found the rate constant to be about 1 order of magnitude lower (0.28 cm/s) though $\Delta\Delta G°_{sol}$ for nitromesitylene is the same as the other three within experimental error.

Bulky ortho substituents force the nitro group to be turned out of the plane of the ring and ESR measurements show that this is accompanied by an increase in spin density on the nitro group in the anion radical.[30] Peover and Powell suggested that the charge density, like the spin density, was also larger on the nitro group for radical anions, like that of nitromesitylene, where the nitro group is turned out of the plane due to the ortho methyl substituents. This more localized charge should lead to a larger solvent-reorganization energy and, hence, a lower rate constant. However, our measurements cast doubt on this interpretation because $\Delta\Delta G°_{sol}$ for nitromesitylene does not differ significantly from that of nitrobenzenes with large rate constants such as 4, 5, and 7.

Other factors must be responsible for the lower rate constants seen for 2,6-dialkylnitrobenzenes.[18,30-34] The most likely would appear to be an increase in the inner reorganization energy associated with resistance to turning of the nitro group toward the plane of the ring upon going from the neutral species to the anion radical. The allowable change in angle is small due to steric crowding, but only a relatively modest increase in activation energy is needed to bring about the observed factor of 10 reduction in the rate constant.

Recently, electron-transfer reactions among nitroaromatic radical anions and neutral species have been investigated in aqueous solution,[35] and it was found that reactions involving 2,6-dimethylnitrobenzene were much slower than for compounds with no or only one ortho substituent. The self-exchange rate constant for 2,6-dimethylnitrobenzene was estimated to be only 0.01-0.1 M^{-1} s^{-1}! The effect was again attributed to increased solvation energy due to greater charge on the nitro group. Though we did not determine $\Delta\Delta G°_{sol}$ in aqueous solution, the results for MeOH (Figure 3) suggest that $\Delta\Delta G°_{sol}$ for nitromesitylene (which is structurally similar to 2,6-dimethylnitrobenzene) would not be very much larger than for compounds that are not 2,6-substituted, so the large diminution in the electron exchange rate constant is likely to be caused by factors other than solvent-reorganization energy. As suggested earlier, increases in the inner reorganization energy may be responsible. Theoretical studies of the small structural changes accompanying electron transfer to substituted nitrobenzenes are likely to be illuminating and helpful.

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Registry No. 1, 603-71-4; **2**, 83-41-0; **3**, 100-17-4; **4**, 88-72-2; **5**, 99-99-0; **6**, 99-08-1; **7**, 98-95-3; **8**, 555-03-3; **9**, 1493-27-2; **10**, 350-46-9; **11**, 88-73-3; **12**, 402-67-5; **13**, 100-00-5; **14**, 121-73-3; **15**, 98-46-4; **16**, 619-24-9; **17**, 612-24-8; **18**, 99-65-0; **19**, 528-29-0; **20**, 619-72-7; **21**, 100-25-4; **22**, 4110-35-4; **23**, 84-65-1; **24**, 58-27-5; **25**, 137-18-8; **26**, 130-15-4; **27**, 719-22-2; **28**, 106-51-4; **29**, 363-03-1; **30**, 117-80-6; **31**, 527-21-9; **32**, 120-12-7; **33**, 119-61-9; **34**, 626-17-5; **35**, 91-15-6; **36**, 623-26-7; **37**, 85-44-9; **38**, 102-54-5.

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Kinetics and Mechanism of the Exo Cyclizations of ω-Formylalkyl Radicals

Athelstan L. J. Beckwith* and Benjamin P. Hay

Contribution from the Research School of Chemistry, Australian National University, GPO Box 4, Canberra, A.C.T. 2601, Australia. *Received September 16, 1988*

Abstract: Kinetic analysis of the reactions of 5-bromopentanal (**1**) and 6-bromohexanal (**7**) indicates that both the formylbutyl radical (**2**) and the formylpentyl radical (**8**) undergo fast exo cyclization. In each case the reaction is reversible and the equilibrium lies in favor of the open-chain form. The reactions are complicated by the propensity of aldehydes to undergo abstraction of formyl hydrogen atoms. Rate constants were measured by competition against reactions of the formylalkyl radicals, **2** and **8**, and the cycloalkoxy radicals, **3** and **9**, with tributylstannane. Values obtained at 80 °C include 8.7×10^5 s^{-1} and 1.0×10^6 s^{-1} for cyclization of **2** and **8**, respectively, and 4.7×10^8 s^{-1} and 1.1×10^7 s^{-1} for the reverse reactions. The Arrhenius parameters for cyclization of **2** and its alkenyl analogue, 5-hexenyl radical, are very similar, but the activation energy for cyclization of **8** is unexpectedly low. Molecular orbital (AM1) and molecular mechanics (MM2) calculations of transition structure strain energies are consistent with these observations.

