Reaction of *N*-Substituted 1,2,4-Triazoline-3,5-diones and *trans*-Cyclooctene. Direct Observation of an Aziridinium Imide

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Abstract: 4-R-1,2,4-triazoline-3,5-diones (R = Me (MTAD), R = Ph (PTAD)) react stereospecifically with *trans*-cyclooctene (**1**) to give addition products **2**, **3**, and **4**. The products of the reaction and those obtained from nucleophilic trapping of the intermediate with methanol and water suggest an aziridinium imide followed by an open cation that can lead to transannular ring closure and hydride shifts. At −83 °C a *trans*-aziridinium imide intermediate is formed nearly quantitatively and can be directly observed via NMR spectroscopy. An activation energy of 16.2 kcal/mol was measured for the decomposition of the aziridinium imide. A mechanism is proposed for the reaction.

Introduction

The high strain and chirality of *trans*-cyclooctene have attracted considerable attention since it was first prepared by Ziegler and Wilms.[1] Many routes to its synthesis have been described,[2−12] its physical and stereochemical properties have been detailed,[13−26] and its reactivity has been probed[27−39] by various researchers. A variety of reactions with *trans*-cyclooctene have been reported, including its photooxidation by singlet oxygen ($^1O_2$).[40,41]

$^1O_2$ undergoes a variety of reactions with olefins. The most studied of these is the $^1O_2$ ene reaction. It has been widely debated whether this reaction occurs by a concerted[42−46] or stepwise[47−57] mechanism. Product analyses,[41,58−61] deuterium isotope effects,[56,57,62−67] thermodynamic measurements,[54,55,68,69]

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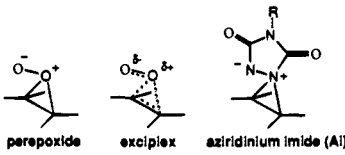

Figure 1. Proposed intermediates in the $^1O_2$ and triazolinedione ene reactions.

and kinetic studies[41] have supported a perepoxide or perepoxide-like exciplex as the reactive intermediate (Figure 1). We recently reported that the unique geometry of *trans*-cyclooctene impedes its ene reaction with singlet oxygen sufficiently to allow trapping of a perepoxide intermediate with triphenyl phosphite.[41] We expected that similar effects on its ene reaction with *N*-substituted 1,2,4-triazoline-3,5-diones (RTAD; R = Me (MTAD); R = Ph (PTAD)) might exist.

Triazolinediones are highly electrophilic reagents which undergo a variety of reactions with alkenes, alcohols, and enolizable ketones.[70,71] The reaction of triazolinediones with olefins has been widely studied,[56,57,72-92] and aziridinium imides (AI's) are generally accepted to be the reactive intermediates (Figure 1). AI's have been directly observed by low-temperature NMR in the [2 + 2] reaction of PTAD with adamantylideneadamantane[89] and the ene reaction of MTAD with *trans*-cycloheptene.[80] Interestingly, the AI formed from *trans*-cycloheptene was the *cis* isomer, requiring isomerization of the cycloheptene ring.[80] In simpler, less structurally unique alkenes, the existence of aziridinium imides has been inferred from isotope effects and product analyses.[56,57,72,73,75,76,78,79,82,83,85,90,92] Studies have also concluded that these three-membered-ring intermediates are capable of opening to form zwitterionic species which undergo carbocationic rearrangements,[77,84,86,88,100,101] and can also be trapped by solvents.[76,86,93]

Both *trans*- and *cis*-cyclooctenes are known to undergo ene reactions with singlet oxygen.[40,94] *cis*-Cyclooctene reacts with $^1O_2$ to give an allylic hydroperoxide as the sole product. *trans*-Cyclooctene, on the other hand, gives many oxidation products including *cis*- and *trans*-cyclooctene oxide, 1,8-octanedial, and an allylic hydroperoxide. The observed rate constant for *trans*-cyclooctene quenching of $^1O_2$ (physical and chemical) was over twice as large as that for the *cis*-cyclooctene reaction. While the *cis*-cyclooctene quenching of $^1O_2$ was purely by chemical reaction, a substantial contribution of physical quenching for the *trans*-alkene was observed. Also, unlike the *cis*-olefin, the rate constant for quenching by *trans*-cyclooctene was solvent dependent. The product analysis and kinetic data supported a unique mechanism for the photooxidation of *trans*-cyclooctene, in which geometrical features of the olefin help to stabilize the perepoxide intermediate.[41]

