by Birney and others.[40−52]

2. C7−C7a Bond. The second mechanism explored for dicarboxymethyl series ***3***, ***4***, and ***6*** was the breaking of the C7−C7a bond shown on the bottom line of Scheme 1c. The dicyano, zwitterion intermediate was found to be stable in a conformation whereby the former alkynyl group is rotated 90° to the ring (Scheme 7); all *syn* structures collapse without barrier back to the cycloadduct structure. These 90° structures can be considered to be the intermediates in the two-step cycloaddition mechanism of the 1,3-dipole with DMAD. Their energies are all above the concerted TS structures (***3***, 3.2; ***4***, 3.8; ***6***, 3.2 kcal/mol). The carbomethoxy groups are perpendicular along the former alkyne bond. The conjugation with one group stabilizes a carbene and the other the anion of a zwitterion. All optimization attempts to find a TS for ring-N atom migration to the nitrile C atom from the zwitterions led to dissociation into the free imidazole or triazole molecules and stabilized carbenes. Thus, the C7−C7a bond breaking mechanism, suggested by results from maleic anhydride cycloadducts,[14] seems not to be viable for dicarboxalato alkynyl cycloadducts.

3. Intermediates. The synthetic cycloaddition−ring-expansion sequences with azolium dicyanomethanide 1,3-dipoles all occur in situ under mild ambient conditions. In only one case has the initial cycloadduct been encountered as an unstable intermediate, namely for the reaction of 1-phenyl-4-dicyanomethanide-1,2,4-triazole with DMAD (series ***4***, Scheme 2) by Elguero et al.[20] It is significant that the computed E_a values herein for the formation of the 1,2,4-triazolo open intermediate **E** (Schemes 3−5) at ca. 20 kcal/mol for this system are more than double the values for the imidazolo series (Table 1), with E_a values < 10 kcal/mol, where cycloadducts have not been intercepted. When the Elguero intermediate cycloadduct was held at 0 °C in CD_3CN in an NMR tube it proved possible for us[14] to monitor it changing to the B/F imine product (Scheme 3). A transient intermediate was observed to grow and fade as the cycloadduct ring-expanded using both proton and carbon-13 NMR spectra. The presence of three separate species showing growing and fading NMR signals simultaneously in the solution gave a multitude of overlapping carbon-13 NMR signals, and it was not possible to extract information on the intermediate from carbon-13 spectra. The proton spectra were simpler, and four definite signals for the intermediate species were identified, two MeO signals at 3.39 and 3.47 δ, an aromatic CH at 7.53 δ, and a signal at 8.55 δ which moved upfield (toward TMS) as it declined with the growth of the B/F imine product (Scheme 3). Accordingly, proton NMR shifts were calculated herein for the range of possible intermediates for the reaction series ***4*** (Scheme 2), including the Elguero intermediate cycloadduct, **C** (X = N, Z = NPh, Scheme 3) and the ring-expanded B/F imine product **Z** (Scheme 3), for both of which measured NMR spectra are available (Table 2). The computed NMR shifts for these two species are in good agreement with the observed values (Table 2, entries 1 and 2). Among the range of possible intermediates, the ylide structures **K** and **M** (Schemes 3 and 4) fit the observed NMR data best (Table 2, entry 7). It is significant that the positive terminus of these ylide intermediates is stabilized for the 1,2,4-triazole case where Z is an N-Ph moiety and a further stabilization arises for the species **K** (Scheme 4) with an intramolecular H-bond. The low-field proton NMR signal of the observed intermediate at 8.55 δ was seen to drift upfield as it declined and had reached 7.9 δ before it finally disappeared. Such an increase in shielding would be expected for an NH proton experiencing the cleavage of an intramolecular H-bond as the proton moves to allow for the formation of the key ketenimine species **O** (Schemes 3 and 4).

Conclusions

(1) Relief of ring strain in five-membered di- and tricyclic products may not be sufficient to surmount barriers to bond breaking and rearrangements in the rings. The ring expansions in these particular Huisgen cycloadditions are facilitated by 2-fold anchimeric assistance in substituted alkyne cycloadducts, first in H-abstraction from the ring by a carboxyl group and thence in the transformation of a CN group to an H-ketenimine. Thus, the alkyne (***3***−***6***) cycloadducts pass through an open intermediate to give an *intra* molecular ketenimine−azole acid−base reaction resulting in a delocalized neutral imine product. The presence of carboxylic derivatives and any other group should thus be carefully considered in the design of heterocyclics.[8]

(2) In the case of dicyano-1,3-dipoles with unsubstituted alkynes ***1*** and ***2***, the ring expansion is still facilitated by assistance in transforming one CN group to a H-ketenimine, an intermediate which might not be envisaged in ordinary ring expansions and proton transfers.

(3) Even in the high energy routes through azirine intermediates, the transformations remain complex. Despite the high release of energy and lack of well-defined symmetry elements in certain cases where "combined" pericyclic mechanisms might be written, "consecutive" pericyclic reactions were found.

(4) Many of the intramolecular H atom transfers found in this study are not accessible to kinetic experiments at low or even ambient temperatures. This work illustrates the value of a combined computational and low-temperature NMR study to probe the paths to unstable intermediates in complicated multistep reactions.

(5) The future of mechanistic organic chemistry is still very challenging and far from over. It lies in unraveling the deceptive complexity in apparently simple transformations.

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Supporting Information Available: Free energies, optimization results for ***1***, ***2***, and ***5*** with the 6-311+G(2d,p) basis set, relative energy diagrams for series ***1*−*6***, coordinates and selected **Z**-matrices for each point, and a "structures.zip" file containing pdb files of all structures in this study. This material is available free of charge via the Internet at http://pubs.acs.org.