Intramolecular radical cyclizations (Scheme I) have generated considerable interest, both synthetically[1] and mechanistically.[2] Although radicals derived from species containing a variety of X=Y functional groups have been investigated, among them alkenes, alkynes, and nitriles, only recently have ketones[3] and

Scheme I

aldehydes[4,5] received much attention. In what follows, we will focus on cyclizations of species containing the aldehyde function,

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Table I. Example Product Distributions for the Reaction of **1** with Bu_3SnH (Benzene, 80 °C, under Argon)[a]

entry	$[1]_0$	$[BuSnH]_0$	[4]	[5]	[6]	[Br-butane]	butane
1	0.010	0.10	0.0084	0.0011	0.0006	nd	nd
2	0.020	0.20	0.014	0.0019	0.0032	nd	nd
3	0.030	0.28	0.018	0.0028	0.0072	nd	nd
4	0.040	0.38	0.022	0.0042	0.013	nd	nd
5	0.20	0.025	0.020	0.0038	nd	0.0026	d
6	0.20	0.070	0.059	0.0098	nd	0.0032	d
7	0.20	0.17	0.14	0.021	nd	0.0007	d
8	0.30	0.025	0.019	0.0052	nd	0.0032	d
9	0.30	0.10	0.083	0.016	nd	0.0024	d
10	0.30	0.22	0.18	0.030	nd	0.0016	d
11	0.40	0.025	0.018	0.0061	nd	0.0057	d
12	0.40	0.10	0.079	0.018	nd	0.0047	d
13	0.40	0.23	0.19	0.034	nd	0.0025	d
14	0.10[b]	0.070	0.056	0.013	nd	0.0013	d
15	0.10[b]	0.070	0.047	0.021	nd	0.0005	d

[a] Final product concentrations in moles/liter; nd, not detected, d, detected. [b] Runs with nonanal added: 14, 0.25 M, and 15, 0.70 M.

i.e., the exo cyclizations of ω-formylalkyl radicals. Specifically, this paper is concerned with mechanistic aspects of the radical cyclizations that ensue upon the reaction of ω-formylalkyl halides with Bu_3SnH (tri-*n*-butyltin hydride).

In the first example of this type of reaction,[4] 6-chlorohexanal was treated with 1 molar equiv (0.4 M) of Bu_3SnH (tri-*n*-butyltin hydride) in benzene at 80 °C to give hexanal and cyclohexanol in approximately equal amounts.[4b] The synthetic utility of this class of cyclization has recently been explored through an examination of the reactions of ω-formylalkyl iodides with Bu_3SnH (0.032 M, refluxing benzene).[5] These studies have demonstrated that radical cyclizations involving intramolecular addition to an aldehyde group can be efficient reactions with yields as high as 85% when forming six-membered rings. It was noted that cyclohexanols were formed in higher yields than cyclopentanols. The cyclizations were sometimes accompanied by β-scission reactions, a phenomenon observed more frequently in the five-membered ring systems.

Although the synthetic utility of these reactions has been demonstrated,[5] their mechanisms await elucidation. The observation that 1,6 exo closures gave higher yields than 1,5 exo closures is particularly intriguing since, for ω-alkenylalkyl radicals, 1,5 cyclizations are generally faster than 1,6 cyclizations.[2] Two possible explanations are (i) that the 1,6 exo closures of ω-formylalkyl radicals are faster than 1,5 exo closures, and (ii) that the reverse reaction, β-scission of the cycloalkoxy intermediates, is much faster in five-membered rings than in six-membered rings.

Recently we reported the results of a mechanistic study of the β-scission of the cyclopentoxy radical.[6] These species were generated in the presence of a large excess (>10 molar equiv) of Bu_3SnH (≥0.30 M) and were found to undergo rapid, reversible β-scission. Arrhenius parameters were obtained for the β-scission (E_a = 6.26 ± 0.56 kcal/mol, log (A/s^{-1}) = 12.55 ± 0.41) and the reverse reaction, the 1,5 exo closure of the 4-formylbutyl radical (E_a = 6.88 ± 0.46 kcal/mol, log (A/s^{-1}) = 10.23 ± 0.31). The β-scission of the cyclohexyloxy radical was, unfortunately, too slow to allow a similar study of the 1,6 exo closure by this method. We have, however, carried out further investigations of these archetypical ω-formyl radical cyclizations by examining the reactions of 5-bromopentanal and 6-bromohexanal with Bu_3SnH. Herein, we report detailed mechanisms for these reactions, results that confirm our previous studies,[6] and Arrhenius parameters for the 1,6 exo closure of the 5-formylpentyl radical.

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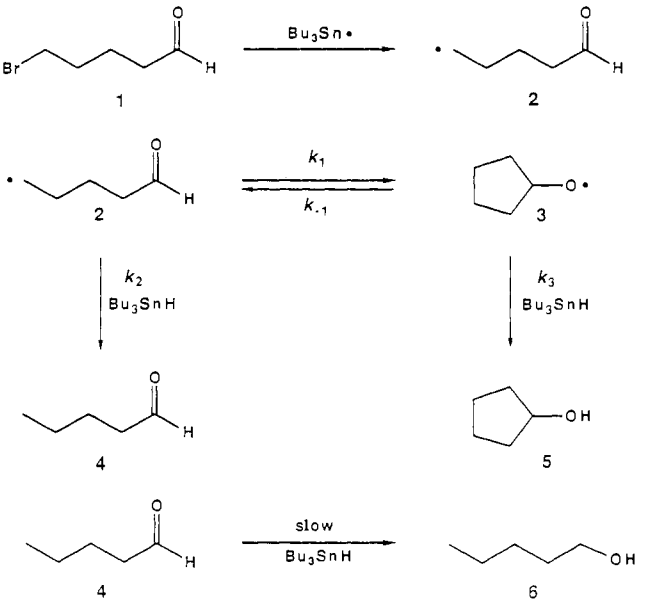
Table II. Example Product Distributions for the Reaction of **7** with Bu_3SnH (Benzene, 80 °C, under Argon)[a]