Whitham and Bridges have reported that *trans*-cyclooctene and PTAD react to give a complex mixture of products which were not identified.[35] We now report that the major product in this reaction occurs via a transannular reaction and have identified it as 2-(4-phenylurazolyl)bicyclo[3.3.0]octane (**2**). Additional products include the normal ene adduct **3** and an unexpected (and previously unprecedented) product of transannular hydride shift, homoene adduct **4**. The primary intermediate *trans*-AI was observed by low-temperature NMR in the reaction of MTAD with *trans*-cyclooctene. A transannular hydride-shifted intermediate could be intercepted by both methanol and water, confirming the intermediacy of carbonium ions in the reaction.

Results and Discussion

The reaction of *trans*-cyclooctene with PTAD in CH_2Cl_2 yields a complex mixture of products (Figure 2). The three major products identified in this reaction are the ene adduct **3** and two unexpected products, a homoene adduct (**4**) and a bicyclic adduct (**2**) (Scheme 1). The relative product yields (Table 1) were found to be temperature dependent by ^1H NMR. At all temperatures, **2** was the major product, while formation of **4** was favored over **3** at lower temperatures and **3** was favored above 0 °C.

The X-ray structure of **2** indicates that there is a *cis* ring fusion and a *trans* relationship between the β bridgehead proton and

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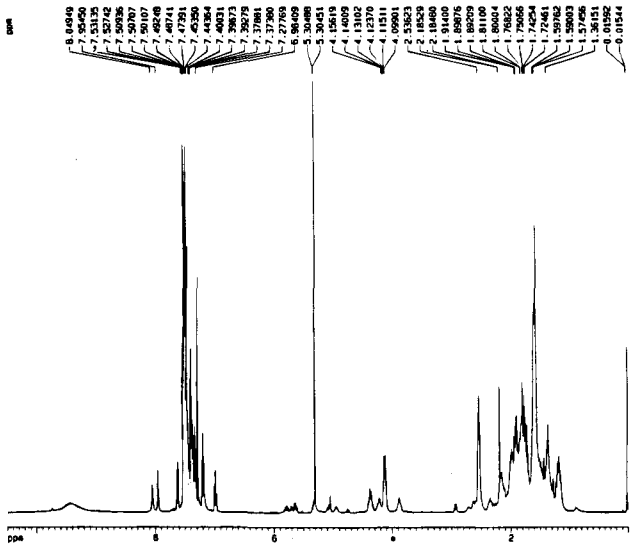


Figure 2. ^{1}H NMR spectrum of the product mixture from the reaction of PTAD with *trans*-cyclooctene in CH_2Cl_2 at −46 °C.

Scheme 1

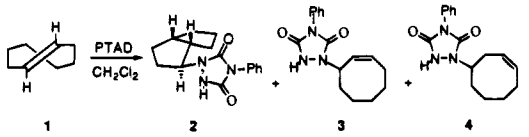
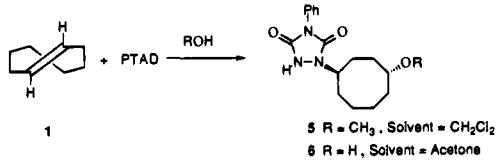


Table 1. Temperature Dependence of PTAD Reaction with **1** in CH_2Cl_2

	relative yield (%)		
reaction temp (°C)	**2**	**3**	**4**
−77	78	2	21
−46	73	8	19
0	62	25	13
22	60	35	5

Scheme 2



the proton α to the urazole. Ene adduct **3** from reaction of PTAD with **1** was identical to the sole product obtained from the reaction of *cis*-cyclooctene with PTAD. The homoene adduct **4** formed in this reaction is the first reported in reactions of PTAD with an olefin.

