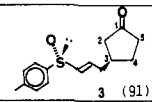
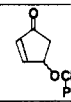
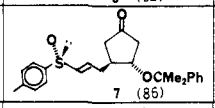
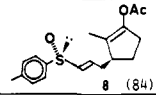
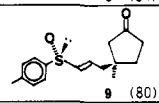
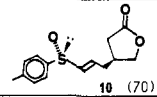
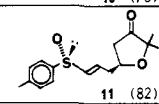
**Table I.** Yields and Optical Purities from the Reactions of the Anion Derived from (*R*)-Allyl *p*-Tolyl Sulfoxide and Various Enones

| Entry | Enones | Product (% yield) | Optical Purity % ee at Carbon 3 |
|---|---|---|---|
| 1 |  |  3 (91) | 96 |
| 2 |  |  7 (86) | 92 |
| 3 |  |  8 (84) | 95 |
| 4 |  |  9 (80) | 90 |
| 5 |  |  10 (70) | 95 |
| 6 |  |  11 (82) | 70 |

[a] The resulting enolate ion was treated with acetyl chloride at −78 °C.

of $LiEt_3BH$[20] in toluene (1 mL/0.12 g) at 90 °C for 18 h, 72% yield.

Deprotection of **24** with 1 equiv of TsOH in THF–MeOH–$H_2O$ (2:3.5:1) at room temperature for 1 h gave 90% yield of the nor ketone **25** ($[\alpha]_D^{22}$ +81°, *c* 0.2 in hexane). Wittig reaction of **25** with 2 equiv of methylenetriphenylphosphorane (derived from $CH_3P^+Ph_3Br^-$ and sodium *tert*-amylate[21]) in refluxing toluene for 2 h afforded (+)-hirsutene (**1**) in 80% yield ($[\alpha]_D^{22}$ +48°, *c* 0.35 in pentane). The spectral data (IR, $^1H$ and $^{13}C$ NMRs, and mass) of **25** and **1** were completely identical with those of the authentic materials.[22]

In summary, the asymmetric induction reaction of chiral sulfinylallyl anion with enones provides a facile enantioselective synthesis of substituted cyclic ketones (70–96% ee). The total synthesis of (+)-hirsutene is stereocontrolled and should prove valuable in analogue construction. The cyclization and isopropylsulfonate displacement reactions discovered in the context should be applicable to other important syntheses.[23] Further results on the asymmetric synthesis using substituted chiral sulfinylallyl anions and enones and the application of this method in natural-product synthesis will be discussed in subsequent papers.

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**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR data for compounds **1** and **12–25** (27 pages). Ordering information is given on any current masthead page.

(21) Short R. P.; Ravol, J. M.; Ranu, B. C.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453–4461.

(22) The IR, NMR ($^1H$, $^{13}C$), and mass spectra of **25** and **1** were provided by Professor Tomas Hudlicky of Virginia Polytechnic Institute and State Univesity and Professor Kuniaki Tatsuta of Keio University.

(23) Experimental procedures will be provided in a full paper to be published at a later date.

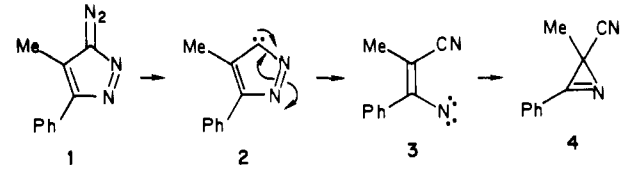
## Electronic and Structural Requirements for Ring Opening of Azacyclopentadiene Carbenes

Daniel J. Pasto* and Jeremiah P. Freeman*

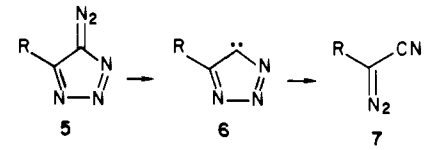
*Department of Chemistry, University of Notre Dame Notre Dame, Indiana 46556*

*Received December 17, 1984*

The chemistry of substituted azolylidenes, derivatives of cyclopentadienylidene containing one or more ring nitrogen atoms,[1] have been extensively studied by Shechter and co-workers.[1] These studies have revealed that these carbene species undergo addition, insertion, and substitution reactions, and, perhaps the most interesting, ring opening to form a nitrene. For example, the thermolysis of the 4,5-disubstituted 3-diazopyrazole **1** results in the formation of **4**.[2] The mechanism for formation of **4** has been

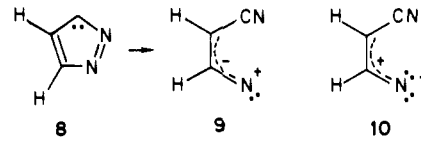


proposed to proceed via ring opening of **2** (as shown by the arrows) to form the intermediate nitrene **3** which closes to **4**.[2] In an apparently related type of reaction the thermolysis of **5** produces an intermediate represented as **6** which undergoes ring opening to the substituted cyanodiazomethane **7**, which in turn undergoes



further reaction under the reaction conditions.[1] In a theoretical study of the structure and reactivity of azacyclopentadienyl reactive intermediates (cations, free radicals, anions, and carbenes),[3] we have discovered that the ring opening occurs spontaneously from only one of the many possible electronic states of the azolylidenes *and* when there are at least two nitrogen atoms present in the 2- and 3-positions.[4]

