

Rule of five cyclizations in 5-hexenyl radicals and photocycloadditions of 1,5-hexadienes: effect of 4-oxa substitution

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ABSTRACT: The effect of 4-oxa substitution on the regiochemistry and rate of 5-hexenyl radical cyclizations was investigated, as a potential model for [2 + 2] photocycloadditions of 2-acyl-4-oxa-1,5-hexadienes. Increasing the electron density in the alkene decreases the rate of cyclization in the 4-oxa-hexenyl radicals, relative to the all carbon analogs, but has little effect on the regioselectivity of the cyclization. The radical model does not reproduce the high degree of 1,6 closure, observed in the [2 + 2] photocycloadditions for 4-oxa-1,5-hexadiene **1a**. However, the radical model does reinforce the interpretation that ground state conformational effects, engendered by substitution remote from the reacting centers have important rate consequences for cyclization reactions. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: hexenyl radical; cyclization kinetics; conformational effects; photocycloadditions

INTRODUCTION

Intramolecular radical cyclizations and intramolecular [2 + 2] photocycloadditions have been the focus of intense mechanistic scrutiny.^{1,2} In addition, these reactions have found broad application in the synthesis of complex carbocyclic ring systems.^{3,4} It has been widely noted that these cyclizations strongly favor, where possible, the formation of five-membered rings. The so-called 'rule of five' closure appears to be another manifestation of the kinetic preference for the formation of five-membered rings. Some years ago, Wolff and Agosta showed that the cyclization of substituted 5-hexenyl radicals could be used as a model to rationalize the regiochemistry of the mode of closure (1,5 vs. 1,6) in intramolecular [2 + 2] photocycloadditions of 1,5-hexadien-3-ones.⁵ In these systems, the excited enone triplet was operationally equivalent to a localized mono-radical at the β -enone carbon.

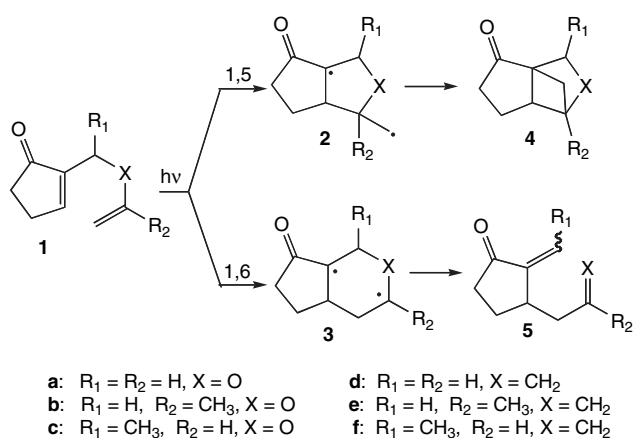
Several years ago, we reported a study on the intramolecular photocycloaddition of a series of 2-acyl-4-oxa-1,5-hexadienes **1a,b,c**, as part of a program designed to explore the effects of oxa substitution on the reactivity of radical and diradical intermediates.⁶ We were interested to explore if oxa substitution would affect the partitioning between 1,5- and 1,6-cyclization modes

of excited dienones (Scheme 1). Previously, Wolff and Agosta had shown that 2-acyl-1,5-hexadienones exclusively undergo photochemical reactions to produce products that were derived from initial closure to a five-membered ring biradical.⁷ In contrast, we found that the oxa-substituted dienones **1a** and **1b** gave almost equal amounts of the 1,5 closure products **4a/4b** and 1,6 closure products **5a/5b** (Table 1). This behavior was very different from that observed with the methylene analog **1e** which despite methyl substitution at C-5 in the hexadiene system, produced only 1,5 closure product **4e**.⁷ We also found that methyl substitution at C-3, remote from the reacting double bonds, had a dramatic effect on the regioselectivity, yield, and the rate of reaction. Irradiation of **1c** produced only 1,5 closure product **4c**. The reaction proceeded 2 to 4.5 times faster than with **1a** and **1b**, and the yield was greatly improved from ~20% (for **1a** and **1b**) to 65%. These results prompted us to inquire if the radical cyclization model, described by Wolff and Agosta could be extended to explain the different photochemistry of the 2-acyl-4-oxa-substituted 1,5-hexadiene systems. Below, we report the results of a study of the regiochemistry and kinetics for a series of 4-oxa-5-hexenyl radical cyclizations.