When methanol is present, the major product becomes the hydride-shifted methanol adduct **5**. Compounds **2**, **3**, and **4** were also present in much lower yields. Reaction of **1** and PTAD in reagent grade acetone containing 1% H_2O yields the analogous 1,4 water adduct **6** as the major product (Scheme 2). The structure of **6** was obtained by X-ray crystallography; the substituents on the cyclooctane ring are *trans*. While minor amounts of **3** and **4** were obtained, the reaction in acetone/H_2O produced no bicyclic adduct **2**.

At −83 °C, the reaction of **1** and MTAD can be followed by low-temperature NMR, and the formation of an aziridinium imide was found to be nearly quantitative. The ^{1}H and ^{13}C spectra (Figures 3 and 4, respectively) of the intermediate show it is the *trans*-fused isomer. The presence of two distinct resonances for the aziridinium ring protons in the ^{1}H NMR requires an asymmetric intermediate. The *trans*-fused aziridinium imide should have 11 resonances in the ^{13}C spectrum and the *cis* isomer **7**; the proton-decoupled ^{13}C NMR spectrum (Figure 4) shows 11 resonances, consistent with *trans*-fused AI. The gated decoupled spectrum of the intermediate gave J_{C-H} values for the aziridinium ring carbons at 64.7 and 59.1 ppm (Figure 4, inset) of 175.7 and 165.4 Hz. These values are consistent with an aziridine ring, and similar to that of the *cis*-fused aziridinium imide from *trans*-cycloheptene and MTAD.[80] The coupling constants differ by 10.3 Hz, suggesting a difference in the hybridization of the two aziridine carbons.

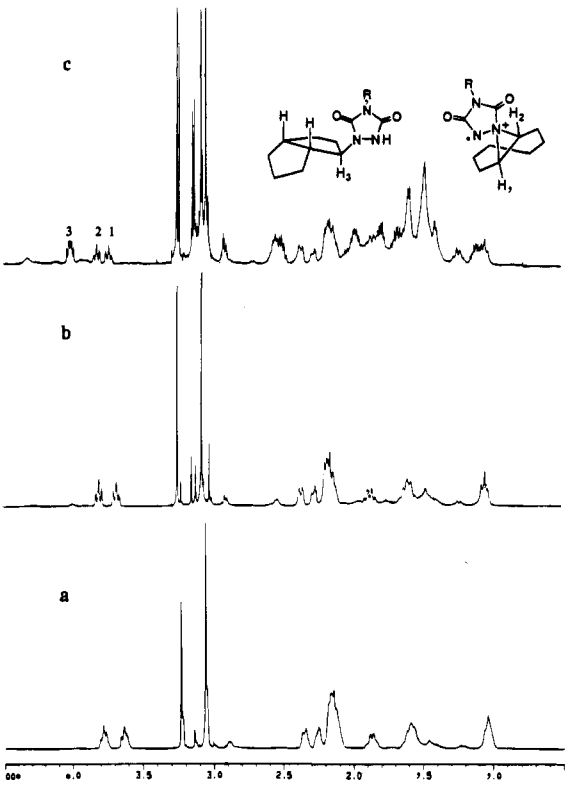


Figure 3. ^{1}H NMR spectra of the *trans*-cyclooctene aziridinium imide in CD_2Cl_2 (500 MHz): (a) at −83 °C, (b) after 10 min at −53 °C, (c) after 60 min at −53 °C.

