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Communications to the Editor

Trapping of Triplet 1,4-Biradicals with Hydrogen Selenide in the Intramolecular Photochemical Cycloaddition Reaction of 3-(4′-Pentenyl)cycloalk-2-enones: Verification of the Rule of Five[1]

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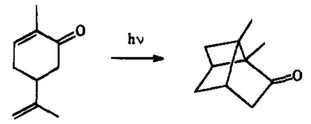
The intramolecular photochemical cycloaddition reaction of cyclic enones with a tethered alkene was first reported over 80 years ago by Ciamician and Silber who found that carvone was converted to carvone camphor on exposure to "Italian sunlight" (Scheme 1).[2] In recent years this intramolecular reaction has frequently been utilized for the synthesis of complex ring systems and natural products.[3] A major attraction of the reaction is that the tether between the enone and the alkene not only becomes a ring in the product, but also can control the regiochemistry and sometimes the stereochemistry of the addition of the alkene to the enone.

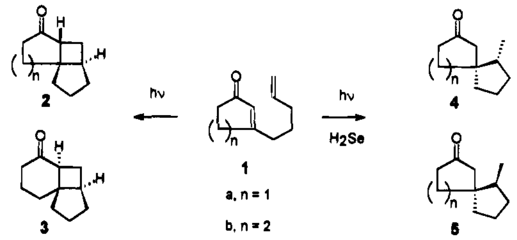
It is well established that the *inter*molecular photochemical cycloaddition reaction between a conjugated cyclic enone and an alkene occurs from the triplet excited state of the enone and involves the intermediacy of one or more triplet 1,4-biradical intermediates.[4] The biradical intermediates can, in principal, be derived from bonding of either the 2-position or the 3-position of the enone to either terminus of the alkene. Experimental evidence for the structures of the biradical intermediates in the intermolecular reaction has recently been obtained using hydrogen selenide as a hydrogen atom donor to reduce the biradicals.[5] This work has revealed that both the 2-position and the 3-position of the enone are involved in biradical formation, and to similar extents. In addition, biradical formation often, but not always, occurs by selective bonding to the less substituted end of the alkene.

In the case of the *intra*molecular photochemical cycloaddition reaction of conjugated cyclic enones tethered to an alkene, the development of ring strain in some of the biradicals can potentially inhibit their formation or prevent their proceeding to products. In the many published examples of the intramolecular reaction, the structures of the products suggest that they are derived from biradical intermediates in which a five-membered ring has been formed. This observation, which appears to be responsible for the reaction regioselectivity, has been termed the "rule of five" by Hammond and Srinivasan.[6] This apparent kinetic preference for 5-membered ring formation is analogous to the observation by Beckwith that the five-hexenyl radical undergoes cyclization to the cyclopentylmethyl radical 75 times faster than cyclization to the cyclohexyl radical.[7]

Scheme 1



Scheme 2



Several groups have examined the effect of structure and substitution on the outcome of the intramolecular enone−alkene photocycloaddition reaction and have interpreted their results in terms of the rule of five.[8] However, as far as we are aware, no unambiguous, direct evidence has been reported which confirms that the only important biradical intermediates are those in which a five-membered ring has been formed. We report here the first direct evidence that this is indeed so; this we have obtained by trapping the biradical intermediates in the photocyclization reaction of two 3-(4′-pentenyl)cycloalk-2-enones with hydrogen selenide.

Ultraviolet light irradiation[9] of a toluene solution of the dienone **1a**[10] (Scheme 2) gave the single racemic cycloadduct **2a**, as has been reported previously.[11] When the reaction was repeated in the presence of hydrogen selenide[12] (*ca.* 0.3 M), the formation of cycloaddition product **2a** was completely suppressed and instead the racemic diastereoisomeric spiroketones **4a** and **5a** were obtained in a 63:37 ratio. Compounds **4a** and **5a** were separated and their structures determined by MS and NMR spectroscopy; the stereochemistry of the methyl group in **4a** was determined by comparison with an authentic sample prepared by an alternative route.[13]

Ultraviolet irradiation[9] of the cyclohexenone derivative **1b**[10] gave the two racemic cycloadducts **2b** and **3** in a 93:7 ratio. The formation of **2b** in this reaction has been reported

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[1] Contribution No. 511 from the Photochemistry Unit, The University of Western Ontario. Dedicated to Professor H.-D. Scharf on the occasion of his 65th birthday.

[2] (a) Ciamician, G.; Silber, P. *Chem. Ber.* **1908**, *41*, 1928. (b) Büchi, G.; Goldman, I. M. *J. Am. Chem. Soc.* **1957**, *79*, 4741.

[3] For a recent review of the intramolecular reaction, see: Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

[4] For a recent review of the reaction mechanism, see: Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

[5] (a) Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8525. (b) Andrew, D.; Hastings, D. J.; Oldroyd, D. L.; Rudolph, A.; Weedon, A. C.; Wong, D. F.; Zhang, B. *Pure Appl. Chem.* **1992**, *64*, 1327. (c) Maradyn, D. J.; Sydnes, L. K.; Weedon, A. C. *Tetrahedron Lett.* **1993**, *34*, 2413. (d) Andrew, D.; Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1994**, *116*, 10870. (e) Maradyn, D. J.; Weedon, A. C. *Tetrahedron Lett.* **1994**, *35*, 8107.

[6] (a) Hammond, G. S.; Liu, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 4930. (b) Carlough, K. H.; Srinivasan, R. *J. Am. Chem. Soc.* **1967**, *89*, 4932.

[7] Beckwith, A. L. *Tetrahedron* **1981**, *37*, 3065.

