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ON THE STEREOSELECTIVITY OF THE INTRAMOLECULAR DIOXENONE PHOTOCYCLOADDITION[¶]

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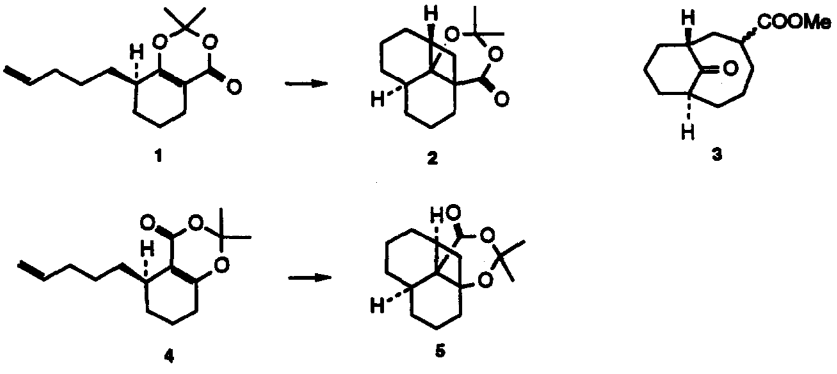
Abstract: The stereoselectivity of the intramolecular photocycloaddition of dioxenone and enone substrates is compared. A mechanistic scheme that is consistent with the striking differences in the observed stereoselectivities is presented.

The intramolecular dioxenone photocycloaddition reaction[3] provides unique approaches to the synthesis of compounds that cannot be otherwise prepared.[4] We have reported that irradiation of 1 leads to the exclusive formation of 2, which on acid-catalyzed fragmentation gives the "inside-outside" bicycloalkanone, 3,[5] with a *trans* intrabridgehead stereochemical relationship.[6] However, irradiation of 4, in which the dioxenone chromophore has been transposed, leads to the exclusive formation of the cis-fused photoadduct 5.[7] Similar stereochemical results have been observed with more complex dioxenone photosubstrates during the course of taxane synthetic studies in our laboratory.[8] We report herein the results of our preliminary studies on 1) the origins of the differences between the stereoselectivities in the photocycloadditions of 1 and 4; and 2) the identification of structural features of the dioxenone chromophore that lead to these striking differences.

Scheme I

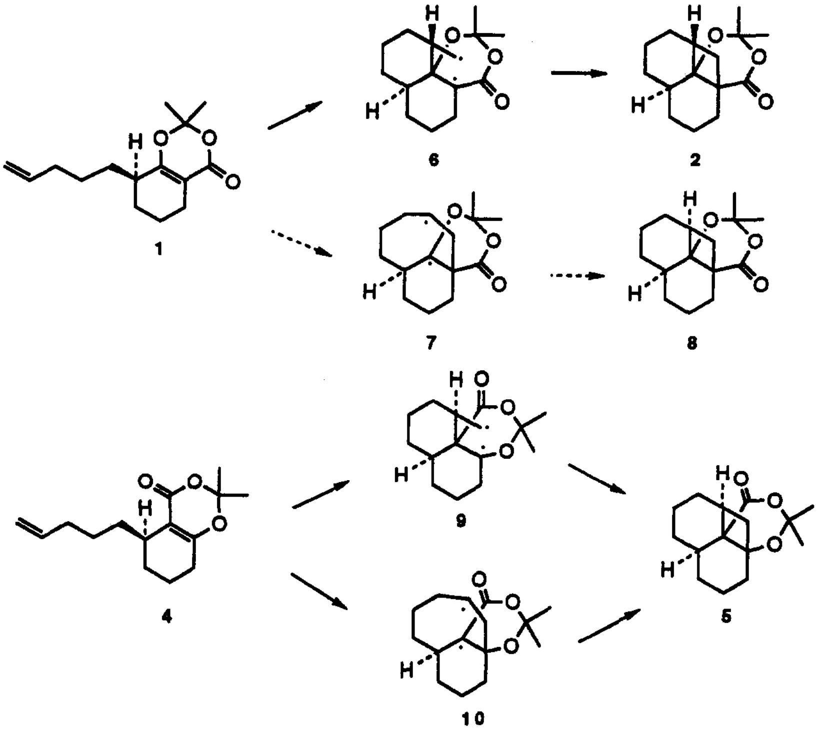


The triplet-sensitized intramolecular dioxenone photocycloaddition of 1 can occur via two isomeric biradical intermediates, 6 (1,6-closure via β-carbon of dioxenone) and 7 (1,8-closure via the α-carbon), as illustrated in Scheme II. However, the exclusive formation of the trans-fused photoadduct 2, which is ca. 6 kcal/mol less stable than the cis-fused photoadduct 8, is consistent only with the intermediacy of 6. Conformational relaxation of the alternative eight-membered ring diyl intermediate 7 would be expected to lead to the formation of the more stable cis-photoadduct 8. The formation of the more stable cis-fused photoadduct 5

