

1: R = X = H 2: R = H, X = Me

3: R = X = Me

4: R = H, X = CO<sub>2</sub>Et

6: R = H. X = OMe

5: R = Me, X = CO<sub>2</sub>Et

0040-4039(95)00595-1

## $\alpha$ -Ethoxycarbonyl and $\alpha$ -Methoxy Substituted Radical Clocks

Martin Newcomb,\* Michelle A. Filipkowski and Cathy C. Johnson

Department of Chemistry, Wayne State University, Detroit, Michigan, 48202, U.S.A.

**Abstract:** Rate constants and Arrhenius functions for 5-*exo* cyclizations of the 1-(ethoxycarbonyl)-5-hexenyl radical, the 1-(ethoxycarbonyl)-1-methyl-5-hexenyl radical and the 1-methoxy-5-hexenyl radical were determined by indirect kinetic methods.

Synthetic applications of radical chemistry have increased dramatically in recent years.<sup>1</sup> Most useful procedures involve radical chain sequences wherein side reactions compete with the reactions of interest. Therefore, some knowledge of the absolute or relative kinetics of the competing reactions is necessary for rational design of experiments. A common method for evaluating radical kinetics has been to employ a "radical clock".<sup>2</sup> The clock reactions are calibrated unimolecular radical rearrangements such as the cyclizations of

5-hexenyl radicals 1-3. In a competition study employing a radical clock, one can determine the rate constant for the reaction of interest from the distribution of unrearranged and rearranged products and the known rate constant for rearrangement of the clock. Although several alkyl radical clocks are available,<sup>3</sup> few rearrangements of simple radicals containing stabilizing groups have been calibrated. Recently, we reported second order rate constants for reactions of tributyltin hydride with radicals containing electron withdrawing groups (ethoxycarbonyl and cyano)<sup>4</sup> and rate constants for reactions of Bu<sub>3</sub>SnH and *t*-BuSH with radicals containing the electron donating methoxy group.<sup>5</sup> In this work, we use these values for calibrations of the 5-*exo* cyclizations of radicals **4**, **5** and **6**.

For calibration of the  $\alpha$ -ethoxycarbonyl substituted radicals **4** and **5**, we employed the phenylselenyl precursors **7**.<sup>6</sup> Radical chain reactions<sup>7</sup> of these precursors in the presence of tin hydride with AIBN initiation gave mixtures of the acyclic ethyl heptenoates **8** and ethyl cyclopentanecarboxylates **9**.<sup>8</sup> For calibration of methoxy substituted radical **6**, the PTOC ester<sup>9</sup> **10** was the radical precursor.<sup>10</sup> Radical chain reactions<sup>11</sup> of **10** in the presence of *t*-BuSH gave 6-methoxy-1-hexene (**11**) and methoxycyclopentanes **12**.<sup>12</sup> Relative Arrhenius functions for cyclization and trapping were determined from 13 reactions of **7a**, 11 reactions of **7b**, and six reactions of **10**. Addition of these relative Arrhenius functions<sup>13</sup> to those, respectively, for reaction of Bu<sub>3</sub>SnH with secondary and tertiary  $\alpha$ -ethoxycarbonyl radicals<sup>4</sup> and that for reaction of *t*-BuSH with a secondary  $\alpha$ -methoxy-substituted radical<sup>5</sup> gave the Arrhenius functions for cyclizations listed in the Table. The rate constants for cyclization at 25 °C are also listed in Table 1 as well as the Arrhenius functions and rate constants for 5-*exo* cyclizations of the 1°, 2° and 3° hexenyl radicals **1-3**.<sup>14,15,16</sup>

Radical	R	Х	Arrhenius func. <sup>a</sup>	$k_{(25)}  (s^{-1})^{b}$	ratioc	reference
1	Н	н	10.4 - 6.8 <sub>5</sub> /θ	$2 \times 10^{5}$		3b, 14
2	Н	Me	10.0 <sub>5</sub> - 6.7/θ	$1 \times 10^{5}$	3:1 <sup>d</sup>	3b, 15
3	Me	Me	9.9 - 6.0/ <del>0</del>	$3 \times 10^{5}$		3b, 16
4	Н	CO <sub>2</sub> Et	11.65 - 8.7/ <del>0</del>	$2 \times 10^{5}$	1.8:1 <sup>e</sup>	this work
5	Me	CO <sub>2</sub> Et	10.2 - 8.4/ <del>0</del>	$1 \times 10^{4}$	1.1:1 <sup>e</sup>	this work
6	н	OMe	10.8 - 7.5/ <del>0</del>	$2 \times 10^{5}$	1.3:1 <sup>d</sup>	this work

Table. Arrhenius Functions and Rate Constants for 5-exo Cyclizations.