[8] (a) Schroder, C.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1987**, *109*, 5491. (b) Becker, D.; Nagler, M.; Sahali, Y.; Haddad, N. *J. Org. Chem.* **1991**, *56*, 4537. (c) Becker, D.; Haddad, N. *Tetrahedron* **1993**, *49*, 947.

[9] Irradiations were performed at room temperature using Pyrex- and water-filtered light from a medium-pressure mercury lamp.

[10] The dienones **1a** and **1b** were prepared by 1,2-addition of the Grignard reagent of 5-bromo-1-pentene to cyclopent-2-enone and cyclohex-2-enone, respectively, followed by oxidative rearrangement with CrO_3 in 10% aqueous H_2SO_4.

[11] Agosta, W. C.; George, C. F.; Matlin, A. R.; Wolff, S. *J. Am. Chem. Soc.* **1986**, *108*, 3385.

[12] Hydrogen selenide was prepared as required by addition of water to aluminum selenide under an inert atmosphere. The gas evolved was dissolved in the toluene solution to be irradiated. ***CAUTION:*** **Aluminum selenide reacts vigorously with water to produce hydrogen selenide which is an extremely toxic gas.**

[13] Cycloadduct **2a** underwent cyclobutane ring opening upon treatment with $ClSiMe_3$/NaI to give an iodomethyl spiroketone which upon reduction with Bu_3SnH yielded an authentic sample of **4a**. Similar reductive ring-opening reactions of acylcyclobutanes have been reported previously: Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435.

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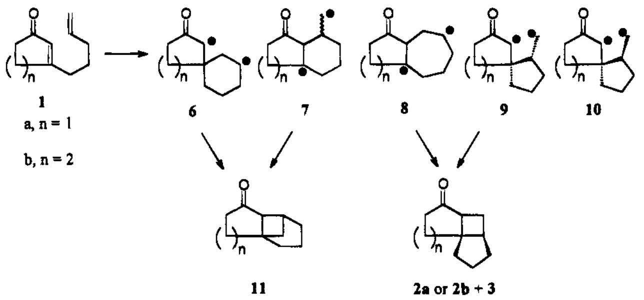
Scheme 3



previously.[14] The structure of **3** followed from its ready conversion to **2b** on treatment with base.[15] Repetition of the reaction in the presence of hydrogen selenide gave the spiroketones **4b** and **5b** in a 91:9 ratio; none of the cycloadducts **2b** and **3** were detected in the reaction mixture. Compounds **4b** and **5b** were separated and shown to be racemic diastereoisomeric spiroketones by MS and NMR spectroscopy; the stereochemistry of the methyl group was determined for **4b** by comparison with an authentic sample generated by light-induced, electron transfer sensitized, reductive opening of **2b**.[16]

The triplet 1,4-biradicals **6**–**10** which could, in principle, be formed by interaction of the cycloalkenone triplet excited state with the side chain alkene are shown in Scheme 3. Since the "crossed" cycloadduct **11** is not observed as a product of the photochemistry of **1a** or **1b** in the absence of hydrogen selenide, either the biradicals **6** and **7** are not intermediates or their exclusive fate is reversion to **1a** or **1b**. The formation of the "straight" cycloadducts **2a** or **2b** and **3** is consistent with the intermediacy of biradicals **8** and **9**. Biradical **10**, if it is formed, must exclusively fragment to starting material since the stereochemistry does not allow closure to a product.

The rule of five predicts that biradicals **9** and **10** should be formed faster than biradicals **6**–**8**. The results obtained when **1a** and **1b** are irradiated in the presence of hydrogen selenide confirm that this is the case since the only biradicals trapped are **9** and **10**, to give **4** and **5**, respectively. Since no cycloadduct is formed in the presence of hydrogen selenide, any biradicals which would normally partition between closure to product and reversion to starting material are being captured quantitatively; therefore, biradical **8** is not a product-forming intermediate in the reaction, and the only cycloadduct precursor is **9**. The failure to observe products of hydrogen selenide trapping of **6**, **7**, or **8** indicates either that they are not present as intermediates or that they fragment exclusively to ground state **1** and at a rate too rapid for reaction with hydrogen selenide to occur.

Since **10** cannot close to a cycloadduct, the complete quenching of cycloadduct formation cannot be used as a criterion that **10** has been quantitatively trapped by the hydrogen selenide. However, the ratio of **4** to **5** formed in the trapping reaction did not change when the hydrogen selenide concentration was increased beyond that necessary to trap all of **9** and completely quench formation of **2a** or of **2b** and **3**. Therefore, the ratio **4**:**5** formed reveals the relative rates of formation of **9** and **10** and their relative yields in the reaction. This ratio is 63:37 for **1a** and 91:9 for **1b**.

The results described confirm unambiguously that the rule of five is an appropriate model for the mechanism of the intramolecular photocycloaddition reaction of **1a** and **1b**. The results also indicate that a substantial proportion of the biradical intermediates (e.g., all of **10**) must fragment to starting material. This has relevance to discussions in the literature concerning the extent to which biradical reversion is important in these intramolecular photocycloaddition reactions.[8]

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(14) Cargill, R. L.; Dalton, J. R.; O'Connor, S.; Michaels, D. G. *Tetrahedron Lett.*, **1978**, *46*, 4465.

(15) A 1:1 mixture of **2b** and **3** was cleanly epimerized to **2b** upon treatment with sodium methoxide. The conversion was monitored by ^{1}H and ^{13}C NMR spectroscopy.

(16) Ultraviolet light irradiation of cycloadduct **2b** in the presence of triethylamine gave spiroketone **4b**. Similar reductive ring-opening reactions of acylcyclobutanes have been reported previously: Bischof, E. W.; Mattay, J.; *Tetrahedron Lett.* **1990**, *31*, 7137.