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# Cycloaddition/Ring Opening Reaction Sequences of *N*-Alkenyl Aziridines: Influence of the Aziridine Nitrogen on Stereoselectivity

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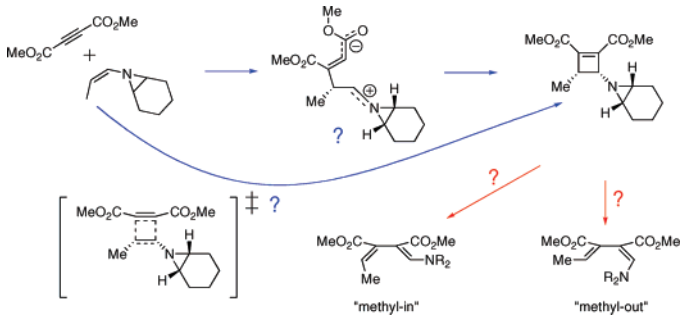
## ABSTRACT




**The cycloaddition of (*Z*)-7-(prop-1-enyl)-7-azabicyclo[4.1.0]heptane with dimethyl acetylene dicarboxylate (DMAD) was reported previously to proceed with complete stereoselectivity. Quantum chemical calculations (B3LYP) were used to evaluate the mechanism of the cyclization process, and it was discovered that a stepwise pathway is preferred. The subsequent electrocyclic ring opening reaction of the cyclobutene was also studied, and it was found that ring opening to the "methyl-in" dienamine is preferred to the "methyl-out" product by some 4–5 kcal/mol.**

*N*-Alkenyl aziridines hold great promise as synthetic intermediates capable of introducing aziridine functionality—a functionality present in several natural products found to possess, for example, anti-cancer properties.[1] In particular, the use of *N*-alkenyl aziridines in highly stereoselective reactions holds great promise. To fully exploit this potential, *N*-alkenyl aziridines of a single stereochemistry (*E* or *Z*) must be accessible. Thus far, most reactions generating enamines have involved equilibration of *E*- and *Z*-stereoisomers[2] and have, therefore, produced predominately the more stable *E*-isomer. Alphonse and Yudin, however, have described the use of rhodium hydride catalysts to isomerize allyl aziridines to selectively yield *Z*-enamines.[3] Such species were trapped via a (2 + 2) cycloaddition reaction (at 60 °C in toluene) that produces a cyclobutene with *syn* substituents, taking advantage of the *cis* stereochemistry of the enamine (scheme in abstract).[3a]

In spite of the complete stereoselectivity observed for this cyclization,[3a] there remains some question as to its mecha-

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(1) Lowden, P. A. S. Aziridine natural products—discovery, biological activity and biosynthesis. In *Aziridines and Epoxides in Organic Synthesis*, 1st ed.; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 399−442 and references therein.

(2) (a) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029−2030. (b) *The Chemistry of Enamines (Parts 1 & 2)*; Rappoport, Z., Ed.; Wiley: New York, 1994. (c) Gawley, R. E.; Aubé, J. In *Principles of Asymmetric Synthesis*; Baldwin, J., Williams, R. M., Bäckvall, J.-E., Eds.; Tetrahedron Organic Chemistry Series 14; Pergamon: Oxford, 1996.

(3) (a) Alphonse, F.-A.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 11754−11755. (b) Tsang, D. S.; Yang, S.; Alphonse, F.-A.; Yudin, A. K. *Chem.—Eur. J.*, in press.

