

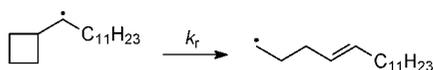
## Rate Constants and Arrhenius Functions for Ring Opening of a Cyclobutylcarbinyl Radical Clock and for Hydrogen Atom Transfer From the Et<sub>3</sub>B–MeOH Complex

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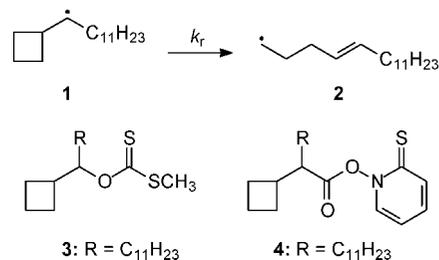


Kinetics of ring opening of the 1-cyclobutyldecyl radical (**1**) were studied, and an Arrhenius function over the temperature range  $-20$  to  $47$  °C was determined. The radical clock reaction has kinetics described by  $\log k = 13.2 - 13.5/2.313RT$  (in kcal/mol), and  $k = 1.5 \times 10^3 \text{ s}^{-1}$  at  $20$  °C. Previous kinetic studies of hydrogen atom transfer trapping of radical **1** by the triethylborane–methanol complex at variable temperatures (*J. Org. Chem.* 2007, 72, 5098) were analyzed with the newly obtained kinetic data.

Synthetic applications of radical chemistry generally involve chain reactions where the radical conversions of interest compete with other radical processes, and knowledge of rate constants for radical reactions is essential for synthetic planning. Although absolute rate constants for several radical reactions have been measured directly, most of the radical kinetics information has been determined via indirect kinetic studies,<sup>1</sup> and a major portion of that data involves competition reactions with “radical clocks”, which are calibrated unimolecular radical rearrangements.<sup>2</sup> Carbon-centered radical clocks span a wide range of reactivity, with clock lifetimes from picoseconds to seconds.<sup>1</sup> The most popular clocks are based on the 5-hexenyl radical cyclization ( $k = 2 \times 10^5 \text{ s}^{-1}$  at  $20$  °C)<sup>3,4</sup> and the cyclopropylcarbinyl radical ring opening ( $k = 7 \times 10^7 \text{ s}^{-1}$  at  $20$  °C).<sup>5</sup>

Among the slower radical clocks, ring openings of cyclobutylcarbinyl radicals to 4-pentenyl radicals are noteworthy. At room temperature, these unimolecular reactions are about 2 orders of magnitude less rapid than cyclizations of 5-hexenyl

SCHEME 1



radicals,<sup>1</sup> but only limited kinetic studies<sup>6,7</sup> and computational studies<sup>8</sup> of cyclobutylcarbinyl radical ring openings are available. Recently, we used the ring-opening reaction of the 1-cyclobutyldecyl radical (**1**) to the *trans*-4-hexadecenyl radical (**2**) (Scheme 1)<sup>9</sup> in kinetic studies of hydrogen atom transfer trappings by water and methanol complexes of triethylborane.<sup>10</sup> In that work,<sup>9</sup> radical **1** was produced from xanthate ester radical precursor **3**, and the rate constant for ring opening of **1** at ambient temperature was estimated from previous competition kinetic studies of the cyclobutylcarbinyl radical ring opening.<sup>6</sup> In this contribution, we report production of radical **1** from a second radical precursor, PTOC ester **4**,<sup>11,12</sup> and kinetic calibration of the ring opening of **1** over a temperature range of  $-30$  to  $40$  °C.

PTOC esters are incompatible with Et<sub>3</sub>B, which precluded the use of radical precursor **4** in our earlier study.<sup>9</sup> Nonetheless, PTOC ester radical precursors are generally more versatile than xanthate esters. The xanthates are limited for practical purposes to precursors for secondary alkyl radicals, and even then can react inefficiently. Moreover, radical chain initiation with PTOC esters can be accomplished with visible light irradiation if desired, which is a significant advantage for low-temperature studies that we exploited in this work.<sup>12b</sup> Thus, as a tool for most radical kinetic studies, PTOC ester **4** will be superior to xanthate ester **3**.

The preparation of radical precursor **4** followed standard methods. In brief, cyclobutylmethanol was converted to its mesylate derivative, which was used for the preparation of cyclobutylacetone nitrile. Alkylation of this nitrile with 1-bromoundecane gave 2-cyclobutyltridecanecarbonitrile. Hydrolysis

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(7) (a) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970–974. (b) Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 173–177. (c) Newcomb, M.; Horner, J. H.; Emanuel, C. J. *J. Am. Chem. Soc.* **1997**, 119, 7147–7148. (d) Choi, S. Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **2000**, 65, 4447–4449. (e) Emanuel, C. J.; Horner, J. H.; Newcomb, M. *J. Phys. Org. Chem.* **2000**, 13, 688–692.