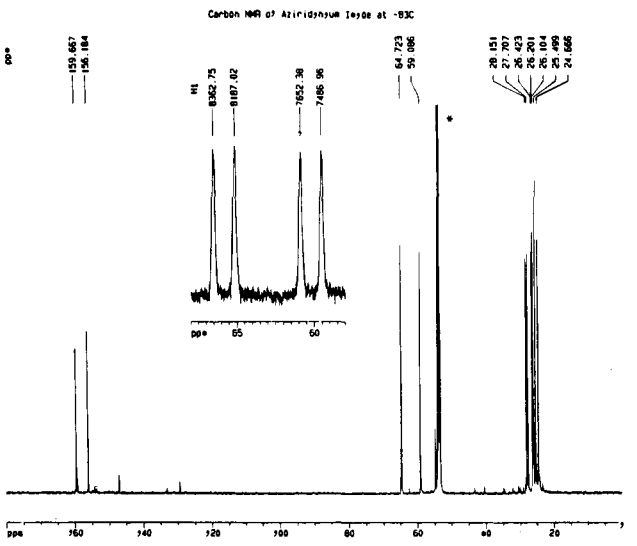


Figure 4. Proton-decoupled and gated decoupled (inset) ^{13}C NMR spectra of *trans*-cyclooctene aziridinium imide at −83 °C in CD_2Cl_2 (125.8 MHz). The solvent is denoted by an asterisk.

The double quantum filtered phase-sensitive COSY and phase-sensitive NOESY spectra (Figure 5) further support the *trans*-fused AI structure and allow assignment of each of the

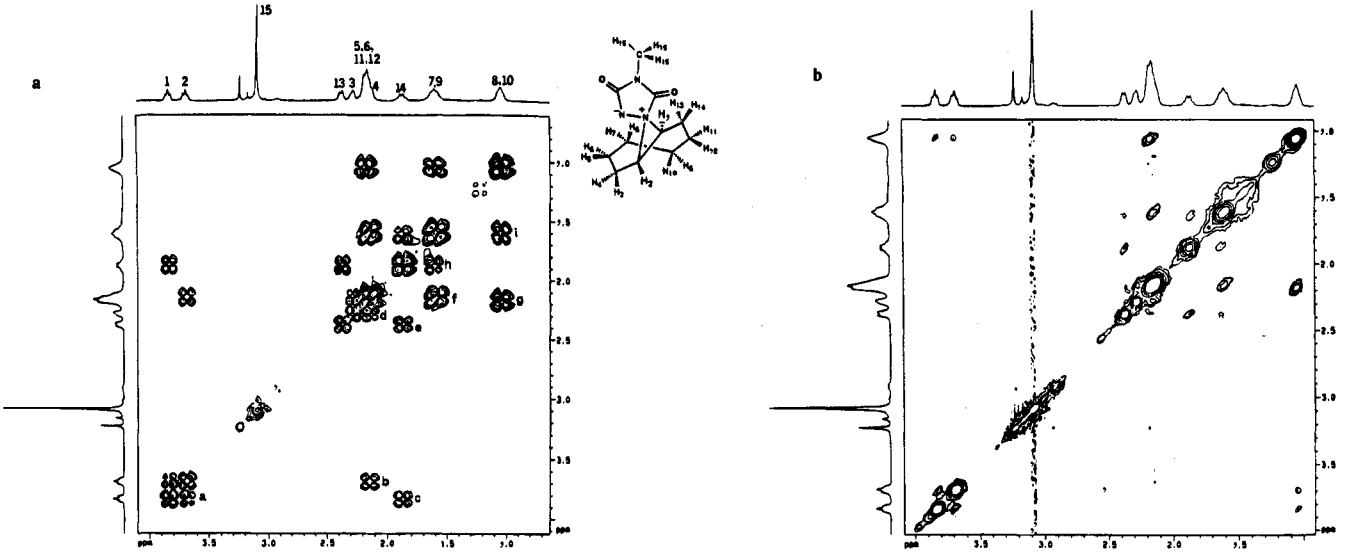


Figure 5. (a) Double quantum filtered phase-sensitive COSY of the *trans*-cyclooctene aziridinium imide. The cross peaks are assigned as follows: (a) J_{1-2}, (b) J_{2-4}, (c) J_{1-14}, (d) J_{4-3}, (e) J_{13-14}, (f) J_{7-5}, J_{7-6}, J_{9-11}, J_{9-12}, (g) J_{8-5}, J_{8-6}, J_{10-11}, J_{10-12}, (h) J_{9-14}, (i) J_{8-9}, J_{7-10}. (b) Phase-sensitive NOESY of the *trans*-cyclooctene aziridinium imide. Both were taken at −83 °C in CD_2Cl_2 (500 MHz).