entry	$[7]_0$	$[Bu_3SnH]_0$	[10]	[11]	[12]	[Br-pentane]
1	0.030	0.25	0.017	0.011	0.0014	nd
2	0.030	0.53	0.021	0.0070	0.0022	nd
3	0.030	0.84	0.022	0.046	0.0030	nd
4	0.20	0.035	0.0076	0.026	nd	0.0055
5	0.20	0.070	0.019	0.049	nd	0.0047
6	0.20	0.10	0.033	0.064	nd	0.0041
7	0.20	0.14	0.054	0.083	nd	0.0033
8	0.20	0.17	0.074	0.096	nd	0.0016
9	0.80	0.035	0.0071	0.028	nd	0.0085
10	0.80	0.070	0.017	0.051	nd	0.0074
11	0.80	0.10	0.031	0.067	nd	0.0100
12	0.80	0.14	0.051	0.088	nd	0.0081
13	0.80	0.17	0.063	0.10	nd	0.0066

[a] Final product concentrations in moles/liter; nd, not detected.

Scheme II

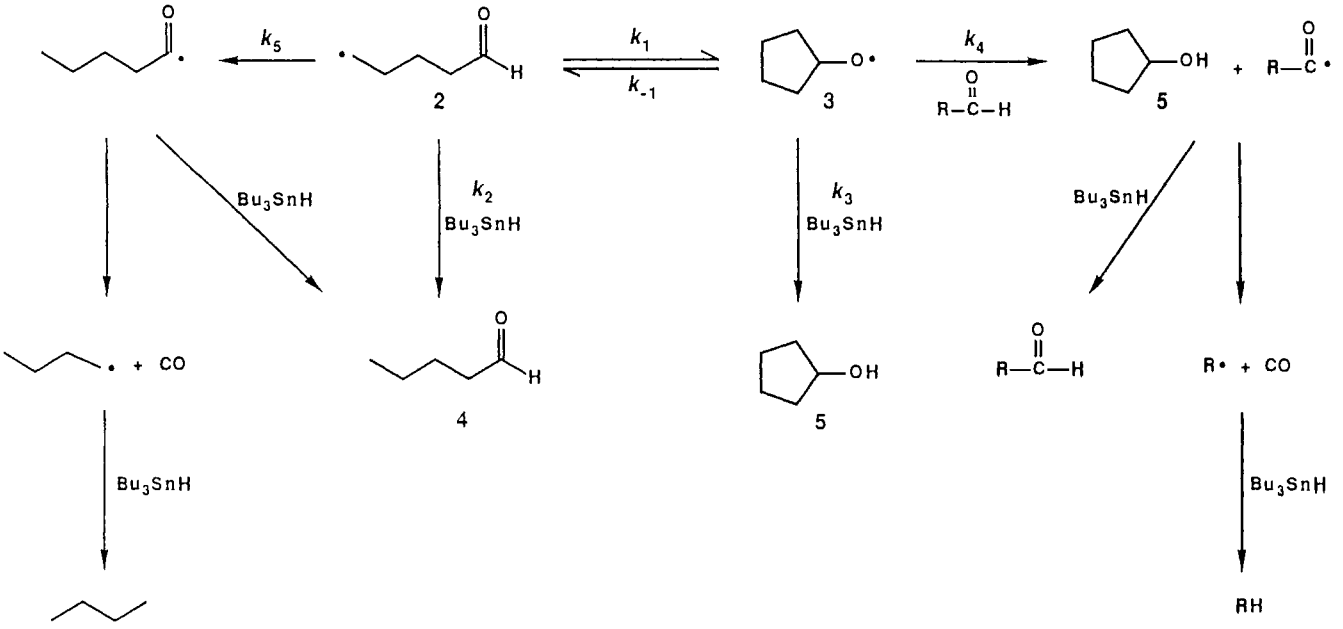


Results

(i) Reaction of 5-Bromopentanal (1) with Bu_3SnH. The reactions of **1** with Bu_3SnH were initiated with AIBN in benzene solution under an argon atmosphere at 80 °C. Over 60 experiments were carried out with a systematic variation of initial reactant concentrations. The products were analyzed by GLC, and typical results are presented in Table I. The identities and yields of the products was found to depend upon the initial reaction conditions. On the basis of this behavior the reactions are divided into two categories: (i) where $[Bu_3SnH]_0 \geq 10 \times [1]_0$ and (ii) where $[Bu_3SnH]_0 \leq [1]_0$. In the former case, e.g., entries 1–4 (Table I), three products account quantitatively for **1**. These are 1-pentanal (**4**), cyclopentanol (**5**), and 1-pentanol (**6**). In the latter case, e.g., entries 5–15 (Table I), **4** and **5** account for 95–100% of the Bu_3SnH consumed, but **6** is not present. Instead, small amounts of bromobutane and butane are formed. Nonanal was added to some of the reactions where $[Bu_3SnH]_0 \leq [1]_0$, e.g., entries 14–15 (Table I), and was found to influence the relative yields of **4** and **5**.

