

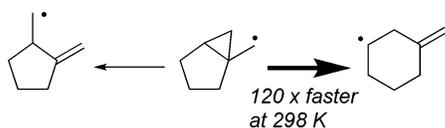
Kinetics and Regioselectivity of Ring Opening of 1-Bicyclo[3.1.0]hexanylmethyl Radical

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Rate constants for the rearrangement of 1-bicyclo[3.1.0]-hexanylmethyl radical (**2**) to 3-methylenecyclohexenyl radical (**3**) and 2-methylenecyclopentyl-1-methyl radical (**1**) were measured using the PTOC–thiol competition method. The ring-expansion pathway is described by the rate equation, $\log(k/s^{-1}) = (12.5 \pm 0.1) - (4.9 \pm 0.1)/\theta$; the non-expansion pathway is described by $\log(k/s^{-1}) = (11.9 \pm 0.6) - (6.9 \pm 0.8)/\theta$. Employing the slower trapping agent, tri-*n*-butylstannane, favors methylenecyclohexane over 2-methyl-methylenecyclopentane by more than 120:1 at ambient or lower temperatures.

Carbon-centered radicals have become valuable players in synthetic strategy. This is due in no small part to the growing catalogue of kinetic data available on a wide variety of radical reactions. This information is especially critical in cases where tandem events are planned.¹ Additionally, radicals have proven highly useful for annulations, intermolecular additions, realizing quaternary centers, ring expansions, and combinations thereof.² Their tolerance of a wide range of functional groups also permits radicals to be utilized without the need to incorporate protecting groups throughout other portions of a molecule.

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Fragmentation of the cyclopropylcarbinyl radical system is of particular interest and has been thoroughly studied by many groups. The prototype system holds a prominent place in radical kinetic investigations and has been accurately characterized³ across a temperature range spanning more than 250 °C with a fragmentation rate of $9.4 \times 10^7 \text{ s}^{-1}$ at 298 K. A wide breadth of substituted derivatives has also been studied and has provided much insight into the influence of substitution, resonance, and stereoelectronic effects.⁴ Unsymmetrically substituted derivatives have a bifurcated reaction pathway available and permit rate comparisons between the two modes of fragmentation. Some aryl-substituted analogues have been shown^{4d,5} to be exceptionally fast with unimolecular fragmentation rates exceeding 10^{11} s^{-1} .

An accurate study of fragmentation rates has necessitated the use of a variety of techniques. These include, for example, the use of spectroscopy (e.g., ESR), competition methods employing a reducing agent (e.g., Bu_3SnH , PhSH , PhSeH), and laser flash photolysis. Of these, stannane and thiol reagents have been useful as indirect methods for probing a wide range of radical reactions. More recently, laser flash photolysis and the use of PhSeH have proven useful for the upper end of the time scale ($> 10^{11} \text{ s}^{-1}$).⁶ Accurate rate expressions for the reaction of these reducing agents with carbon-centered radicals have been established and cross-calibrated with each other using several radical reactions.^{3a,4g,7}

In the present study, the effect of angularly fusing a cyclopentyl ring onto the cyclopropylcarbinyl radical moiety was investigated (Scheme 1). The unsymmetrically substituted strained ring system gives rise to two fragmentation pathways. Fission along the shared (endo) bond of the bicyclic structure (**2**) realizes a ring-expansion event, providing methylenecyclohexane (**6**) after reduction. Alternatively, fission of the bond exo to the cyclopentyl group leads to 2-methyl-methylenecyclopentane (**4**).

The cyclopropylcarbinyl radical **2** framework played an early role in demonstrating the importance that stereoelectronic factors

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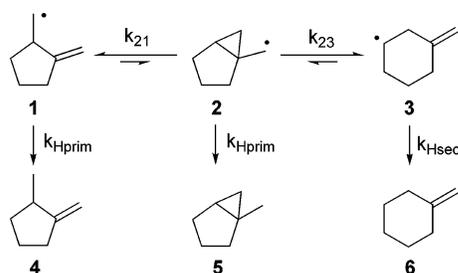
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SCHEME 1



impart on the direction of radical fragmentation. However, in these examinations it was invariably an embedded portion of a larger structure (e.g., A-norsteroid derivatives) that conformationally restricted the orientation of the radical. When liberated from such larger structures, radical **2** is not subject to the same rotational restriction, promoting other criteria such as radical stability and ring strain to greater importance.