proton resonances. Many of the expected cross peaks are observed; however, weak coupling between certain protons (e.g., J_{1-13}, J_{2-3}) may have not have been observable. Cross peak **h** (Figure 5a) indicates strong long-range coupling between H_9 and H_{14}. This probably arises from the "W-conformation" [95] of the protons.

Of particular interest are the NOE's between the aziridinium ring protons (H_1 and H_2) and the transannular protons (H_8 and H_{10}). In the MM3-minimized structure[96,97] of **1**, the distance between the vinyl protons and the cross-ring protons is only 2.50 Å . Since a *trans*-fused aziridinium imide would be expected to have a rigid structure similar to **1**, an NOE between these protons is expected.

This is the first reported observation of an unisomerized aziridinium imide intermediate in the ene reaction of a triazoline-3,5-dione. The reaction is extremely fast. There is an immediate color change even at temperatures as low as −100 °C from the fluorescent pink of the MTAD to a bright orange for the intermediate. NMR analysis revealed the intermediate to be very stable at −83 °C, showing practically no decomposition after more than 5 h. At higher temperatures, disappearance of the aziridinium imide and formation of products can be followed by ^{1}H NMR. Rate constants were obtained for conversion of the intermediate to products by monitoring the decay of the AI over time. The reaction temperature was varied from −60 to −43 °C, and an activation energy of 16.2 kcal/mol was obtained from an Arrhenius plot (Figure 6). This E_a is only 2.8 kcal/mol larger than that for the breakdown of the cycloheptene aziridinium imide.[80]

The bicyclic adduct **2**, homoene adduct **4**, and trapping adducts **5** and **6** suggest that carbocations are formed in the reaction of **1** with PTAD. Cope and co-workers proposed carbonium ion intermediates in the oxidation of *cis*- and *trans*-cyclooctene with peroxyformic acid to give various diols and hydroxyalkenes.[27,28,98] However, Prelog et al. found only small

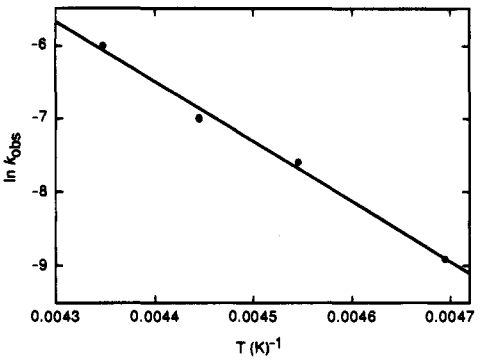


Figure 6. Arrhenius plot of k_{obs} for **AI** conversion to products.

isotope effects from peroxy acid oxidations in deuterium-labeled cyclooctenes. This, along with the stereochemistry of the products argued against C−H bond breaking in the rate-determining step and ruled out concerted processes and long-lived carbonium ions.[99] Trapping of aziridinium imides in nucleophilic solvents is known to give stereospecific *trans* addition products.[76,86,93] These trapping experiments yield 1,4-difunctional adducts similar to those found by Cope and Prelog and require a hydride shift in an intermediate, giving a carbocation at the transannular carbon.