RESULTS AND DISCUSSION

Bromo-vinyl ethers **6** were prepared by mercuric acetate catalyzed alcohol exchange of 1-bromo-3-propanol or

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Scheme 1

1-bromo-3-butanol with either ethyl vinyl ether or 2-methoxypropene. Radicals **9a**, **9b**, **9c** were generated by treating degassed decalin solutions of the appropriate bromide **6** with tri-*n*-butyltin hydride, in the presence of AIBN as an initiator. The products (**7**, **8**, **12**) were determined by comparison of GC and GC-MS data with authentic samples. The regiochemical selectivity (1,5 vs. 1,6 closure) of radicals **9a**, **9b**, and **9c** are summarized in Table 2, along with comparative data for other 5-hexenyl radical cyclizations. These data show that the regioselectivity of 4-oxa-substituted radicals **9a**, **9b**, and **9c** do not significantly deviate from the trends reported for the all carbon analogs **9d**, **9e**, and **9f**. In all these cases, the

Table 1. Regiochemistry of photocycloaddition of dienones **1**: 1,5 (**4**) versus 1,6 closure (**5**)

Dienone	4:5
1a	1.6:1 ^a
1b	1.1:1 ^a
1c	Only 4c ^a
1e	Only 4e ^b

^a See ref. 6.

^b See ref. 7.

Table 2. Regiochemistry of 5-hexenyl radicals cyclization: 1,5 (**7**) versus 1,6 closure (**8**)

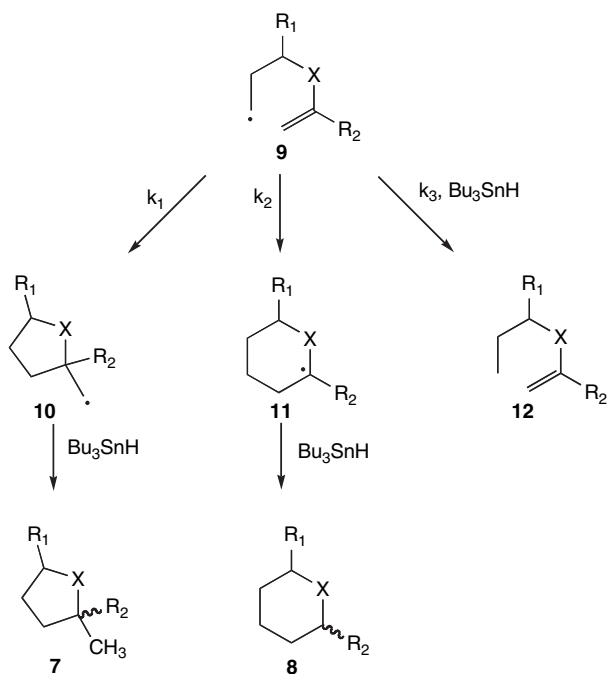
Radical	7:8 ^a
9a	>100:1
9b	1.6:1
9c	>100:1
9d	49:1 ^b
9e	0.67:1 ^b
9f	>24:1 ^c

^a Cyclizations performed at 40 °C except for **9f** (80 °C).

^b See ref. 8.

^c See ref. 18.

oxa-substituted systems show a slightly greater preference for 1,5 closure than the carbon systems. Radicals **9a** and **9c** undergo 1,5 cyclization to give, respectively, tetrahydrofuran products **7a** and **7c**, with only trace amounts of the 1,6 closure products tetrahydropyrans **8a** and **8c**. Methyl substitution at C-5 promotes 1,6 closure in both radicals **9b** and **9e**. The oxa system **9b** gives 40% 1,6 cyclization (**8b**) and the methylene analog **9e** gives 60% 1,6 closure (**8e**). The generally accepted mechanism for tri-*n*-butyl radical generated hexenyl radical cyclizations is shown in Scheme 2.⁸ Previous studies have shown that the observed product composition is determined by the initial mode of cyclization of the radical **9**, since the intermediate cyclized radicals **10** and **11** do not revert to the acyclic radicals under the reaction conditions.^{9–11} Thus, despite the fact that 4-oxa substitution greatly perturbs the electronic nature of the double bond being attacked, there is no significant effect on the partitioning of radical **9** to cyclize to either radical **10** or **11**. This result reinforces the computational analysis which shows that radical addition reactions have early transition states and that the regioselectivity can be largely attributed to steric



Scheme 2

factors.¹² Houk and Beckwith have both reported computational models which attribute the change in the regiochemistry of the cyclization with 5-methyl substitution to steric factors which destabilize the chair-like conformation, leading to 1,5 cyclization and permit the 1,6-cyclization mode to become competitive^{13,14}.