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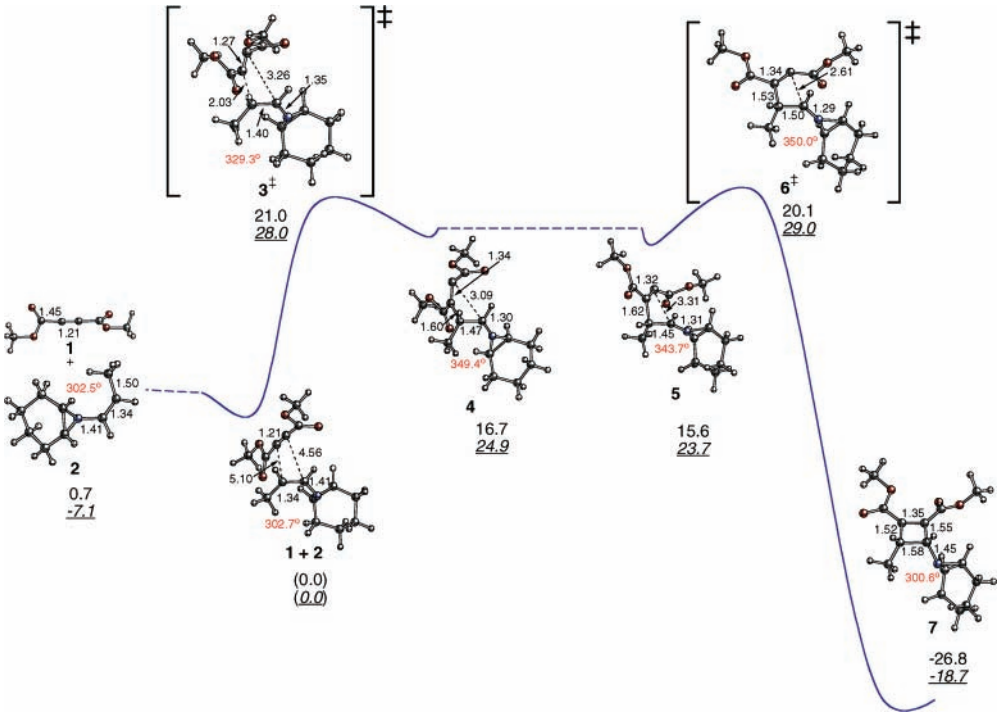



**Figure 1.** Species involved in the cyclization of DMAD (**1**) and *N*-alkenyl aziridine **2** (see also the scheme in the abstract). For each structure, energies (kcal/mol; $\Delta E$ + ZPE in normal text; $\Delta G$ at 60 °C in *underlined italics*),[5] select distances (in Å), and the sum of bond angles (SOA, red) around the nitrogen atom are shown. Structures **4** and **5** are connected via multiple conformational changes with low barriers.[9]

nism.[4] If the cyclization proceeds by initial attack of the electron-rich double bond (of the enamine) on the alkyne, a doubly resonance-stabilized zwitterionic intermediate would result (see scheme in abstract), and if this intermediate were short-lived enough, complete stereoselectivity could be observed, even in the absence of a concerted cycloaddition. Quantum chemical calculations (B3LYP/6-31+G(d,p))[5] were used to (1) determine whether a stepwise or concerted cyclization pathway is more favorable for the cyclization and (2) predict and explain the torquoselectivity[6] for electrocyclic ring opening of the cycloadduct.

**Cyclization.** As a non-photochemical four-electron process, the (2 + 2) cycloaddition, if concerted, requires a transition structure with a Möbius orbital array.[7] However, achieving a Möbius array puts substantial geometric constraints on such a small system and is generally accompanied by a significant strain penalty.[8] Our first goal was to determine whether or not a concerted [2 + 2] process was possible for the reaction of dimethyl acetylene dicarboxylate (DMAD, **1**) with (*Z*)-7-(prop-1-enyl)-7-azabicyclo[4.1.0]-heptane (**2**; Figure 1, left) and, if not, why complete stereoselectivity was observed for this reaction.