A likely mechanism for the reaction of RTAD with *trans*-cyclooctene is proposed based on the transannular attack products (Scheme 3). The AI **7** is formed quickly and is stable at low temperatures. Because of the poor dihedral angles for proton abstraction to form the ene adduct **3**, the intermediate may relieve strain by opening the aziridine ring to give zwitterionic intermediate **8**. The less constrained **8** can then abstract an allylic hydrogen to produce ene adduct **3** or give transannular attack on the C−H bond to form bicyclic adduct **2**. Analogous products of rearrangement and closure have been reported by Prinzbach et al. in polycyclic systems.[100,101]

The fact that **2** is the major product suggests that **8** is incapable of efficient allylic proton abstraction to give the ene product. The remainder of the products can result from

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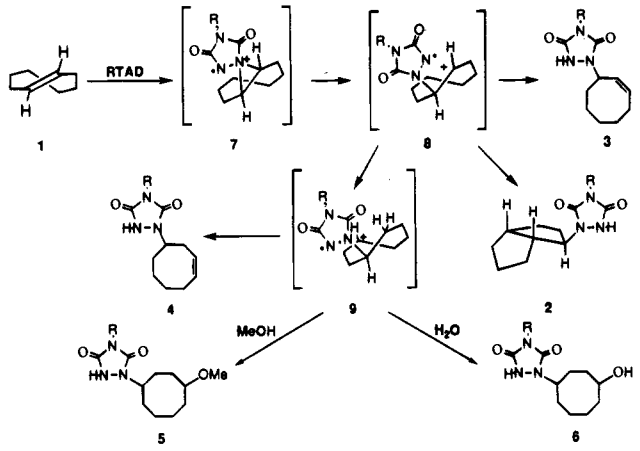
Scheme 3



carbocation **9**, formed via a 1,5-hydride shift. This intermediate can be trapped with methanol and water to give **5** and **6**, respectively, or lose a proton to give homoene adduct **4**. Intermediate **9** must be sufficiently long-lived to undergo nucleophilic trapping. While stereospecific product formation usually excludes the intermediacy of carbocations, a carbocation formed from the twist geometry of the *trans*-cyclooctene ring would presumably be formed in the same geometry as the parent alkene and thus present only one face to attack, leading to stereospecific product formation. Concerted hydride shift and nucleophile addition is also a possibility, but not required.

Conclusion

The unusual geometry of *trans*-cyclooctene alters the course of its ene reaction with MTAD and PTAD. The expected ene product is suppressed in favor of a bicyclic adduct formed from a transannular attack. Nucleophilic trapping studies and an unexpected homoene adduct support the intermediacy of carbonium species in the reaction. An aziridinium imide is also an intermediate in this reaction as evidenced by its direct observation using low-temperature NMR. The stability of the aziridinium imide at low temperatures along with its high efficiency of formation will allow studies of its properties and reactivity.

Experimental Section

General Information. MTAD, PTAD, $CDCl_2$, $CDCl_3$, acetone, DMSO-d_6, and acetone-d_6 were used as purchased from Aldrich Chemical Co. Methylene chloride was distilled over CaH_2 prior to use. *trans*-Cyclooctene was prepared by a published procedure.[7] *cis*-Cyclooctene as obtained contained 5% cyclooctane. NMR spectra (δ, TMS) were taken on a Bruker AM360 or ARX500 MHz NMR spectrometer, in $CDCl_3$ except as noted. IR analyses were performed in KBr on a Nicolet 205 FT-IR spectrometer.

2-(4-Phenylurazolyl)bicyclo[3.3.0]octane (2). A 0.104 g (9.43×10^{-4} mol) sample of *trans*-cyclooctene in CH_2Cl_2 reacted with a 0.165 g (9.43×10^{-4}) of PTAD solution at −77 °C. The characteristic red color of PTAD in solution rapidly disappeared, and the reaction was allowed to proceed for 6 h. Removal of the solvent gave 0.135 g of a flaky yellow solid. SiO_2 flash chromatography of the product mixture gave **2**. ^{1}H NMR (500 MHz): δ 8.68 (br s, 1H), 7.48 (m, 4H), 7.38 (m, 1H), 4.13 (dt, 1H), 2.53 (m, 2H), 2.00−1.20 (m, 10H). ^{13}C NMR (90.556 MHz): δ 154.1 (s), 152.5 (s), 131.3 (s), 3.0 (d), 128.1 (d), 125.5 (d), 64.1 (d), 45.7 (d), 42.0 (d), 33.3 (t), 31.6 (t), 31.0 (t), 30.4 (t), 25.2 (t). IR (KBr): 3440, 3062, 2942, 2869, 1772, 1695, 1493, 1433, 1128, 766, 732, 680, 502 cm^{-1}. MS (EI): *m/z* calcd 285.1477, exptl 285.1468.