(ii) Reaction of 6-Bromohexanal (7) with Bu_3SnH. The reactions of **7** with Bu_3SnH were initiated with AIBN in benzene solution under argon at temperatures ranging from 40 to 80 °C. More than 60 experiments were conducted with a systematic variation of initial reactant concentrations. The products of these reactions were analyzed by GLC, and typical results are presented in Table II. As with the reactions of **1**, the product distributions can be divided into two categories. When $[Bu_3SnH]_0 \geq 10 \times [7]_0$ the reaction yields 1-hexanal (**10**), cyclohexanol (**11**), and 1-hexanol (**12**), e.g., entries 1–3 (Table II). When $[Bu_3SnH]_0 \leq$

Scheme III



$[7]_0$ the products **10** and **11** account for 95–100% of the Bu_3SnH consumed, but **12** is not present, e.g., entries 4–13 (Table II). Bromopentane, but not pentane, is formed under the latter conditions.

Discussion

(i) Reaction of 5-Bromopentanal (1) with an Excess of Bu_3SnH (Scheme II). Of the three compounds formed when **1** reacts with Bu_3SnH in large excess, only 1-pentanal (**4**) and cyclohexanol (**5**) are expected radical products under these conditions.[6] 1-Pentanol (**6**) cannot be formed by a primary reaction of the 4-formylbutyl radical **2** and is postulated, therefore, to arise via a secondary side reaction.

The variation in the yields of **4** and **6** with reaction time support this hypothesis. It was found that shorter reaction times gave lesser relative yields, [**6**]/[**4**], while longer reaction times gave corresponding increases in [**6**]/[**4**]. The product **6** is not formed under second-order conditions where $[\mathbf{1}]_0 \geq [Bu_3SnH]_0$ (vide infra). Moreover, **6** was not formed in the reactions at 80 °C for *N*-cyclopentoxypyridine-2-thione with Bu_3SnH (0.25–0.85 M) where **4** is a product, due to the much shorter time (5 min vs 2 h) of those reactions.[6] These observations are consistent with previous reports that Bu_3SnH is capable of reducing aldehydes and ketones, when reductions are carried out in very concentrated solutions or in the presence of Lewis acid catalysts. They would, therefore, be expected to be slow under our reaction conditions.[7]

The concentrations of **4**–**6** were measured as a function of $[Bu_3SnH]_0$ at 80 °C. The results are given in Figure 1 as a plot of ([**4**] + [**6**])/[**5**] vs $[Bu_3SnH]_0$. The product distribution is consistent with the mechanism presented in Scheme II. At the pseudo-first-order concentrations of Bu_3SnH in these experiments, the ratio ([**4**] + [**6**])/[**5**] is related to $[Bu_3SnH]_0$ by eq 1. The rate constant ratios in eq 1 have previously been measured; k_2/k_1

$$\frac{([4] + [6])}{[5]} = \left[\frac{k_2}{k_1}\frac{k_{-1}}{k_3}\right] + \frac{k_2}{k_1}[Bu_3SnH]_0 \qquad (1)$$

$= 6.65 \pm 1.46\ M^{-1}$ and $k_{-1}/k_3 = 1.28 \pm 0.07$ M at 80 °C in benzene.[6] These rate constant ratios and eq 1 are found to predict correctly the observed $[Bu_3SnH]_0$ dependence (see the line in Figure 1), thus demonstrating that the results obtained in this study of the cyclization of **2** are in quantitative agreement with those obtained in the study of the β-scission of **3**.[6]

(ii) Reaction of an Excess of 1 with Bu_3SnH (Scheme III). In order to test further the mechanism presented in Scheme II, the reaction was carried out under second-order conditions with $[\mathbf{1}]_0 \geq [Bu_3SnH]_0$. Under these conditions **4** (major) and **5** (minor) accounted for 95 to 100% of the Bu_3SnH consumed. The reduced aldehyde **6** was not detected as a product. The results are presented as plots of percent cyclization ($100 \times [\mathbf{5}]/[Bu_3SnH]_0$) vs $[Bu_3SnH]_0$ in Figure 2. Surprizingly, the percentage of cy-

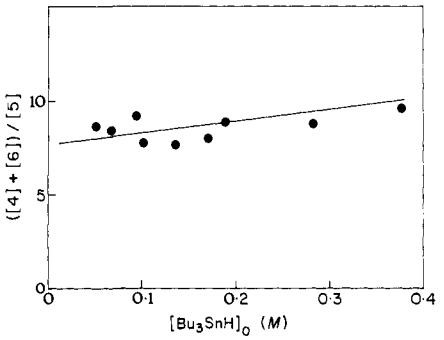


Figure 1. Plot of ([**4**] + [**6**])/[**5**] vs $[Bu_3SnH]_0$ for the reaction of **1** with ≥10 molar equiv of Bu_3SnH in benzene at 80 °C. The line was calculated with eq 1 using $k_2/k_1 = 6.65\ M^{-1}$ and $k_{-1}/k_3 = 1.28$ M (see text).