Radical **2** has also appeared as an intermediate in several rearrangements both as the prototype and substituted derivatives. Beckwith⁸ and Stork⁹ independently studied 5-*exo-trig* ring closures of vinyl radicals and noted that **2** was a likely intermediate en route to the methylenecyclohexane derivative. The kinetics of the fragmentations were not explored in these studies. However, the rate of formation of **3** from **1** was established in Beckwith's study and pointed to the six-membered ring as the thermodynamically more stable intermediate in this reaction manifold. More evidence in support of this was found by Kilburn who generated several analogues of **2** by a 5-*exo-trig* ring closure of a substituted methylenecyclopropyl propyl radical.¹⁰ A ring-expansion event followed (cf., **2** → **3**) leading invariably to substantial yields of the corresponding cyclohexyl derivatives. More recently, a molecular modeling study correctly predicted **3** as the kinetically favored intermediate.¹¹ A closely related unsaturated analogue of **2** has also been invoked in the biogenesis of the expanded and aromatized D-ring of the nic-1 antifeedant steroid.¹² Our present investigation firmly establishes the rates of these fragmentation pathways and identifies radical **3** as thermodynamically and kinetically favored.¹³

The preparation of the radical precursor **11** is shown in Scheme 2. Subjecting cyclopentanone to Wadsworth–Emmons¹⁴ conditions (triethylphosphonoacetate, NaH) resulted in exclusive formation of α,β -unsaturated ester **7**. The desired β,γ -unsaturated ester (**8**) could be obtained by generation of the extended enolate (LDA, THF) followed by kinetic trapping (NH_4Cl , -78°C).^{4c} Cyclopropanation¹⁵ with diethyl zinc and diiodomethane and subsequent saponification with 1.0 M

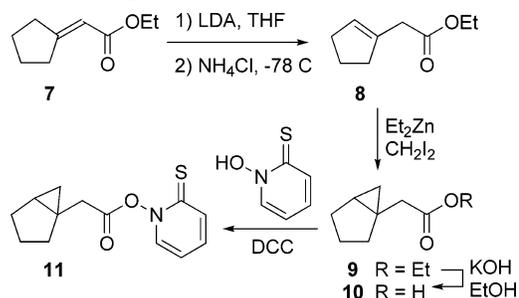
SCHEME 2. Preparation of Radical Precursor **11**

TABLE 1. Product Distribution and Rate Constants from Reduction of **11** with PhSH

T ($^\circ\text{C}$)	$[\text{PhSH}]_m$	relative % yield			$\log k_{21}$	$\log k_{23}$
		4	5	6		
48	0.89	1.00	6.00	93.00	7.38	9.24
35	0.89	0.83	9.29	89.88	7.06	8.99
23	0.89	0.70	10.40	88.89	6.89	8.88
19	0.46	0.37	5.37	94.26	6.60	8.90
19	1.62	0.51	17.62	81.88	6.77	8.87
10	0.89	0.31	15.14	84.54	6.32	8.64
1	0.89	0.32	14.91	84.77	6.29	8.61
-42	0.89	0.21	32.82	66.97	5.51	7.91
-79	0.89	0.00	66.53	33.47	--	6.99

ethanolic KOH afforded carboxylic acid **10**. The carboxylic acid was converted to PTOC ester radical precursor¹⁶ **11** with 2-mercaptopyridine-*N*-oxide and dicyclohexylcarbodiimide.