3-(4-Phenylurazolyl)cyclooctene (3). A solution of 0.010 g (0.172 mmol) of *cis*-cyclooctene and a solution of 0.030 g (0.172 mmol) of PTAD in CH_2Cl_2 gave **3** as the only product. The chemical shifts and splitting patterns of the resonances of the product formed in this reaction were among those seen in the complex product mixture of the PTAD/*trans*-cyclooctene reaction. ^{1}H NMR (500 MHz): δ 8.89 (br s, 1H), 7.48 (m, 4H), 7.38 (tt, 1H), 5.81 (m 1H), 5.61 (m, 1H), 5.08 (m, 1H), 2.27 (m, 1H), 2.15 (m, 1H), 1.86 (m, 1H), 1.64 (br m, 9H), 1.37 (m, 1H). ^{13}C NMR (125.8 MHz): δ 154.51 (s), 152.78 (s), 132.2 (d), 131.17 (s), 129.08 (d), 128.21 (d), 125.67 (d), 125.54 (d), 55.17 (d), 33.13 (t), 28.71 (t), 26.42 (t), 25.93 (t), 24.11 (t). MS (EI): *m/z* calcd 285.1477, exptl 285.1472.

4-(4-Phenylurazolyl)cyclooctene (4). A solution of 0.0715 g (0.649 mmol) of *trans*-cyclooctene and a solution of 0.114 g (0.651 mmol) of PTAD in acetone reacted at −77 °C for 24 h. **4** was extracted with $CHCl_3$ and isolated using SiO_2 flash column chromatography. ^{1}H NMR (500 MHz): δ 8.67 (br s, 1H), 7.49 (m, 4H), 7.38 (m 1H), 5.72 (m 1H), 5.65 (m, 1H), 4.22 (m, 1H), 2.35 (m, 1H), 2.17 (m, 4H), 1.80 (m, 4H), 1.61 (m, 1H), 1.56 (m, 2H). ^{13}C NMR (125.8 MHz): δ 154.36 (s), 152.29 (s), 132.2 (d), 131.22 (s), 129.09 (d), 128.84 (d), 128.17 (d), 125.48 (d), 57.13 (d), 32.46 (t), 31.77 (t), 26.16 (t), 25.68 (t), 22.77 (t). MS (EI): *m/z* calcd 285.1477, exptl 285.1474.

***trans*-4-(4-Phenylurazolyl)methoxycyclooctane (5).** A CH_2Cl_2 solution of 0.300 g (2.722 mmol) of **1** and 0.174 g (5.44 mmol) of methanol was added to a solution of 0.480 g (2.741 mmol) of PTAD at −77 °C. The reaction mixture contained **2**, **3**, and **4** along with the desired product **5**, which was separated by SiO_2 flash column chromatography. ^{1}H NMR (360 MHz): δ 9.5 (br s, 1H), 7.47 (m, 5H), 4.14 (br m, 1H), 3.37 (br m 1H), 3.26 (s, 3H), 2.58−1.20 (br m, 12H). ^{13}C NMR (90.556 MHz): δ 154.23 (s), 151.86 (s), 131.29 (s), 129.08 (d), 128.18 (d), 125.55 (d), 79.99 (d), 57.72 (d), 55.96 (q), 29.71 (t), 29.58 (t), 28.35 (t), 26.76 (t), 25.14 (t), 22.13 (t). MS (EI): *m/z* calcd 317.1739, exptl 317.1749.