There are several singlet and triplet, closed- and open-shell electronic configurations possible for each azolylidene. Preliminary calculations on the closed-shell, six-$\pi$-electron singlet state of **8** indicated that a cyclic structure did not represent a local energy minimum on the potential energy surface.[5] Geometry optimization calculations at the 3-21G basis level[6] resulted in a continual lengthening of the N2–N3 bond and the shortening of the C1–N2 bond, ultimately resulting in the six-$\pi$-electron structure **9**.[7] The



geometry optimized structural parameters of **9** are given in Figure 1. The alternative four-$\pi$-electron structure **10** (Figure 1) is

(1) Hui, H. K.-W.; Shechter, H. *Tetrahedron Lett.* **1982**, *49*, 5115 and references cited therein.

(2) Magee, W. L.; Shechter, H. *J. Am. Chem. Soc.* **1977**, *99*, 633.

(3) Pasto, D. J.; Freeman, J. P.; Fettes, M. K., investigation in progress.

(4) It is conceivable that other electronic states may undergo similar ring openings; however, the present studies have focused only on defining minimum-energy structures and not energy surfaces for reactions.

(5) A number of starting geometries were selected on the basis of optimized structures of other six-$\pi$-electron structures which were calculated to be energy minima.

(6) Calculations were carried out by using the GAUSSIAN80 package of programs.

(7) The six $\pi$-electrons include the four of the aza-allyl anion and nitrile function and not the in-plane $\pi$-electrons of the nitrile function.

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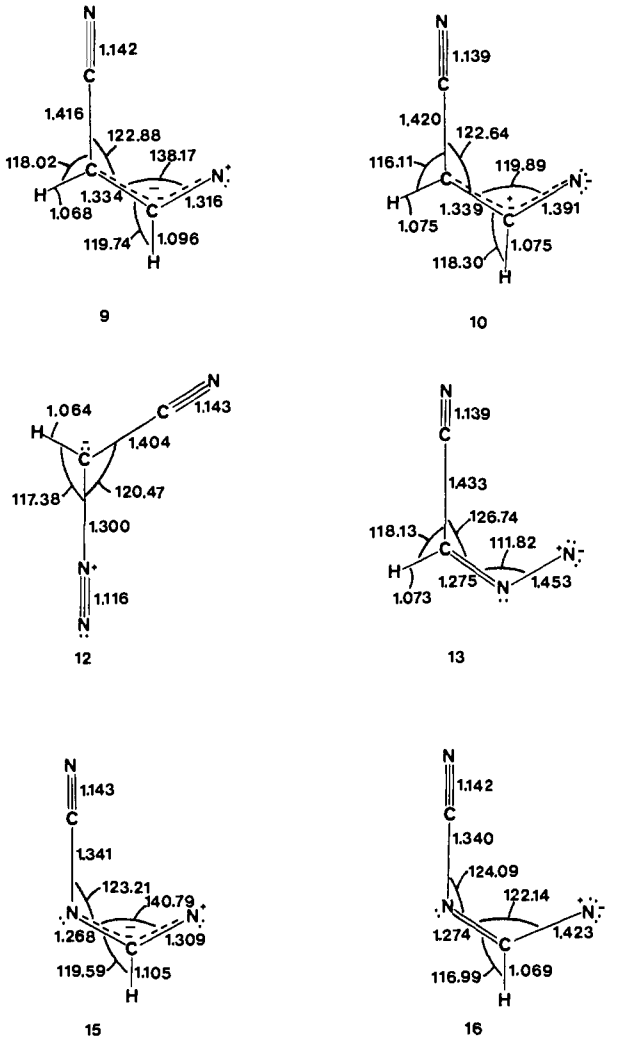


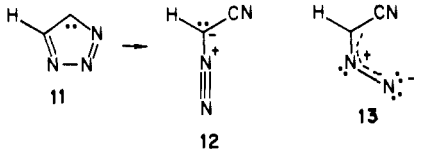

Figure 1.