The competition method using PhSH was employed to establish fragmentation rates of **2**.¹⁷ A stock 0.02 M solution of PTOC **11** in THF was used for all kinetic runs. Thiophenol was used in >10 equiv to apply steady-state conditions. The rate of reduction of primary alkyl radicals **1** and **2** by thiophenol was taken to be equal to the rate of reduction of *n*-butyl radical by thiophenol ($\log k_{\text{H(prim)}}/(\text{M}^{-1} \text{s}^{-1}) = 9.41 - 1.74/\theta$, where $\theta = 2.303RT$ in kcal/mol); the rate of reduction of secondary alkyl radical **3** by thiophenol was taken to be equal to the rate of reduction of isopropyl radical by thiophenol ($\log k_{\text{H(sec)}}/(\text{M}^{-1} \text{s}^{-1}) = 9.26 - 1.70/\theta$).¹⁸ As the rate of reduction of alkyl radicals by PhSH is largely unaffected by the structure of the radical, the use of these rate functions is sound.¹⁹ The product distribution for hydrocarbon products **4**–**6** using thiophenol is shown in Table 1. The rate for rearrangement of **2** → **1** is shown in eq 1; the rate for rearrangement of **2** → **3** is shown in eq 2. Here, $[\text{PhSH}]_m$ represents the average thiophenol concentration over the course of the reaction, and **4/5** and **6/5** represent the ratio of hydrocarbon products as determined by GC. Analysis across a temperature range of -79 to -48°C provided Arrhenius functions for the two fragmentation pathways (Figure 1).

$$k_{21} = k_{\text{H(prim)}}[\text{PhSH}]_m \mathbf{4/5} \quad (1)$$

$$k_{23} = k_{\text{H(sec)}}[\text{PhSH}]_m \mathbf{6/5} \quad (2)$$

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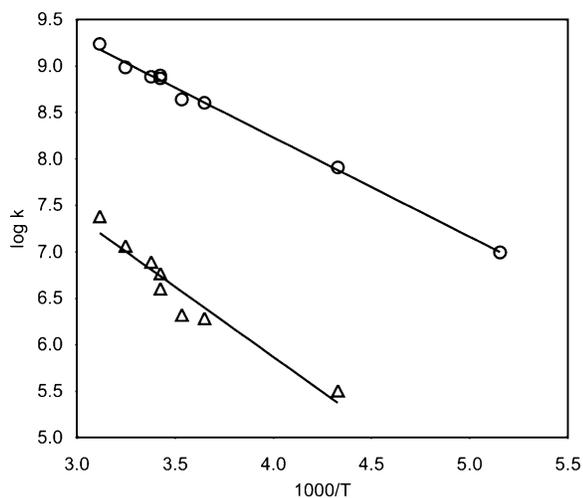


FIGURE 1. Arrhenius functions for fragmentation of radical **2** → **1** (Δ) and **2** → **3** (○).

From the Arrhenius analysis, fragmentation of the endo bond leading to ring-expansion (**2** → **3**) is described by the rate equation, $\log(k_{23}/s^{-1}) = (12.5 \pm 0.1) - (4.9 \pm 0.1)/\theta$; the exo fragmentation leading to non-expansion (**2** → **1**) is described by, $\log(k_{21}/s^{-1}) = (11.9 \pm 0.6) - (6.9 \pm 0.8)/\theta$. At 298 K, the unimolecular ring-expansion pathway proceeds at a rate of $8.4 \times 10^8 s^{-1}$. This rate is surprisingly fast considering that, other than incipient secondary radical character, **2** is not equipped with substituents known to enhance the fragmentation rate (e.g., carbonyl or aromatic groups). At 298 K, the nonexpansion pathway (k_{21}) occurs at a rate of $6.9 \times 10^6 s^{-1}$. Hence, at 298 K, fission along the shared bond occurs 120 times faster than along the exo bond.

The ΔS^\ddagger term is negative for both fragmentation events. Cyclopropyl ring opening along the endo bond ($\Delta S^\ddagger = -3.3$ eu) or the exo bond ($\Delta S^\ddagger = -6.1$ eu) necessitates that ordering occurs within the system. This can be understood in terms of the requirement of the methyl radical rotor to align with one of the σ bonds of the cyclopropyl ring and ultimately become locked in the nascent methylene unit.