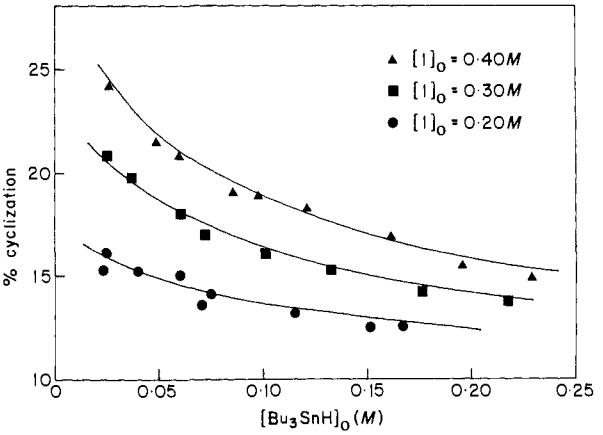


Figure 2. Plots of the percentage of cyclization ($100 \times [\mathbf{5}]/[Bu_3SnH]_0$) vs $[Bu_3SnH]_0$ for reactions of $[\mathbf{1}]_0 = 0.20$, 0.30, and 0.40 M with Bu_3SnH in benzene at 80 °C. Curves were generated with eq 2 (see text).

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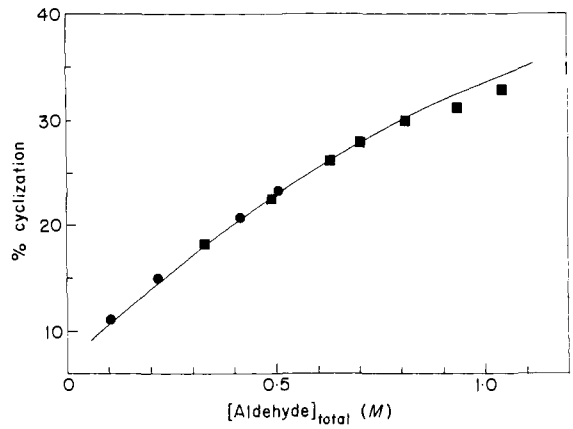


Figure 3. Plot of the percentage of cyclization ($100 \times [\mathbf{5}]/[Bu_3SnH]_0$) vs $[aldehyde]_{total}$ for the reaction of **1** with 0.070 M Bu_3SnH in benzene at 80 °C; ●, **1** only; ■, **1** + nonanal. The curve was generated by eq 2 (see text).

clization depended not only upon $[Bu_3SnH]_0$, but also upon $[\mathbf{1}]_0$! In addition, two new products were also present in small amounts: butane and bromobutane.

These observations are not accounted for by the first-order mechanism in Scheme II. Under second-order conditions, the reaction is more complicated due to the availability of other pathways that are too slow to compete when $[\mathbf{1}]_0$ is low and $[Bu_3SnH]_0$ is high. Several experiments were designed to elucidate the change in mechanism under these second-order conditions and the results, discussed below, require the more complex mechanism given in Scheme III.

From the results obtained under the first-order reaction conditions (vide supra), we know that **2** and **3** rapidly interconvert, $\mathbf{2} \rightleftharpoons \mathbf{3}$, with $k_1 = 8.7 \times 10^5\ s^{-1}$ and $k_{-1} = 4.7 \times 10^8\ s^{-1}$ at 80 °C.[6] The increasing yield of **5** that accompanies increasing $[\mathbf{1}]_0$ can be explained if **1** acts as a selective H• donor, resulting in the trapping of the alkoxy radical **3** in preference to the alkyl radical **2**. This hypothesis is supported by the fact that alkoxy radicals generally undertake H• abstractions from organic substrates with rate constants $\geq 10^3$ times larger than those of alkyl radicals.[8] Moreover, aldehydes are known to be good H• donors since they contain relatively weak aldehydic C–H bonds (BDE = 86 kcal/mol).[9] Thus, it is not surprising to find that when *tert*-butoxy radicals are generated in the presence of aldehydes, H• abstraction yielding acyl radicals is the predominant reaction.[10]

If this hypothesis is correct, then any aldehyde should cause similar increases in the yield of **5**. A series of reactions was carried out with $[Bu_3SnH]_0$ fixed at 0.070 M and $[\mathbf{1}]_0$ varied from 0.10 to 0.50 M. A second set were run at the same $[Bu_3SnH]_0$, but now with the $[\mathbf{1}]_0$ fixed at 0.10 M and a second aldehyde, nonanal, present at concentrations ranging from 0.10 to 5.8 M (as the solvent). The results are given as a plot of percent cyclization vs $[aldehyde]_{total}$ in Figure 3. The extent of cyclization ranges from 15% at 0.10 M aldehyde to 35% at 1.0 M aldehyde and a maximum yield of 39% when the reaction is carried out in nonanal as a solvent. In agreement with our hypothesis, the amount of cyclization depends upon the total concentration of aldehyde, but not the type of aldehyde.