Kinetic analyses of the radical cyclizations provide some insight to the effect of remote methyl substitution at C-3. Kinetic studies on the cyclization of bromides **6a** and **6c** (Fig. 1) were performed at three temperatures (40 °, 65 °, and 90 °C). The data analysis was based on the accepted mechanistic scheme (Scheme 2). The relative rate constants are listed in Table 3 and were determined by fitting the data to the integrated rate equation reported by Smith and Butler for the 3-oxa-5-hexenyl radical.¹⁰ Following previous studies, estimates of the absolute rates were made by assuming that the rate of bimolecular

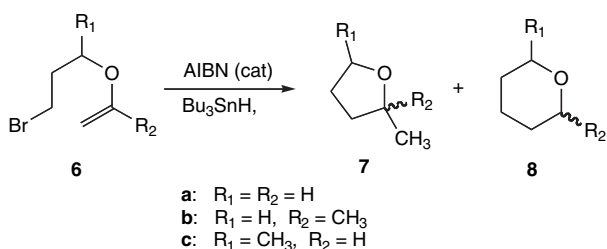


Figure 1

Table 3. Relative cyclization rate constants^a

Radical	Temperature (°C)	k_1/k_2	k_1/k_3
9a	40	697	0.030
	65	546	0.047
	90	327	0.062
9c	40	1214	0.183
	63	954	0.216
	90	679	0.276

^a Rate constants are $\pm 10\%$.

capture of **9** by Bu_3SnH is not significantly different than the value determined for the *n*-hexyl radical.^{8,10} The values are listed in Table 4. 4-Oxa substitution retards the rate of cyclization of the unsubstituted system **9a** by 3.7-fold, relative to the carbon analog **9d**.⁸ The reduced rate of the radical addition to an electron-rich vinyl ether has also been seen in intermolecular reactions of alkyl radicals to vinyl ethers, and is consistent with attributing some nucleophilic character to simple alkyl radicals.¹⁵ This effect may also explain the slight increased preference for 1,5- cyclization seen with 4-oxa substitution, where the nucleophilic radical prefers to add to the less electron-rich end of the double bond.¹⁶ Methyl substitution at C-3 (**9c**) enhances the rate of cyclization six-fold at 40 °C and 4.5-fold at 90 °C, relative to **9a**. The effect of substitution, remote from the reacting centers is most likely the result of conformational factors, where

Table 4. Estimated absolute rate constants k_1

Radical	k_1 (s ⁻¹) ^a
9a	3.0×10^4
9c	1.8×10^5
9d	1.1×10^5 ^b

^a 40 °C.

^b See ref. 8.

C-3 substitution increases the energy of the ground state extended conformation but has little effect on the transition state. This results in a decrease in the activation energy of the cyclization reaction ('gem-dialkyl effect'¹⁷). A similar effect was noted by Beckwith where **9f** cyclized 3.2-fold faster at 80 °C than the parent system **9d**.¹⁸