The behavior of radical **2** was also examined at several temperatures and concentrations of stannane reducing agent. The rate at which *n*-Bu₃SnH is able to reduce simple alkyl radicals (k_H , Scheme 1) is significantly slower than for that of PhSH ($\sim 10^6 M^{-1} s^{-1}$ vs $10^8 M^{-1} s^{-1}$) and should therefore permit identification of the thermodynamic product. The rate of reduction of primary alkyl radicals **1** and **2** and secondary radical **3** by tri-*n*-butyltin hydride was taken to be equal to the rate of reduction of *n*-butyl radical ($\log k_{H(\text{prim})}/(M^{-1} s^{-1}) = 9.06 - 3.65/\theta$) and cyclohexyl radical ($\log k_{H(\text{sec})}/(M^{-1} s^{-1}) = 9.24 - 3.97/\theta$) by tri-*n*-butyltin hydride, respectively.²⁰ For all runs, **4** and **6** are the only hydrocarbon products observed under these conditions with no evidence of unopened cyclopropyl **5** even at $-78^\circ C$.

In all instances the expansion pathway (**2** → **3**) is highly favored (Table 2). This observation is consistent with the greater stability of secondary radicals over primary radicals as well as the negligible ring strain associated with methylenecyclohexane. Extrapolation to lower concentrations of reducing agent identi-

TABLE 2. Product Distribution from Reduction of **11** with Bu₃SnH

<i>T</i> (°C)	[Bu ₃ SnH] _m	6/4	<i>T</i> (°C)	[Bu ₃ SnH] _m	6/4
50	0.19	115.6	0	0.66	144.5
50	0.44	89.8	-41	0.19	136.4
50	0.66	93.4	-41	0.44	142.8
19	0.19	126.7	-41	0.66	162.4
19	0.44	123.4	-78	0.19	148.0
19	0.66	124.8	-78	0.44	167.4
0	0.19	132.4	-78	0.66	189.6
0	0.44	139.7			

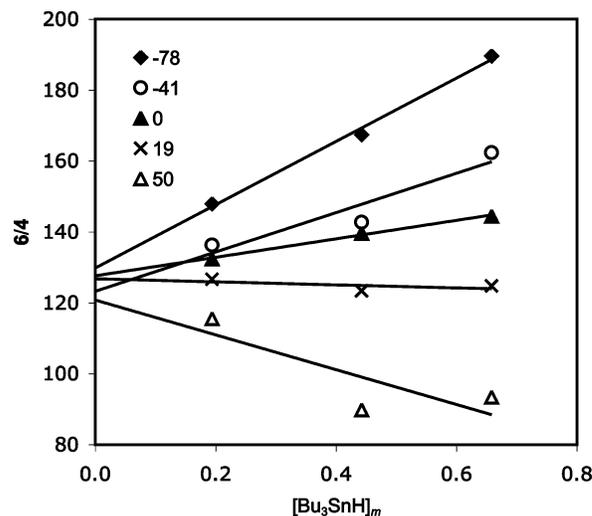


FIGURE 2. Product ratio of **6** to **4** using Bu₃SnH.

fies **3** as the thermodynamically favored intermediate (Figure 2). At low temperatures and high concentrations of reducing agent the pathway leading to radical **3** is further implicated as kinetically favored in agreement with the Arrhenius analysis. At elevated temperatures, it is observed that a greater amount of radical **1** is accessible, although still inferior to the amount of **3**.²¹ The large disparity between activation energies (6.9 vs 4.9 kcal/mol) for the two pathways makes the equilibrium more sensitive to temperature changes as reflected in Figure 2.