(8) (a) Baker, J. M.; Dolbier, W. R. *J. Org. Chem.* **2001**, 66, 2662–2666. (b) Shi, J.; Chong, S.-S.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* **2008**, 73, 974–982.

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(10) (a) Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, 127, 12513–12515. (b) Medeiros, M. R.; Schacherer, L. N.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2007**, 9, 4427–4429.

(11) The acronym PTOC is derived from pyridine-2-thioneoxycarbonyl. PTOC esters, which are anhydrides of a carboxylic acid and the thiohydroxamic acid *N*-hydroxypyridine-2-thione, were developed by Barton's group for synthetic applications (see ref 12a).

(12) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, 41, 3901–3924. (b) Newcomb, M.; Park, S.-U. *J. Am. Chem. Soc.* **1986**, 108, 4132–4134.

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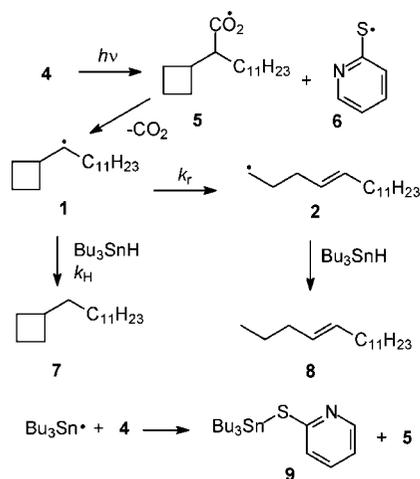
(2) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, 13, 317–323.

(3) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, 94, 6059–6064.

(4) (a) Chatgililoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, 103, 7739–7742. (b) Chatgililoglu, C.; Newcomb, M. *Adv. Organomet. Chem.* **1999**, 44, 67–112.

(5) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, 98, 7024–7026. (b) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, 111, 275–277. (c) Newcomb, M.; Choi, S. Y.; Horner, J. H. *J. Org. Chem.* **1999**, 64, 1225–1231.

SCHEME 2

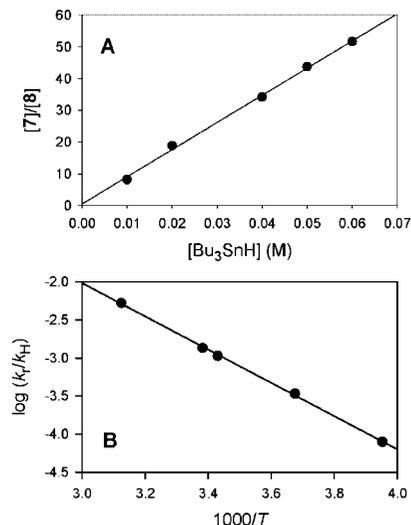


of the latter nitrile gave 2-cyclobutyltridecanoic acid, which was converted to PTOC ester **4** via the acid chloride that reacted with the sodium salt of *N*-hydroxypyridine-2-thione. Radical precursor **4** was characterized by NMR spectroscopy and high resolution mass spectrometry, and the samples employed in kinetic studies were >98% pure as determined by  $^1\text{H}$  NMR spectroscopy.

PTOC esters react in radical chain reactions that can be initiated either thermally or photochemically with visible light irradiation to give the sequence of reactions shown in Scheme 2.<sup>12</sup> Reaction of **4** in either an initiation reaction or a chain propagation reaction gives acyloxy radical **5**, which rapidly decarboxylates to give the desired radical **1**. Byproduct radical **5** is also formed in the initiation reactions. In the indirect kinetic study in this work, hydrogen atom trapping of **1** by tin hydride to give product **7** competes with ring opening, and the ring-opened radical **2** also will react with tin hydride to give acyclic product **8**; previous studies established that the ring-opening reaction ultimately gives *trans*-4-hexadecene as the major product.<sup>9</sup> The stannyl radical formed in the trapping reactions reacts with another molecule of precursor **4** in a chain propagation step.

A number of hydrogen atom transfer trapping agents can be used to trap the alkyl radical when PTOC esters are the precursors,<sup>12</sup> and  $\text{Bu}_3\text{SnH}$  provides a well-calibrated rate constant for the competition reaction.<sup>4</sup> PTOC esters also react in "self-trapping" reactions, reaction of a carbon radical intermediate with the thione group of a second molecule of PTOC ester to give an alkyl 2-pyridinyl sulfide product, and the rate constant at room temperature for this self-trapping reaction is similar to the rate constant for reaction of an alkyl radical with  $\text{Bu}_3\text{SnH}$ .<sup>13</sup> Therefore, when tin hydride is present in large excess to the PTOC ester radical precursor, the self-trapping reaction is not important.