While all attempts to locate a transition structure for concerted cycloaddition failed, a stepwise pathway was found. Figure 1 shows the intermediates and transition structures involved in this process. A critical juncture in the reaction is reached once initial C−C bond formation is complete (i.e., zwitterion **4** is formed). Rotation about the 1.60 Å bond of **4** is necessary to proceed to **5** (a conformer capable of forming the final C−C bond of the ring system). This rotation, though, is in competition with rotation about the 1.47 Å bond of **4**—a rotation that would result in scrambled stereochemistry in the final product. The transition structure for scrambling is 8.9 kcal/mol ($\Delta E$ + ZPE; 9.3 kcal/mol, $\Delta G$ at 60 °C) above **4**, however, indicating that scrambling requires significantly more energy than collapse

(4) For leading references on both thermal and photochemical (2 + 2) cycloaddition reactions, see: (a) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3−22. (b) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7501−7505.

(5) All calculations were performed with *GAUSSIAN03*. All geometries and energies reported herein are from B3LYP/6-31+G(d,p) optimizations. All reported energies include zero-point energy corrections, unscaled. Free energies were calculated at 60 °C, the temperature used experimentlly for the cycloaddition reaction.[3a] See Supporting Information for additional details, including full reference for *GAUSSIAN03*. We consider the gas phase calculations described here to be a reasonable approximation of the reactivity of **1** and **2** in the nonpolar solvent toluene, which was used experimentally.[3a]

(6) For seminal discussions, see: (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (c) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708. (d) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125.

(7) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970. (b) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17−22 and references therein. (c) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781−853.

(8) See Supporting Information for a movie of the reaction coordinate for a thermally allowed, concerted, suprafacial/antarafacial [2 + 2] reaction.

to the *syn* product. Thus, the stepwise process shown in Figure 1 is consistent with the formation of only the *syn*-cyclobutene product.

Of note throughout the cyclization process is the degree to which the nitrogen lone pair is able to interact with its adjacent functionality. The degree of planarity of the nitrogen center may be measured by summing the three bond angles (SOA) with the N atom as their vertex. A trigonal planar geometry would be described by an SOA of 360°, while a perfectly tetrahedral (pyramidal) geometry would be described by an SOA of 328.5° (3 × 109.5°). Enamine **2** was found to have an SOA of 302.3°, reflecting both the effective size of a lone pair and the geometric constraints of the three-membered ring. Initial bond formation (proceeding through transition structure **3**‡; Figure 1) leads to a plateau[9] upon which the nitrogen now feels the demand of an adjacent cationic center, leading to an increase in the SOA to ~350° as these structures tend toward iminium ions. Finally, as the cyclization is completed and **7** is formed, the SOA returns to ~300°. These changes in SOA suggest that the aziridine nitrogen interacts significantly with the cationic ends of **4** and **5**, which is likely the reason that these zwitterions exist as minima.

**Ring Opening.** We are also interested in the possibility of using the aziridine-substituted cyclobutene products as precursors to useful dienamines (Figure 2). Thermal electrocyclic ring opening of the substituted cyclobutene cycloadducts also requires a Möbius arrangement of orbitals; this is achieved by conrotatory ring opening (Figure 2a) as predicted based on orbital symmetry considerations.[7] Conrotation, however, can occur in either of two directions, introducing the possibility of two distinct products, herein referred to as "methyl-in" or "methyl-out" (see Figure 2b).[6]

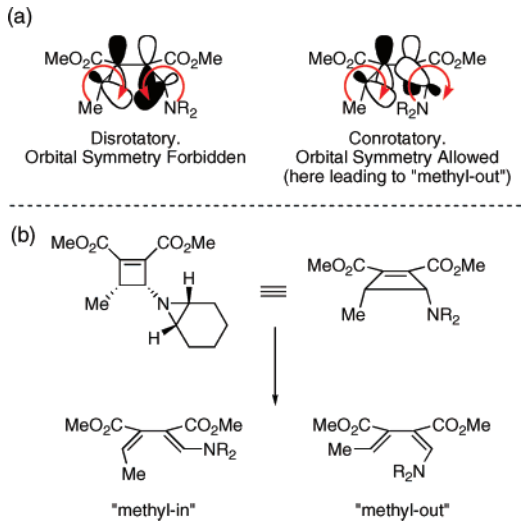
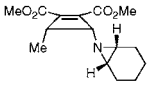
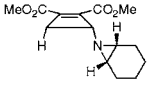
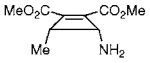
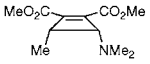
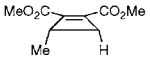