Beckwith established the rate expression for **1** → **3** as part of his study of vinyl radical ring closures.⁸ Direct generation of **1** from the corresponding bromide provided $\log(k/s^{-1}) = (10.9 \pm 0.4) - (8.7 \pm 0.9)/\theta$.²² Thus at 298 K, formation of **3** from **1** occurs at $3.3 \times 10^4 s^{-1}$. From the stannane data in the present study, the rate of the reverse reaction is therefore estimated to be $\sim 2 \times 10^2 s^{-1}$.

The ring-expansion pathway available to radical **2** is greatly favored both kinetically and thermodynamically. The secondary radical character and methylenecyclohexyl ring system offer an energetic advantage to the available fragmentation pathways in favor of the endo cyclopropyl bond. A small entropic advantage is also realized along this same course. We are presently engaged in investigating higher homologues in this series to identify the influence of ring size on the direction and rate of cyclopropyl fragmentation and as an approach to access medium-sized rings.

(21) Syringe pump addition of Bu₃SnH (in THF) over 1 h to a refluxing THF solution of PTOC ester **11** provided **6** and **4** in a ratio of 195:1.

(22) When **1** was generated via the vinyl radical precursor, the expression was found to be $\log(k/s^{-1}) = (11.0 \pm 0.3) - (8.9 \pm 0.5)/\theta$. See ref 8.

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Experimental Section

General Experimental Methods. Reagents were used as received. Solvents (THF, CH₂Cl₂) were anhydrous (over molecular sieves). All reactions were conducted under a nitrogen atmosphere. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ at 300 and 75 MHz, respectively.

Ethyl 2-(1-Cyclopentenyl)acetate (8).²³ To a 0 °C solution of diisopropyl amine (4.371 g, 43.2 mmol) in THF (100 mL) was slowly added *n*-butyllithium (28.96 mL, 1.45 M). The solution was stirred for 30 min and then cooled to -78 °C. A solution of ethyl 2-cyclopentylideneacetate (**7**, 6.249 g, 40.0 mmol) in THF (30 mL) was added dropwise over 15 min and allowed to stir an additional 20 min. Saturated aqueous NH₄Cl (100 mL) was added dropwise over 20 min, and the quenched reaction was allowed to warm to ambient temperature, poured into water (200 mL), and extracted with Et₂O (2 × 75 mL). The extracts were dried (Na₂SO₄), filtered, and concentrated to afford 3.501 g (22.69 mmol, 53%) of the β,γ-unsaturated ester as a colorless liquid in high purity. ¹H NMR δ 5.54 (1H, br s), 4.15 (2H, q, *J* = 7.4 Hz), 3.11 (2H, s), 2.37–2.29 (4H, m), 1.95 – 1.84 (2H, m), 1.26 (3H, t, *J* = 7.4 Hz). ¹³C NMR δ 171.5, 136.6, 128.1, 60.5, 37.1, 35.1, 32.5, 23.4, 14.2. IR (neat) 1736 cm⁻¹.

Ethyl 2-(Bicyclo[3.1.0]hexan-1-yl)acetate (9). To a -5 °C solution of Et₂Zn (30.0 mL, 1.2 M in hexanes) in CH₂Cl₂ (130 mL) was added dropwise CH₂I₂ (19.5 g, 73.14 mmol) over 10 min. The solution became turbid and turned milky white when the addition was approximately half complete. After an additional 10 min, ethyl 2-(1-cyclopentenyl)acetate (**8**, 3.501 g, 22.69 mmol) in CH₂Cl₂ (20 mL) was added in one portion, and the reaction was allowed to stir at room temperature for 12 h during which time the reaction was a clear liquid with a white precipitate distributed on the bottom of the flask. The reaction was quenched by the addition of saturated aqueous NH₄Cl (100 mL), extracted with ether (2 × 100 mL), dried (Na₂SO₄), and concentrated. The crude material could be used without further purification. Silica gel chromatography (30% EtOAc in 60–90 ligroin) provided 2.796 g (16.62 mmol, 73%) of **9** as a colorless liquid. Spectral data was identical to that reported.²³