[¶] Dedicated to the memory of Professor Gerhard L. Closs, a colleague whose penetrating insights and boundless enthusiasm and curiosity about science have enriched our lives.

on irradiation of the isomeric dioxenone **4** could arise from closure of either diyl **9** or **10**, as shown in Scheme II, as formation of the initial bond to either the α- or β-position of the dioxenone could lead to the cis-fused photoadduct **5**.

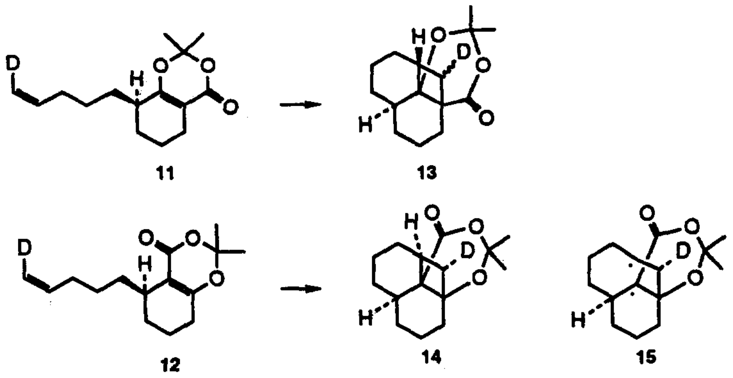
Scheme II



To determine whether the order of bond formation was in fact the same for **1** and **4**, the deuterated photosubstrates, **11** and **12**, were prepared in analogy to the previously reported syntheses of **1**^{5} and **4**,^{7} starting from (Z)-1-deuterio-5-iodo-1-pentene (Scheme III). Irradiation of **11** (8×10^{-4} M in 10% acetone/acetonitrile, 450 W Hg lamp, Pyrex filter, 0°C) led to the formation of **13**, as a 1:1 mixture of epimers at the deuterium-substituted carbon. To determine whether Z-**11** was undergoing double bond isomerization during the course of the photocycloaddition, either through reversal of the intermediate triplet diyl^9 or by energy transfer from the enone to the alkene, the reaction mixture was analyzed by ^{1}H NMR during the course of the irradiation at 30% and 60% conversion. No isomerization of the photosubstrate geometry was observed during the course of the reaction.

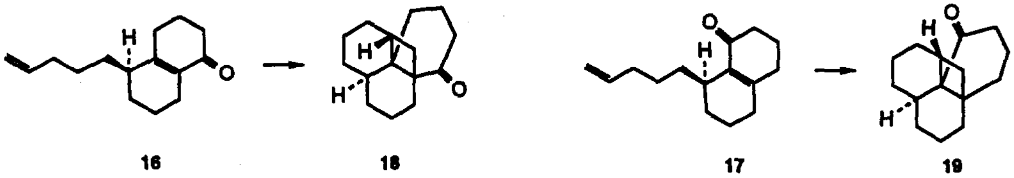
In contrast to the results obtained with **11**, photocycloaddition of the isomeric deuterated substrate **12** under identical reaction conditions led to the formation of a single deuterated product, **14**. The formation of **14** as a single stereoisomer is consistent only with the intermediacy of the eight-membered ring diyl, as shown in **15**. A six-membered diyl intermediate would have led to deuterium scrambling in the formation of **14**.

Scheme III



To determine the role of the dioxenone heteroatoms on the observed reversal in the order of bond formation for the isomeric dioxenone photosubstrates, the irradiation of the isomeric enones **16** and **17** was examined (Scheme IV). Photoaddition of **16** led to the exclusive formation of trans-**18**, the stereochemistry of which was determined by high-field ^{1}H NMR.[10] In contrast to the different stereochemical outcomes observed on irradiation of dioxenones **1** and **4**, photocycloaddition of the isomeric enone substrate **17** also led to the exclusive formation of a trans-fused photoadduct, **19**.