The 4-oxa-5-hexenyl radical does not provide a direct model to explain the regiochemistry observed in the intramolecular photocycloadditions of 2-acyl-4-oxa-1,5-hexadienes **1a,b,c**. The significant amount of 1,6-closure product observed for **1a** does not correlate with the radical system (**9a**). However, the radical model may give some insight into the course of the photocycloadditions. Mechanistically, these two reactions are significantly different. In the radical reactions, the product distributions are governed by the irreversible kinetically controlled cyclizations to radicals **10** and **11**. The regiochemistry of the cyclization displays little sensitivity to electronic effects, but is highly sensitive to non-bonded interactions at C-3 and C-5. In contrast, the formation of products in the photocycloaddition reactions are much more complex and depend on the partitioning of the initial mode of cyclization of the dienone excited state to biradicals **2** and **3**, coupled with the relative rates of reversion to starting material *versus* closure/fragmentation to products by the transient biradicals. In addition, the photochemical reaction is further complicated by the various possible spin multiplicities (singlet and triplet) of the excited dienone and biradical intermediates, along the reaction pathway. If the radical system can be used as a guide, we would expect the regioselectivity of the initial bond formation in the photocycloaddition of **1** would be largely unaffected by oxa substitution. The dramatic increase in 1,6-closure products observed for **1a** and **1b**, relative to the analogous carbon systems, would then arise by an increase in the rate of fragmentation of 1,4-biradical intermediate **3** (X=O) to the photo-Claisen product **5**. Formation of a carbonyl group (vs. an alkene) promotes this fragmentation pathway. The radical model shows that C-3 methyl substitution increases the overall rate of cyclization and promotes 1,5 over 1,6 closure. This suggests that the effect of C-3 substitution in the photochemical cyclization of **1c** is to facilitate the preferential formation of biradical intermediate **2c** over **3c**. The less likely alternative explanations require that C-3 substitution increases the relative rates of reversion of biradical **3c**, compared with fragmentation to photoproduct **5c** and/or C-3 substitution increases the relative rates of collapse of biradical **2c** to photoproduct **4c**, compared with reversion to starting material.

CONCLUSIONS

4-Oxa-substituted 5-hexenyl radicals cyclize to give tetrahydrofurans and tetrahydropyrans. While the regio-

selectivity of the cyclization (1,5 vs. 1,6) is largely unchanged compared to the all carbon system, the electronic perturbation caused by oxa substitution decreases the rate of cyclization. These results are consistent with the view that radical cyclizations have early transition states¹² and that the regioselectivity is largely determined by geometric constraints, imposed by the competing transition states.^{13,14}

Although the radical model does not offer a direct parallel to the regioselectivity observed for the photocyclizations of the 4-oxa-1,5-hexadienes, the radical model does offer mechanistic insights to the more complex photochemical reaction and suggests that the regioselectivity in the photocyclization may be governed by the reversion rates of the biradical intermediates. In addition, the radical model reinforces the interpretation that ground state conformational effects, engendered by modest substitutions, remote from the reacting centers have important consequences on the rates of cyclization reactions.

EXPERIMENTAL

General

NMR spectra were obtained on a Bruker NR200 MHz spectrometer in CDCl₃. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard 5890A chromatograph, equipped with a 12 m × 0.2 mm OV-101 capillary column. Mass spectra were recorded on an Hewlett-Packard 5970 MS coupled to an Hewlett-Packard 5890 GC.

Azoisobutyronitrile (AIBN) was recrystallized from methanol and stored under argon. Anhydrous decalin (*cis*, *trans* mixture) was used without further purification. Tri-*n*-butyltin hydride was distilled at reduced pressure, prior to use. Ethyl vinyl ether and 2-methoxypropene were distilled over sodium metal, prior to use.

General synthesis of bromo-vinyl ethers (6). The appropriate bromo-alcohol was mixed with a large excess (~30×) of either ethyl vinyl ether or 2-methoxypropene in an oven-dried 100 ml round bottom flask. A catalytic amount of mercuric acetate (~0.1 equivalents) was added and the reaction was heated at reflux for 24 h in a nitrogen atmosphere. The reaction mixture was diluted with ether, washed with sodium bicarbonate and brine solutions, and dried over sodium sulfate. The ether was removed by simple distillation. The product was purified by flash chromatography (silica gel, 2% ether, pentane), followed by bulb-to-bulb distillation at reduced pressure. The pure bromo-vinyl ethers were stored over K₂CO₃ under N₂ and stored in the freezer.

1-Bromo-4-oxa-5-hexene (6a). 3-Bromo-1-propanol (2.20 g, 15.8 mmol) was allowed to react with 50 ml of

ethyl vinyl ether and mercuric acetate (0.51 g, 1.6 mmol). The bromo-vinyl ether product (1.94 g, 11.8 mmol, 75% yield) distilled at 60–80 °C at 28 torr. ¹H NMR: 6.45 (1 H, dd, *J* = 14.3, 6.9 Hz), 4.19 (1 H, dd, *J* = 14.3, 2.2 Hz), 4.01 (1 H, dd, *J* = 6.8, 2.2 Hz), 3.81 (2 H, t, *J* = 5.9 Hz), 3.50 (2 H, t, *J* = 6.5 Hz), 2.18 (2 H, quintet, *J* = 6.2 Hz). ¹³C NMR: 151.6, 86.8, 65.2, 32.1, 30.0. GC–MS: 164 (M+), 166 (M + 2).