On the basis of previous studies,[10] if **3** abstracts H• from **1**, and to a lesser extent from **4**, then acyl radicals will be formed. These radicals can either abstract H• from Bu_3SnH or undergo decarbonylation to yield bromobutane and butane, respectively. Under second-order reaction conditions, at $[\mathbf{1}]_0 = 0.20$–0.40 M, bromobutane is formed in yields corresponding to ~40% of **[5]** when $[Bu_3SnH]_0 = 0.050$ M and ~10% of **[5]** when $[Bu_3SnH]_0 = 0.20$ M. Small amounts of butane were also detected, but not quantified. Furthermore, when nonanal is present, *n*-octane is formed in low yields.

As mentioned above, decarbonylation of acyl radicals may compete with H• transfer from Bu_3SnH to regenerate the aldehyde. Therefore, if reactions are carried out with Bu_3SnD, some deuterium should be incorporated in the aldehyde. A set of reactions was conducted with $[Bu_3SnD]_0$ fixed at 0.10 M and $[\mathbf{1}]_0$ at 0.10, 0.30, and 0.50 M. GLC revealed no detectable bromobutane at $[\mathbf{1}]_0 = 0.10$ M, but it was present at 0.30 M and in increased amount at 0.50 M. Deuterium NMR revealed no detectable signal at the aldehydic position of **1** (9.16 ppm, benzene) in the products of the reaction with $[\mathbf{1}]_0 = 0.10$ M, but a signal at 9.16 ppm was present in the products of the reaction with $[\mathbf{1}]_0 = 0.30$ M and in increased intensity when $[\mathbf{1}]_0 = 0.50$ M. The observation that both the yield of bromobutane and the extent of deuterium incorporation increase with increasing $[\mathbf{1}]_0$ is consistent with the presence of 5-bromopentanoyl radical intermediates.

In addition to providing evidence for the role of **1** as an H• donor, these experiments with Bu_3SnD revealed the existence of another competing pathway since peaks at 9.28 and 0.66 ppm were also present in the ^2H spectra of the product mixtures. These two peaks, present in all three samples, correspond to deuterium incorporation at the aldehyde and methyl positions, respectively, of **4**. When $[\mathbf{1}]_0 = 0.10$ M, 9.2% of the deuterium in **4** is in the aldehyde position. This value drops to 7.1% when $[\mathbf{1}]_0 = 0.50$ M. While a small amount of intermolecular H• abstraction from **4** is expected, these results are not accounted for by intermolecular H• abstraction alone. Such H• abstraction from **4** ($[\mathbf{4}] \leq 0.075$ M in these experiments) is in competition with H• abstraction from **1** and should be greatly decreased when $[\mathbf{1}]_0$ is increased from 0.10 to 0.50 M. The fact that the extent of deuterium incorporation at the aldehyde position of **4** is only slightly decreased requires that the majority of the pentanoyl radicals arise via an intramolecular pathway. The existence of this pathway is not totally unexpected, since 1,5 hydrogen transfer in **2** is a known reaction. At temperatures of ≥150 °C, the radical **3** has been observed to undergo β-scission to **2** followed by intramolecular H• transfer to yield the acyl radical.[11] This process is facilitated by a six-membered transition state and favorable enthalpy changes: aldehyde C–H (86 kcal/mol) vs a primary alkyl C–H (98 kcal/mol).[9]

Scheme III comprises the minimum number of mechanistic steps required to account for the product distributions found under the second-order reaction conditions. Further support for this mechanism is obtained by demonstrating its ability to predict quantitatively the percentage of cyclization as a function of $[Bu_3SnH]_0$ and $[aldehyde]_0$. In accord with Scheme III, **[5]** is related to the concentrations of the starting materials by the differential equation, eq 2.[12] This equation was used to calculate

$$\frac{-d[\mathbf{5}]}{d[Bu_3SnH]} = \frac{k_1}{k_2}\left(\frac{k_4}{k_3}([aldehyde]_0 - [\mathbf{5}]) + [Bu_3SnH]\right) \Big/ \left([Bu_3SnH]^2 + \left(\frac{k_1}{k_2} + \frac{k_{-1}}{k_3} + \frac{k_5}{k_2} + \frac{k_4}{k_3}([aldehyde]_0 - [\mathbf{5}])\right)[Bu_3SnH] + \left(\frac{k_5}{k_2}\frac{k_{-1}}{k_3}\right) + \left(\frac{k_5}{k_2} + \frac{k_1}{k_2}\right)\frac{k_4}{k_3}([aldehyde]_0 - [\mathbf{5}])\right) \quad (2)$$

(8) *CRC Handbook of Bimolecular and Termolecular Gas Reactions*; Kerr, J. A., Ed.; CRC: Boca Raton, FL, 1981.