Table I. 3-21G Optimized Energies of Open Carbenic Species

| struct | $E$, au | struct | $E$, au |
|---|---|---|---|
| **9** | −222.240 89 | **13** | −238.092 90 |
| **10** | −222.230 61 | **15** | −238.125 67 |
| **12** | −238.213 94 | **16** | −238.104 44 |

higher in energy than the six-$\pi$-electron structure **9** (see Table I).[8]

Calculations on the six-$\pi$-electron, singlet **11** also result in the spontaneous opening to the cyanodiazomethane structure **12**. The

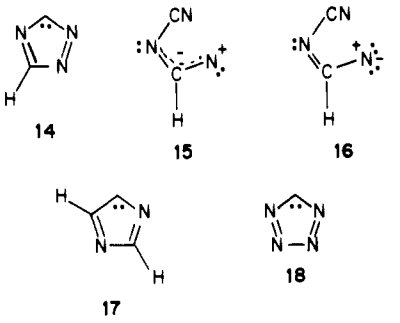



alternative four-$\pi$-electron open structure **13** possesses a different geometry (Figure 1) and is considerably higher in energy (75.8 kcal per mol at the 3-21G basis level, see Table I).

Of the other possible azolylidene species, only the 2,3,5-triaza six-$\pi$-electron species **14** undergoes spontaneous ring opening to **15**. (As in the other cases, the four $\pi$-electron structure **16** is higher in energy). 2,4-Diazolyidene (**17**) does not spontaneously undergo ring opening, which is consistent with experimental observations.[9]

(8) Reaction coordinate calculations on the possible ring closure of **9** and **10** to **4** have not yet been attempted, and, thus, it is not known which electronic state closes more favorably to **4**.

(9) Kang, U. G.; Shechter, H. *J. Am. Chem. Soc.* **1978**, *100*, 651.




Interestingly, the 2,3,4,5-tetraza species **18** does not undergo spontaneous ring opening. Experimentally, **17** is observed to undergo fragmentation to generate a free carbon atom.[10,11]

In summary, the ring opening of an azolylidene occurs spontaneously from the six-$\pi$-electron carbene species and only when there are nitrogen atoms in the 2- and 3-positions.

An analysis of the forces indicate a repulsion between N2 and N3 and an attraction between C1 and N2. The repulsion between N2 and N3 appears to arise from a repulsive nonbonded pair interaction. These calculations support the mechanistic proposals put forth earlier and predict the ring opening of **14** not previously observed.

**Acknowledgment.** We thank the Computing Center of the University of Notre Dame for computer time and Dr. Daniel Chipman of the Radiation Laboratory of the University of Notre Dame for helpful discussions.

(10) Dyer, S. F.; Shevlin, P. B. *J. Am. Chem. Soc.* **1979**, *101*, 1303.

(11) Our present calculations do not indicate which electronic state of **14** undergoes this fragmentation reaction. All electronic states thus far calculated give rise to local minimum energy structures. Reaction coordinate calculations will be carried out in order to gain this information.

## Stereospecific Reaction of 3-Methoxy-4-chloro-7-aminoisocoumarin with Crystalline Porcine Pancreatic Elastase

Edgar F. Meyer, Jr.,* Leonard G. Presta, and R. Radhakrishnan

*Department of Biochemistry and Biophysics*
*Texas A&M University*
*College Station, Texas 77843*
*Received October 26, 1984*

There has been considerable interest in designing small molecules that will inhibit elastases because these proteolytic enzymes have been associated with pancreatitis,[1] emphysema[2] and arthritis.[3] Recently, a variety of nonpeptide inhibitors of elastases, and other serine proteases, have been investigated, including *N*-acylsaccharins,[4] isocoumarins,[5] benzoxazinones,[6,7] sulfonyl fluorides,[8] and 5-butyl-3*H*-1,3-oxazine-2,6-dione.[9] The mode of binding and mechanism of inhibition of these compounds have been previously

(1) Geokas, M. C.; Rinderknecht, H.; Swanson, V.; Haverback, B. J. *Lab. Invest.* **1968**, *19*, 235–239.

(2) Janoff, A. "Molecular Basis of Biological Degradative Processes"; Berlin, R. D., Herrman, H., Lepow, I. H., Tanzer, J. M., Eds.; Academic Press: New York, 1973; pp 225–260.

(3) Janoff, A. "Neutral Proteinases of Human Polymorphonuclear Leukocytes"; Havemann, K., Janoff, A., Eds.; Urban and Schwartzenberg: Munich, 1973; pp 390–417.

(4) Zimmerman, M.; Morman, H.; Mulvey, D.; Jones, H.; Frankshun, R.; Ashe, B. M. *J. Biol. Chem.* **1980**, *255*, 9848–9851.

(5) Harper, J. W.; Hemmi, K.; Powers, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6518–6520.

(6) Teshima, T.; Griffin, J. C.; Powers, J. C. *J. Biol. Chem.* **1982**, 257, 5085–5091.

(7) Hedstrom, L.; Moorman, A. R.; Dobbs, J.; Abeles, R. H. *Biochemistry* **1984**, *23*, 1753–1759.

(8) Yoshimura, T.; Barker, L. N.; Powers, J. C. *J. Biol. Chem.* **1982**, *257*, 5077–5084.

(9) Wiedmann, B.; Abeles, R. H. *Biochemistry* **1984**, *23*, 2373–2376.

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