1-Bromo-5-methyl-4-oxa-5-hexene (6b). 3-Bromo-1-propanol (2.52 g, 18 mmol) was allowed to react with 50 ml of 2-methoxypropene and mercuric acetate (0.60 g, 1.8 mmol). The bromo-vinyl ether product (0.86 g, 4.8 mmol, 27% yield) distilled at 70–80 °C at 30 torr. ¹H NMR: 3.84 (2 H, brs), 3.77 (2 H, t, *J* = 5.8 Hz), 3.51 (2 H, t, *J* = 6.5 Hz), 2.2 (2 H, quintet, *J* = 6.2 Hz), 1.8 (3 H, s). ¹³C NMR: 159.5, 81.4, 64.5, 32.1, 30.1, 20.8. GC–MS: 178 (M+), 180 (M + 2).

1-Bromo-3-methyl-4-oxa-5-hexene (6c). 1-Bromo-3-butanol (4.83 g, 31.6 mmol) was allowed to react with 60 ml of ethyl vinyl ether and mercuric acetate (1.2 g, 3.8 mmol). The bromo-vinyl ether product (1.53 g, 8.6 mmol, 27% yield) distilled at 65–75 °C at 30 torr. ¹H NMR: 6.63 (1 H, dd, *J* = 14.2, 6.6 Hz), 4.28 (1 H, dd, *J* = 14.2, 1.2 Hz), 4.07 (1 H, m), 4.0 (1 H, dd, *J* = 6.6, 1.6 Hz), 3.45 (2 H, t, *J* = 6.1 Hz), 2.0 (2 H, m), 1.2 (3 H, d, *J* = 6.2 Hz). ¹³C NMR: 150.7, 88.6, 73.4, 39.5, 29.7, 19.6. GC–MS: 178 (M+), 180 (M + 2).

KINETICS AND PRODUCT STUDIES

The kinetics studies were modeled after the studies by Butler and Walling.^{8,10} Decalin solutions of the bromo-vinyl ethers **6** (80–350 mM), tri-*n*-butyl tin hydride (30–100 mM), AIBN (0.6–3.2 mM), and an internal standard (octane) were prepared and sealed in Pyrex tubes, following degassing by three freeze-pump-thaw cycles. The ratio of bromo-vinyl ether to tin hydride was ~3:1 in each sample. Three concentrations were examined at each temperature studied and duplicate tubes of each concentration were prepared. The samples were heated at the desired temperatures until the reactions consumed all of the hydride and then analyzed by capillary GC. Each tube was analyzed at least twice and the results were averaged. Products were identified by comparison to authentic samples and GC–MS. The combined chemical yields (GC) of products **7**, **8**, and **12** (based on the initial hydride concentration), where 84–91% for radical **9a**, 80–90% for radical **9b**, and 95–100% for radical **9c**. Response factors were determined for all products with reference to the internal standard. The data were fitted to the integrated rate

equation (the integrated rate equation was essentially taken from ref. 10 after correcting for the typographical error that omitted the minus sign).

$$[12]_F = [\text{Bu}_3\text{SnH}]_I - \frac{k_1 + k_2}{k_3} \ln \frac{k_1 + k_2 + k_3 [\text{Bu}_3\text{SnH}]_I}{k_1 + k_2}$$

where $[12]_F$ is the final concentration and $[\text{Bu}_3\text{SnH}]_I$ is the initial concentration. This analysis allowed determination of the values of k_1/k_2 and k_1/k_3 or k_2/k_3 by using the substituted equation:

$$[12]_F = [\text{Bu}_3\text{SnH}]_I - x(r + 1) \ln \frac{1 + [\text{Bu}_3\text{SnH}]_I}{x(r + 1)}$$

where $x = k_2/k_3$ and $r = k_1/k_2 = [7]/[8]$. For an experimentally determined value of r , x was varied until the value for $[12]_F$ calculated matched the value of $[12]_F$ observed.

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