<sup>a</sup>Arrhenius function in kcal/mol;  $\theta = 2.3RT$ . <sup>b</sup>Rate constant at 25 °C. <sup>c</sup>Ratio of diastereomers at 25 °C. <sup>d</sup>The major diastereomer is *trans*. <sup>e</sup>Stereochemistry of diastereomers not determined.



One seemingly unexpected feature of the kinetic values in the Table is that the "stabilized" secondary radicals 4 and 6 cyclize with rate constants equal to those of the alkyl radicals 1-3. In fact, however, the same behavior was found in 5-*exo* cyclizations of the series of secondary radicals 13 and 6-*exo* cyclizations of secondary radicals 14; for both series, the rate constants for cyclization of the carboethoxy substituted (b) and methoxy substituted (c) radicals were similar to those of their methyl substituted analog.<sup>4,5</sup> The obvious lesson is that the acceptor and donor groups have little electronic influence on the kinetics of cyclizations despite any "radical stabilizing" effects as evaluated by differences in the C-H bond dissociation energies of a hydrocarbon in comparison to an ester or ether.

The results with 6 support the reasoning of Beckwith and Glover regarding the substantially reduced rate constant for cyclization of the 2-oxa-5-hexenyl radical (15,  $k = 5 \times 10^4 \text{ s}^{-1}$  at 25 °C) in comparison to its appropriate model, the 3-oxa-5-hexenyl radical ( $k = 9 \times 10^6 \text{ s}^{-1}$  at 25 °C).<sup>17</sup> Specifically, the reduced rate constant for cyclization of 15 results not from the inherent stability of the radical but from an increased activation energy required to adopt a conformation for cyclization in which resonance between the radical center and the oxygen atom is lost.<sup>17</sup> Such conformational constraint is unnecessary for cyclization of radical 6.



The cyclization of the tertiary ethoxycarbonyl substituted radical (5) is the special case. The reduced rate constant for cyclization of 5 in comparison to those of 4 and the tertiary alkyl radical analog 3 is similar to the kinetic effects observed in the 5-*exo* cyclizations of the tertiary ethoxycarbonyl (16b) and cyano (16c) substituted radicals. Both 16b and 16c were found to cyclize about two orders of magnitude less rapidly than radicals 13 and the alkyl tertiary analog 16a.<sup>4</sup> The kinetic effects in cyclizations of 5, 16b and 16c almost certainly are not related to only to radical stabilities or else similar kinetic retardations should have been found for 4, 13b and 14b. We have argued that the reduced rate constants for radicals 16b and 16c are a result of steric effects enforced by the planar structure of the radical center,<sup>18</sup> and the same reasoning explains the reduction in the rate constant for cyclization of 5. Thus, one may envision a transition structure for cyclization of carboethoxy or cyano substituted radicals in which the radical center is essentially planar (17) and a steric effect (indicated by the arrow) should be more important for the tertiary systems (R = Me) than for secondary systems (R = H). In the absence of the conjugating group, a more pyramidalized radical center in the transition structure in which steric effects are less important would be expected,<sup>18</sup> and, hence, tertiary alkyl radicals 3 and 16a cyclize with rate constants quite similar to those of their secondary radical counterparts 2 and 13a.

In conclusion, the simple ethoxycarbonyl substituted (4, 5) and methoxy substituted (6) radical clocks are now calibrated and can be used in competition kinetic studies<sup>3b</sup> to determine the rate constants of other reactions. One important result from this work is the observation that the secondary systems (4 and 6) cyclize with rate constants that are the same as those of the analogous alkyl radicals. In this regard, it is interesting to note that the second order hydrogen transfer trapping reactions of radicals with these substituents are also quite similar to those of alkyl radicals when the radical and trapping reagent are polarity matched.<sup>4,5</sup> An equally important point is that the reduced rate constant for cyclization of the tertiary ethoxycarbonyl substituted radical 5 compared to those of 4 and 3 (analogous to the kinetic effects observed in radicals  $16)^4$  is not a result of radical stability per se. Instead, for radical 5 and radical 15, the retardations in the cyclization. Few rate constants for substituted radicals are known, but those researchers employing radicals with acceptor or donor groups in synthetic applications should be able to use the information in this work in combination with the more extensive body of alkyl radical kinetics<sup>3</sup> to deduce reasonably good estimates of rate constants for their systems.

Acknowledgment. We thank the National Science Foundation (CHE-9117929) for support.

## **References and Notes**

- (a) Giese, B. Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press: Oxford. 1986. (b) Curran, D. P. Synthesis 1988, 417-439, 489-513. (c) Jasperse, C. P.; Curran, D. P. Chem. Rev. 1991, 91, 1237-1286.
- 2. Griller, D.; Ingold, K. U. Acc. Chem. Res. 1980, 13, 317-323.
- For reviews of calibrated radical clock reactions, see the following. (a) Beckwith, A. L. J.; Ingold, K. U. in *Rearrangements in Ground and Excited States*, de Mayo, P., ed., Vol. 1; Academic Press: New York. 1980; pp. 161-310. (b) Newcomb, M. *Tetrahedron* 1993, 49, 1151-1176.
- 4. Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S.-U. J. Am. Chem. Soc. 1995, 117, 0000-0000.

- Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. J. Am. Chem. Soc. 1995, 117, 1684-1687.
- 6. Precursors 7 were prepared from the corresponding ethyl heptenoates by LDA deprotonation and treatment with Ph<sub>2</sub>Se<sub>2</sub>. Silica gel chromatography afforded the selenides in 39-45% yield. They were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and HRMS.
- 7. A solution of 5 mg of 7, Bu<sub>3</sub>SnH, a hydrocarbon internal standard and 1 mg of AIBN in 1 mL of benzene or toluene was equilibrated at the desired temperature (10-90 °C). Reactions were initiated thermally or by irradiation in a photochemical reactor (300 nm light, 70 W, 1 h). Reaction mixtures were treated with a solution of iodine in Et<sub>2</sub>O until a faint pink color persisted, extracted with saturated KF solution, dried (MgSO<sub>4</sub>) and analyzed by GC with an FID detector. Predetermined response factors were employed to calculate yields and product ratios. Yields ranged from 45 to 87% and averaged 71%.
- 8. An authentic mixture of diastereomers of 9a was prepared by dialkylation of ethyl malonate with 1,4-dibromopentane, saponification of the diester to the monoester with one equiv. of KOH, and thermal decarboxylation of the sodium carboxylate. Silica gel chromatography gave a 2:1 mixture of diastereomers of 9a in 64% yield which were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and HRMS. Methylation (LDA, MeI) of 9a gave, after silica gel chromatography, a 50% yield of a 5:2 mixture of diastereomers of 9b that were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and HRMS.
- 9. Barton, D. H. R.; Crich, D.; Motherwell, W. B. Tetrahedron 1985, 41, 3901-3924.
- 10. Precursor 10 was prepared by alkylation of dimethyl methoxymalonate with 5-bromo-1-pentene, saponification of the diester to the diacid, thermal decarboxylation to the monoacid, and sequential reaction of this acid with oxalyl chloride and the sodium salt of N-hydroxypyridine-2-thione. All intermediates and PTOC ester 10 had appropriate <sup>1</sup>H and <sup>13</sup>C NMR spectra. 2-Methoxy-6-heptenoic acid was also characterized by HRMS.
- 11. Reactions of **10** were conducted in THF between -78 and 52 °C and contained no AIBN but were otherwise similar to those of **7**.<sup>7</sup> After temperature equilibration, the reactions were initiated by irradiation with a 150 W tungsten filament lamp at a distance of 0.5 m, and crude reaction mixtures were analyzed by GC without workup.
- 12. Products 11 and 12 were identified by GC and GC-MS comparison to authentic samples prepared by methylation (NaH, CH<sub>3</sub>I) of the corresponding alcohols. 5-Hexenol and *trans*-2-methylcyclopentanol are commercially available. A mixture of *cis* and *trans*-2-methylcyclopentanol (*cis/trans* = 1/3) was prepared by LiAlH<sub>4</sub> reduction of commercially available 2-methylcyclopentanone. From a reaction of precursor 10 at 25 °C, the 5-*exo* products 12 were produced in a 1:1.3 (*cis:trans*) ratio; the 6-*endo* product, methoxycyclohexane, was not detected. We are indebted to Mr. M.-H. Yoon for conducting the latter two studies.
- 13. The relative Arrhenius function for **4** was  $\log ((k_c/k_T)M^{-1}) = (3.5 \pm 0.4) (6.5 \pm 0.6)/\theta$ . That for **5** was  $\log ((k_c/k_T)M^{-1}) = (1.7 \pm 0.4) (4.1 \pm 0.6)/\theta$ . That for **6** was  $\log ((k_c/k_T)M^{-1}) = (2.4 \pm 0.2) (5.4 \pm 0.2)/\theta$ .  $\theta = 2.3 RT$  in kcal/mol, and errors are  $2\sigma$ .
- 14. Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. J. Am. Chem. Soc. 1981, 103, 7739-7742.
- Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. Aust. J. Chem. 1983, 36, 545-556. Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. J. Org. Chem. 1987, 52, 3509-3514.
- 16. Chatgilialoglu, C.; Dickhaut, J.; Giese, B. J. Org. Chem. 1991, 56, 6399-6403.
- 17. Beckwith, A. L. J.; Glover, S. A. Aust. J. Chem. 1987, 40, 157-173.
- 18. See the discussion and references in ref. 4.

(Received in USA 28 February 1995; accepted 29 March 1995)