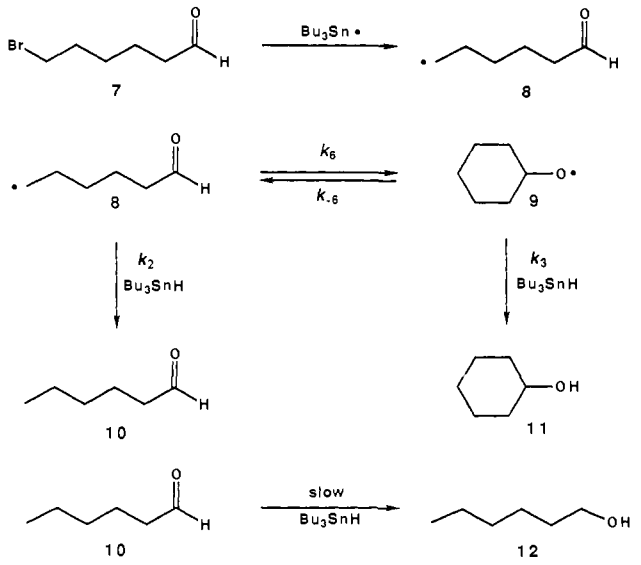
(9) Kerr, J. A. In *CRC Handbook of Chemistry and Physics*; CRC: Boca Raton, FL, 1986; p F-178.

(10) See, for example: (a) Fuller, G.; Rust, F. F. *J. Am. Chem. Soc.* **1958**, *80*, 6148. (b) Rust, F. F.; Seubold, F. H.; Vaughn, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 4253. (c) Murayama, K.; Taniuchi, M.; Oka, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 712.

(11) (a) Druliner, J. D.; Kitson, F. G.; Rudat, M. A.; Tolman, C. A. *J. Org. Chem.* **1983**, *48*, 4951. (b) Wallace, T. J.; Gritter, R. J. *J. Org. Chem.* **1961**, *26*, 5256.

(12) Equation 2 was derived from Scheme III with the following assumptions: (i) that the steady-state approximation applies to **[3]**, (ii) that $-d[Bu_3SnH] \simeq d[\mathbf{4}] + d[\mathbf{5}]$ (neglecting small amounts of butane arising from the decarbonylation of pentanol radicals generated via intramolecular 1,5 H• transfer), and (iii) that $[aldehyde] \simeq [aldehyde]_0 - [\mathbf{5}]$ (neglecting small amounts of butane and bromobutane).

Scheme IV



theoretical yields of **5** by an iterative technique (Runge–Kutta method)[13] which could be compared with observed yields of **5** given in Figures 2 and 3. The calculated yields of **5** were then adjusted to give the best fit to the observed yields of **5** by the variation of k_1/k_2, k_{-1}/k_3, k_4/k_3, and k_5/k_2 using the Simplex algorithm with χ^2 minimization.[14]

A good fit, shown as the curves in Figures 2 and 3, was obtained with $k_1/k_2 = 0.154 \pm 0.013$ M, $k_{-1}/k_3 = 1.11 \pm 0.09$ M, $k_4/k_3 = 0.204 \pm 0.022$, and $k_5/k_2 = 0.0241 \pm 0.0017$ M. The excellent agreement between these second-order k_1/k_2 and k_{-1}/k_3 ratios and those obtained under first-order conditions, i.e., $k_1/k_2 = 0.150 \pm 0.033$ M and $k_{-1}/k_3 = 1.28 \pm 0.07$ M (vide supra), strongly supports Scheme III. These results also provide values at 80 °C of k_4 and k_5. If $k_3 = 3.7 \times 10^8$ M^{-1} s^{-1} at 80 °C,[6] then $k_4 = 7.5 \times 10^7$ M^{-1} s^{-1}. This value is comparable to the rate constants observed for other alkoxy radical hydrogen abstractions which generally fall in the range of 10^6 to 10^8 M^{-1} s^{-1}.[15] A value of $k_2 = 6.4 \times 10^6$ M^{-1} s^{-1} at 80°C,[16] affords the first measurement of k_5, 1.5×10^5 s^{-1}.

(iii) Reaction of 6-Bromohexanal (7) with an Excess of Bu_3SnH (Scheme IV). The reactions of **7** with Bu_3SnH in excess ($[Bu_3SnH]_0 \geq [7]_0$) were examined over the temperature range of 40–100 °C and found to yield products analogous to those observed in the first-order reactions of **1**. The reaction products 1-hexanal (**10**), cyclohexanol (**11**), and 1-hexanol (**12**) accounted quantitatively for the starting material. The concentrations of these products were measured as a function of $[Bu_3SnH]_0$, and the results are given in Figure 4 as plots of ([**10**] + [**12**])/[**11**] vs $[Bu_3SnH]_0$.