Scheme IV



The β-oxygen of the dioxenone chromophore appears to be the critical factor in determining the order of bond formation and therefore the stereoselectivity of the cycloadditions of **1** and **4**. We propose that, in the dioxenone photocycloadditions, the first bond is formed from the oxygen-substituted dioxenone carbon (C-β) to give diyls **6** and **10** (Scheme II), *whether a six- or an eight-membered ring intermediate is formed.* With the enone photosubstrates, **16** and **17**, which lack the β-oxygen substitution in the chromophore, the stereochemical results are consistent with formation of six-membered ring biradical intermediates in both cases, as the formation of trans-fused photoadducts is observed with both enones. The order of bond formation in the enone photocycloadditions appears to be very dependent on the ring size of the intermediate diyl, as Becker has recently reported that both 1,5- and 1,7-closures are observed in a related system.[11]

These studies establish that the regiochemical discrimination observed in the initial bond formation in the intramolecular dioxenone photocycloaddition reactions is exceedingly high and follows criteria different from those of the better studied enone chromophores.[12] Further studies directed towards testing the model that we have proposed for the stereoselectivity of the dioxenone photocycloaddition as well as the development of a theoretical basis for the observed selectivities are currently underway and our results will be reported in due course.

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References

1 Recipient of the American Cyanamid Young Faculty Award (1989-1992) and a National Institutes of Health Research Career Development Award (1988-1993).

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3 Winkler, J. Hey, J.; Hannon, F.; Williard, P. *Heterocycles* **1987**, *25*, 55.

4 a) Winkler, J.; Henegar, K.; Williard, P. *J. Am. Chem. Soc.* **1987**, *109*, 2850; b) Winkler, J.; Hey, J.; Williard, P. *Tetrahedron Lett.* **1988**, 4691; c) Winkler, J.; Hong, B. *J. Am. Chem. Soc.*, **1991**, *113*, 8839; d) Winkler, J.; Hong, B.; Bahador, A.; Kazanietz, M.; Blumberg, P. *Bioorg. Med. Chem. Lett.*, in press.

5 Winkler, J.; Hey, J.; Williard, P. *J. Am. Chem. Soc.* **1986**, *108*, 6425.

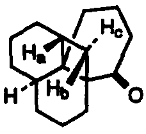
6 For a review, see Alder, R. *Acc. Chem. Res.* **1983**, *16*, 321. For other syntheses of inside-outside bicycloalkanes, see a) Funk, R.; Olmstead, T.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298; b) McMurry, J.; Hodge, C. *J. Am. Chem. Soc.* **1984**, *106*, 6450; c) Gassman, P. G.; Hoye, R. *J. Am. Chem. Soc.* **1981**, *103*, 215, 2496, 2498; d) Haines, A.; Karntiang, P. J. Chem. Soc., Perkin I 1979, 2577; e) Gassman, P.; Thummel, R. *J. Am. Chem. Soc.* **1972**, *94*, 7183; f) Park, C.; Simmons, H. *J. Am. Chem. Soc.* **1972**, *94*, 7184.

7 Winkler, J.; Muller, C.; Hey, J.; Ogilvie, R.; Haddad, N.; Squattrito, P. and Williard, P. *Tetrahedron Lett.* **1989**, 5211.

8 a) Winkler; J. Hey, J.; Darling, S. *Tetrahedron Lett.* **1986**, 5959; b) Winkler, J.; Lee, C.; Rubo, L.; Muller, C.; Squattritro, P. *J. Org. Chem.*, **1989**, *54*, 4491; c) Winkler J.; Subrahmanyam, D. *Tetrahedron* **1992**, *48*, 7049.

9 Reversibility in the intramolecular photocycloaddition of enones is typically not observed; c.f., Becker, D.; Nagler, M.; Hirsh, S. and Ramun, J. *J. Chem. Soc., Chem. Comm.* **1983**, 371.

10 A combination of COESY and HETCOR experiments established the location of the critical three-spin system ($H_aH_bH_c$) indicated in **18**. NOEDIFF experiments then led to the assignment of the relative stereochemical relationships of H_a, H_b, and H_c. Finally, NOEDIFF and long-range COESY experiments established the relationship between H_b and the methylene protons of the cyclohexanone ring, allowing for the definitive stereochemical assignment as indicated in **18**.



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11 Becker, D.; Haddad, N. and Sahali, Y. *Tetrahedron Lett.* **1989**, 2661.

12 Schuster, D. In *The Chemistry of Enones*; Patai, S. and Rappaport, Z., Eds.; Wiley: New York, 1989; p. 623.

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