***trans*-4-(4-Phenylurazolyl)cyclooctanol (6).** A 0.128 g (1.16×10^{-3} mol) sample of *trans*-cyclooctene and 0.203 g of PTAD were reacted in a similar fashion to **2** except that acetone was used as the solvent. A 0.238 g sample of crude product was obtained. The flaky yellow solid was washed several times with $CHCl_3$ and then recrystallized from acetone. ^{1}H NMR (360 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.44 (m, 5H), 4.44 (s, 1H), 4.08 (br s 1H), 3.67 (br s, 1H), 1.86-1.33 (br m, 12H). ^{1}H NMR (360 MHz, acetone-d_6): δ 7.48 (d, 4H), 7.40 (q, 1H), 6.82 (br s, 1H), 4.23 (tt, 1H), 3.89 (tt, 1H), 2.12−1.27 (br m, 13H). ^{13}C NMR (90.556 MHz,DMSO-d_6): δ 152.9 (s), 152.1 (s), 131.9 (s), 128.8 (d), 127.8 (d), 126.1 (d), 69.4 (d), 57.4 (d), 33.5 (t), 31.7 (t), 29.4 (t), 26.3 (t), 25.2 (t), 22.0 (t). ^{13}C NMR (90.556 MHz, acetone-d_6): δ 154.6 (s), 154.1 (s), 133.7 (s), 129.6 (d), 128.4 (d), 126.6 (d), 71.5 (d), 59.4 (d), 35.2 (t), 33.5 (t), 30.8 (t), 27.6 (t), 26.6 (t), 23.4 (t). IR (KBr): 3410, 3080, 2940, 1795, 1765, 1705, 1510, 1550, 1415, 1278, 1257, 1172, 1119, 1028, 985, 910, 763, 740, 700, 682, 640, 502 cm^{-1}. MS (EI): *m/z* calcd 303.1583, exptl 303.1588.

Aziridinium Imide 7. A 0.0309 g (0.280 mmol) sample of **1** was diluted with CD_2Cl_2 in a 5 mm NMR tube and precooled in a dry ice/diethyl ether bath (−100 °C). A 0.0478 g (0.420 mmol) sample of MTAD was dissolved in CD_2Cl_2 and precooled before being transferred to the NMR tube. An immediate color change from pink to orange was observed. The NMR tube was then placed in the spectrometer probe at −83 °C. All ^{1}H NMR spectra (1D, COSY, NOESY) were taken at 500 MHz while ^{13}C spectra (PDC, GDC, DEPT) were acquired at 125.77 MHz; all spectra were taken in CD_2Cl_2. ^{1}H NMR: δ 3.72 (m, 1H), 3.58 (m, 1H), 2.98 (s, 3H), 2.26 (br d, 1H), 2.17 (br d, 1H), 2.05 (br m, 5H), 1.76 (br m, 1H), 1.49 (br t, 2H), 0.94 (br s, 2H). ^{13}C NMR: 159.67 (s), 156.18 (s), 64.72 (d, J_{C-H} = 175.7 Hz), 59.09 (d, J_{C-H} = 165.4 Hz), 28.15 (t), 27.71 (t), 26.42 (t), 26.20 (t), 26.10 (t), 25.50 (q), 24.67 (t).

Kinetic Data. The aziridinium imide was formed and observed in a 500 MHz NMR spectrometer as described above at −83 °C. For each rate constant (k_{obs}) determination, the probe was warmed to the appropriate temperature and the decay of the aziridinium imide was measured by integration of the aziridinium ring protons at 3.72 and 3.58 ppm. Data acquisition was performed at various intervals. The total time for each acquisition was 20 s for four scans. The data were

fit to the integrated first-order rate equation (eq 1).[102] The energy of

$$k_{obs} = \frac{2.303}{t} \log \frac{AI^{\circ}}{AI} \quad (1)$$

activation was obtained by plotting the natural logarithm of k_{obs} versus the reciprocal of the reaction temperature according to eq 2.

$$\ln k_{obs} = \ln A - E_a/RT \quad (2)$$

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Supporting Information Available: Figures showing the ^{1}H NMR, ^{13}C NMR, FT-IR, and mass spectra for compounds **2**–**6** and X-ray crystal structures of **2** and **6** (46 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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