In competition kinetic studies, PTOC ester radical precursor **4** (0.002 M) in toluene with excess  $\text{Bu}_3\text{SnH}$  was thermally equilibrated, and reactions were initiated by visible light irradiation. Following the reactions, an internal standard was added, and the product mixtures were analyzed by GC to determine the yields of products **7** and **8**. The total yields of **7** and **8** as determined by GC analysis using an internal standard typically were greater than 90%. The results from a series of



**FIGURE 1.** Kinetics of radical **1** ring openings. (A) Product ratios as a function of tin hydride concentration for reactions at 18.5 °C. (B) Relative Arrhenius function for ring opening and tin hydride trapping of radical **1**.

studies conducted at 18.5 °C are shown in Figure 1A. Ring-opened product **8** was the minor product in all cases and accounted for less than 2% of the product yield when 0.06 M  $\text{Bu}_3\text{SnH}$  was employed. Nonetheless, the plot of  $[7]/[8]$  versus the initial concentration of  $\text{Bu}_3\text{SnH}$  gave a good line. In these experiments, the ratio of rate constants is given by eq 1,<sup>1</sup> and the slope of the line in Figure 1A is  $k_{\text{H}}/k_{\text{r}} = 860 \pm 20 \text{ M}^{-1}$  ( $1\sigma$ ). Using a rate constant for reaction of tin hydride with a secondary alkyl radical at 18.5 °C of  $k_{\text{H}} = 1.32 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ ,<sup>4</sup> one calculates a rate constant for ring opening of **1** at 18.5 °C of  $k_{\text{r}} = 1.5 \times 10^3 \text{ s}^{-1}$ . This value is about 1.5 times as great as the value previously estimated for the ring-opening reaction of radical **1** at 20 °C.<sup>9</sup> One might have thought that the estimated value would be more accurate, but the literature values for kinetics of ring opening of cyclobutylcarbonyl radicals are somewhat varied.<sup>14</sup>

$$[7]/[8] = (k_{\text{H}}/k_{\text{r}})[\text{Bu}_3\text{SnH}] \quad (1)$$

$$\log(k_{\text{r}}/k_{\text{H}}) = \log\{[8][\text{Bu}_3\text{SnH}]/[7]\} \quad (2)$$

An Arrhenius function for reaction of radical **1** was determined by conducting a series of reactions of precursor **4** (ca. 0.002 M) with  $\text{Bu}_3\text{SnH}$  (ca. 0.02 M) at temperatures between -20 and 47 °C. The expression for analysis of the data is given in eq 2, which is the logarithmic form of eq 1 after rearrangement. A plot of the log of the kinetic ratio against the inverse of temperature gave the relative Arrhenius function shown in Figure 1B, which gives  $\log(k_{\text{r}}/k_{\text{H}}) = (4.52 \pm 0.12) - (10.02 \pm 0.16)/2.313RT$  (errors at  $1\sigma$ ). Combination of these values with the Arrhenius function for reaction of  $\text{Bu}_3\text{SnH}$  with a secondary alkyl radical<sup>15</sup> gives an Arrhenius function for the ring opening of radical **1** in eq 3, where the errors are at  $1\sigma$ . This Arrhenius function predicts a rate constant for ring opening of **1** at 20 °C

(14) From the original product ratios reported by Beckwith and Moad for reaction of the cyclobutylcarbonyl radical with tin hydride (ref 6) and the recommended Arrhenius function for reaction of a primary alkyl radical with  $\text{Bu}_3\text{SnH}$  (ref 4b), one obtains an Arrhenius function for ring opening of the cyclobutylcarbonyl radical of  $\log k = 12.9 - 13.1/2.313RT$ . When low-temperature ESR data were included; however, the reported Arrhenius function was  $\log k = 12.6 - 12.2/2.313RT$  (ref 7b).

(15) The Arrhenius function for reaction of the 2-propyl radical with  $\text{Bu}_3\text{SnH}$  is  $\log k = (8.71 \pm 0.37) - (3.47 \pm 0.49)/2.313RT$  (see ref 4b).