**Figure 2.** (a) Rotational preferences for 4$\pi$-electrocyclic ring opening of the substituted cyclobutenes (shaded based on butadiene HOMO); and (b) possible products of conrotatory ring opening.

Figure 3 depicts the electrocyclic ring opening of **8** (a conformer of **7**).[10] Intermediate **8** is connected directly to a transition structure (**13**‡; Figure 3, right) for ring opening to a methyl-out product. To reach a methyl-in product, **8** must first rotate the aziridine N lone pair into alignment with the breaking C−C bond (**10**; Figure 3, left). Since interconversion of conformers **8** and **10** (through transition structure **9**‡) involves a barrier that is considerably smaller than the barriers for ring opening, the Curtin−Hammett principle[11] suggests that the relative energies of the ring opening transition structures can be used to predict the product distribution. The transition structure for methyl rotation inward (**11**‡) is some 4−5 kcal/mol lower than that for methyl rotation outward (**13**‡), indicating that methyl rotation inward should predominate experimentally.

In an attempt to isolate steric and electronic preferences for each group attached to the C−C bond that breaks in these reactions, the ring opening of several truncated systems was studied (Table 1). From Table 1, it is apparent that the most electron-donating group always prefers to rotate outward, consistent with previous studies on torquoselectivity.[6] Comparison of entries 1 and 2 reveals a penalty of 8 kcal/mol for rotating a methyl group inward in the presence of the bicyclic aziridine system. The inherent preference for a methyl group to rotate outward is shown by entry 5, which when compared to entry 1 suggests that the combined steric and electronic effects of the bicyclic aziridine group are in excess of 10 kcal/mol (sum of effects from entries 1 and 5). Of particular note, however, is the difference between entries 1 and 3. When the amine is no longer constrained in a bicyclic system, preference for rotation outward *increases*, which indicates that the loss of steric bulk must also be

**Table 1.** Conrotatory Ring Opening Preferences ($\Delta G$ at 60 °C) for Several Truncated Cyclobutenes

| entry | cyclobutene | preference | by (kcal/mol) |
|---|---|---|---|
| 1 |  | Me in, amine out | 4.3 |
| 2 |  | H in, amine out | 12.6 |
| 3 |  | Me in, amine out | 8.1 |
| 4 |  | Me in, amine out | 6.2 |
| 5 |  | Me out, H in | 5.9 |

(9) Structures **4** and **5** are conformers connected by several transition structures and intermediates that were elusive due to the small barriers. See Supporting Information for more details regarding the methods used in our attempts to locate said transition structures.

(10) Structures **7** and **8** are conformers connected by two transition structures with energies of 0.6 and 1.5 kcal/mol relative to **7** (Figure 1). **8** sits at −2.1 kcal/mol relative to **7**. See Supporting Information for details.