2-(Bicyclo[3.1.0]hexan-1-yl)acetic Acid (10). The ester **9** was refluxed with ethanolic KOH (1.0 M) for 3 h. The reaction was diluted with water, acidified (1 M HCl), extracted with ether (2 × 50 mL), dried (Na₂SO₄), and concentrated. Silica gel chromatography afforded 2.13 g of the pure acid as a colorless oil (67% from **8**). ¹H NMR δ 10.1 (1H, br), 2.54 (1H, d, *J* = 15.4 Hz), 2.42 (1H, d, *J* = 15.4 Hz), 1.89–1.54 (5H, m), 1.25–1.10 (2H, m), 0.49 (1H, t, *J* = 4.6 Hz), 0.40 (1H, dd, *J* = 8.3, 5.3 Hz). ¹³C NMR δ 179.4, 40.9, 31.7, 27.4, 24.9, 23.5, 21.4,

12.1. IR (neat) 3400–2400 (br), 1702 cm⁻¹. HRMS (ESI-TOF) calcd for C₈H₁₂O₂Na [M + Na]⁺ 163.0735, found 163.0729.

1-[2-(Bicyclo[3.1.0]hexan-1-yl)acetoxy]-2(1H)-pyridinethione (11). Carboxylic acid **10** (0.981 g, 7.00 mmol), 2-mercaptopyridine-*N*-oxide (0.890 g, 7.00 mmol), and DMAP (0.086 g, 0.70 mmol) were dissolved in CH₂Cl₂ (75 mL). The reaction flask was covered with foil to protect it from light, and DCC (1.603 g, 7.77 mmol) in CH₂Cl₂ (25 mL) was added dropwise over 30 min. The bright-yellow reaction mixture was allowed to stir at ambient temperature for 20 h. The urea byproduct was filtered off, and the yellow filtrate was concentrated. Silica gel chromatography (30% EtOAc in 60–90 ligroin) provided PTOC ester **11** as a viscous yellow oil which required protection from light and oxygen for any extended storage. ¹H NMR δ 7.67 (1H, dd, *J* = 8.8, 1.8 Hz), 7.60 (1H, dd, *J* = 7.0, 1.5 Hz), 7.21 (1H, m), 6.66 (1H, dt, *J* = 7.0, 1.8 Hz), 2.90 (1H, d, *J* = 16.5 Hz), 2.83 (1H, d, *J* = 16.5 Hz), 1.96–1.58 (5H, m), 1.30–1.16 (2H, m), 0.58 (1H, t, *J* = 4.6 Hz), 0.52 (1H, dd, *J* = 8.1, 5.5 Hz). ¹³C NMR δ 175.6, 167.9, 137.6, 137.1, 133.4, 112.5, 38.2, 31.5, 27.3, 24.2, 23.5, 21.2, 12.3. IR (neat) 1803, 1606, 1524, 1445, 1409, 1129 cm⁻¹. HRMS (ESI-TOF) calcd for C₁₃H₁₅NO₂SNa [M + Na]⁺ 272.0721, found 272.0715.

Kinetic Runs. A 0.02 M stock solution of PTOC ester **11** in THF was used for all runs. A 2.0 mL aliquot was transferred to an N₂-flushed test tube capped with a rubber septum. With stirring, the solution was equilibrated to the desired temperature, and reducing agent (PhSH or Bu₃SnH) was added via syringe. The sample was irradiated for 60 s with a 200 W tungsten bulb. TLC analysis confirmed consumption of the PTOC ester, and for the stannane reactions the yellow color was discharged. The reaction was immediately analyzed by GC-MS (HP-5MS, 30 m × 0.25 mm × 0.25 μm, 40 °C isothermal; *t*_R = **5** < **4** < **6**). Authentic samples were prepared to confirm peak identities; weight response factors were assumed to be equal. Isothermal reactions were conducted simultaneously.

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Supporting Information Available: Spectral data (¹H NMR, ¹³C NMR, and IR) for compounds **10** and **11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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