(13) Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615–1618.

of  $k_r = 1.5 \times 10^3 \text{ s}^{-1}$ , in good agreement with the results from the 18.5 °C studies discussed above.

$$\log k_r = (13.2 \pm 0.4) - (13.5 \pm 0.6)/2.313RT \quad (3)$$

The log  $A$  term in the Arrhenius function for ring opening of radical **1** is consistent with expectations. Due to the rigidity of the system, the reaction should display little entropy demand in the transition state (i.e.,  $\Delta S^\ddagger \approx 0$ ), which would give a predicted log  $A$  term of 13.1 at room temperature. Correcting for the degenerate ring opening paths for radical **1** gives log  $A = 12.9$  for cleavage of one bond in radical **1**. Also as expected, both terms in the Arrhenius function for ring opening of radical **1** are similar to those for the cyclobutylcarbinyl radical,<sup>14</sup> and one notes that the more appropriate model, the 1-cyclobutylethyl radical, was reported to react slightly slower than the cyclobutylcarbinyl radical.<sup>6</sup>

The ring opening of radical **1** was initially used in a study of the rate constants for hydrogen atom trapping of the alkyl radical by the triethylborane complexes of water and methanol,<sup>9</sup> reactions representative of a general class of radical trapping reactions that can be synthetically important.<sup>10,16</sup> The kinetic results of the present work indicate that the rate constants for the hydrogen atom transfer trapping reactions by these complexes are about 1.5 times as great as previously reported. The kinetic difference will not affect synthetic planning greatly, but the more important ramification is that these results provide an Arrhenius function for ring opening of radical **1** that is reliable at low temperatures. This, in turn, can be combined with the relative Arrhenius function for reaction of  $\text{Et}_3\text{B}-\text{CH}_3\text{OH}$  with this radical that was previously determined.<sup>9</sup>

The resulting Arrhenius function for reaction of the  $\text{Et}_3\text{B}-\text{CH}_3\text{OH}$  complex with a secondary alkyl radical is given in eq 4. Due to accumulated errors in the previous<sup>9</sup> and present relative Arrhenius function determinations, the precision for a rate constant at a given temperature calculated from eq 4 might be poor, with an error of a factor of 2 or even greater, but the value of the log  $A$  term is the more important point. The pre-exponential factor in the Arrhenius function is quite small, indicating either a highly organized transition state for the hydrogen atom transfer reaction or an entropically unfavorable prior equilibration before the rate-determining step in the process, which we assume would be the actual hydrogen atom transfer step.

$$\log k_H = (7.2) - (4.7)/2.3RT \quad (4)$$

More careful studies at variable temperatures are necessary for detailed mechanistic conclusions about H-atom transfer

reactions of  $\text{Et}_3\text{B}$  complexes, but one point is seemingly undeniable. The hydrogen atom transfer reaction of the  $\text{Et}_3\text{B}-\text{CH}_3\text{OH}$  complex is increasingly competitive at reduced temperatures in comparison to “typical” radical reactions. That is, the H-atom transfer reaction might be “relatively slow” at room temperature, but it becomes “moderately fast” at low temperatures such as  $-30$  °C. This conclusion, if it proves to be general for hydrogen atom transfer reactions of  $\text{Et}_3\text{B}$ -water and -alcohol complexes, has important synthetic ramifications because it suggests that product distributions might be dramatically altered by changing the reaction temperature instead of the reagent concentrations.

The ring opening of radical **1** can now be used for calibration of slow radical reactions using “radical clock” indirect kinetic methods.<sup>1</sup> Synthetic methods for the preparations of two precursors for radical **1**, the xanthate ester **3** and the PTOC ester **4**, have been reported, and alkyl halide precursors for **1** are expected to be readily available. The long alkyl side chain in the clock results in high molecular weight products that do not evaporate under typical workup conditions and are well resolved from solvents when analyzed by GC.

## Experimental Section

The preparation of 1-cyclobutyltridecanoic acid and PTOC ester **4** is described in the Supporting Information.

**Kinetic Studies.** Toluene solutions of PTOC ester **4**, ca. 0.002 M, and  $\text{Bu}_3\text{SnH}$  at the desired concentration were deoxygenated by bubbling nitrogen through the solutions and equilibrated in a temperature-regulated bath while shielded from light. The stirred solutions were irradiated with visible light to initiate the radical chain reactions. After ca. 30 min, the yellow color of the initial mixtures was dissipated, and the mixtures were evaluated by thin layer chromatography to ensure that the reactions were complete. An internal standard of dodecane was added. The reaction mixture was washed with 3 M aqueous sodium hydroxide solution, dried over  $\text{MgSO}_4$ , and filtered through a short pad of silica gel with hexane elution. The eluent was analyzed by GC with TCD detection using a low-polarity column (bonded phase DB-5, 15 m  $\times$  0.53 mm). 1-Cyclobutyl dodecane and *trans*-4-hexadecane were identified by GC and GC-mass spectrometry as previously reported.<sup>9</sup>

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**Supporting Information Available:** Synthetic details for preparation of PTOC ester **4** and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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