(11) For a review, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

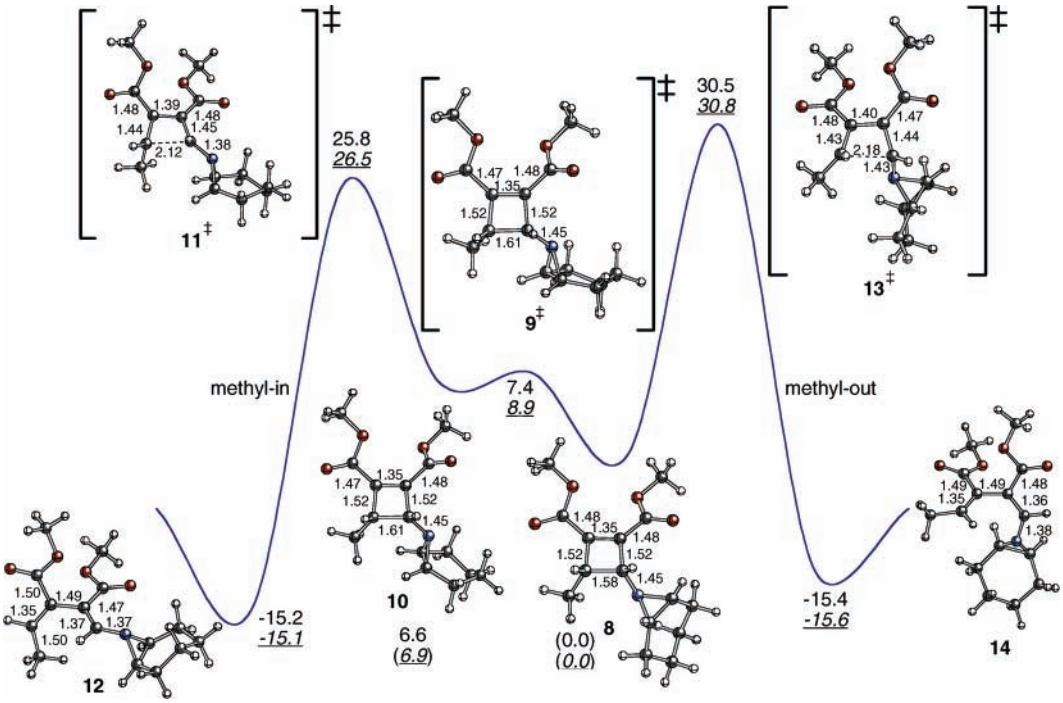



**Figure 3.** Species involved in the electrocyclic ring opening of cyclobutene **8** (center). For each structure, energies ($\Delta E$ + ZPE in normal text; $\Delta G$ at 60 °C in *underlined italics*)[5] are shown in kcal/mol and select distances are shown in Å. Structures **7** (Figure 1) and **8** (above) are connected by several conformational changes with low barriers.[10]

accompanied by an increased ability of the aziridine nitrogen to share its lone pair of electrons[12] (the usual driving force for outward rotation of electron-donating groups).[6] Interestingly, if the ring constraint is lifted while leaving degree of substitution of the nitrogen center unchanged (entry 4, cf. entry 1), the effect is smaller.[13]

Overall, our calculations[5] indicate the following: (1) The cycloaddition reaction reported by Alphonse and Yudin[3a] proceeds through a stepwise mechanism, and the observed stereoselectivity is likely a result of the short lifetime of the zwitterionic intermediate. (2) Electrocyclic ring opening of the cyclobutene should occur in a conrotatory manner, forming, preferentially, the methyl-in product. We hope to see this prediction put to the test and the cycloaddition−electrocyclic ring opening reaction sequence implemented as a unique and efficient way to generate substituted dienamines in the laboratory.

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**Supporting Information Available:** Additional computational details and data, including coordinates, energies, IRC information, and a movie of a [2 + 2] cycloaddition proceeding in a thermally allowed supra-antara fashion. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) In an attempt to measure the donating ability of the lone pair, proton affinities (PA) for various systems were calculated. No correlation was realized between PAs and the relative barrier height for the electrocyclic ring opening reaction, however. We will discuss this and other related topics in a future report. (b) For another report of the unique directing ability of a N lone pair, see: Zhang, X.; Houk, K. N.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 938−941.

(13) It appears as though the barrier height for electrocyclic ring opening depends more upon $\sigma$ donating effects of the alkyl groups than geometric effects of the aziridine. We will discuss this and other related topics in a future report.