These product distributions are consistent with the mechanism presented in Scheme IV. At the pseudo-first-order concentrations of Bu_3SnH used in these experiments, the ratio ([**10**] + [**12**])/[**11**] is related to $[Bu_3SnH]_0$ by eq 3. Thus, the slopes of the plots

$$\frac{[\mathbf{10}] + [\mathbf{12}]}{[\mathbf{11}]} = \left[\frac{k_2}{k_6}\frac{k_{-6}}{k_3}\right] + \left[\frac{k_2}{k_6}\right][Bu_3SnH]_0 \qquad (3)$$

in Figure 4 provide values of k_6/k_2 at several temperatures.[17]

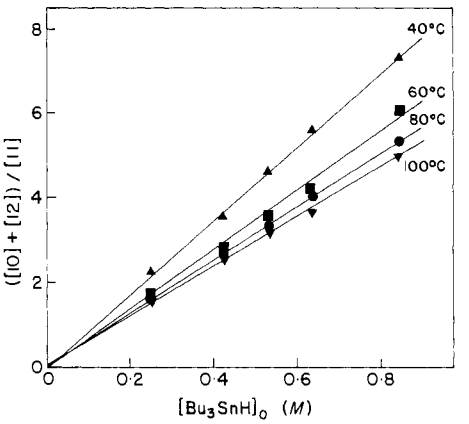
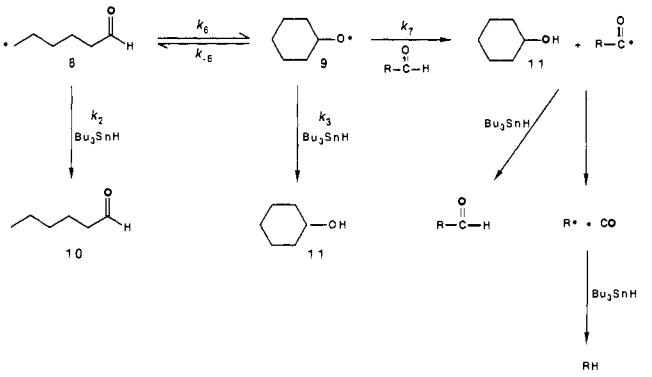


Figure 4. Plots of ([**10**] + [**12**])/[**11**] vs $[Bu_3SnH]_0$ for the reaction of **7** with ≥10 molar equiv of Bu_3SnH in benzene at 40, 60, 80 and 100 °C. The slopes of these plots yield values of k_2/k_6.[17]

Scheme V



Linear regression analysis of a ln (k_6/k_2) vs $1/T$ plot yields the relative Arrhenius parameters given by eq 4, $\theta = 2.303RT$

$$\log [(k_6/k_2)/\mathrm{M}] = (0.28 \pm 0.04) - \frac{(1.73 \pm 0.06)}{\theta} \qquad (4)$$

$$\log (k_6/\mathrm{s}^{-1}) = (9.38 \pm 0.20) - \frac{(5.43 \pm 0.30)}{\theta} \qquad (5)$$

(kcal/mol). Substitution of the known Arrhenius parameters for the H• abstraction from Bu_3SnH by a primary alkyl radical ($E_a = 3.7 \pm 0.3$ kcal/mol, $\log (A/\mathrm{M}^{-1}\,\mathrm{s}^{-1}) = 9.1 \pm 0.2$)[16] yields eq 5, which gives the temperature dependence of k_6 (the rate constant for the 1,6 exo cyclization of **8**). Values of k_6 calculated from eq 5 are 2.5×10^5 s^{-1} at 25 °C and 1.0×10^6 s^{-1} at 80 °C.

The $[Bu_3SnH]$ dependence given in Figure 4 is consistent with cyclization of **8** to give **9** in competition with transfer of H• to **8** from Bu_3SnH. However, it neither requires nor rules out the β-scission of **9**. Information concerning the reversibility of the cyclization comes from the intercepts of the plots in Figure 4: intercept = $(k_2/k_6)(k_{-6}/k_3)$. For these plots the intercepts lie between 0 and 0.15, but given their associated uncertainties of ±0.2, one can conclude only that $0 \leq (k_2/k_6)/(k_{-6}/k_3) \leq 0.35$. At one extreme, $k_{-6}/k_3 = 0$ and the cyclizations are irreversible. At the other extreme, $k_{-6}/k_3 = 0.35$ (k_6/k_2) in which case a significant amount of β-scission is occurring. Further reactions, carried out under second-order conditions, reveal that the latter situation obtains at 80 °C (vide infra).

(iv) Reaction of an Excess of 7 with Bu_3SnH (Scheme V). To test further the mechanism in Scheme IV, the reaction was carried out under second-under conditions with $[7]_0 \geq [Bu_3SnH]_0$ at 80 °C. Under these conditions, **10** (minor) and **11** (major) account

(13) Simmons, G. F. *Differential Equations*; McGraw-Hill: New York, 1972; p 69.

(14) (a) Nelder, J. A.; Mead, R. *Comput. J.* **1965**, *7*, 308. (b) Daniels, R. W. *An Introduction to Numerical Methods and Optimization Techniques*; North Holland: New York, 1978; p 183.

(15) Howard, J. A.; Scaiano, J. C. In *Radical Reaction Rates in Liquids*; Fischer H., Ed.; Springer: Berlin, 1984; Landolt–Bornstein, New Series Vol. 13d.

(16) (a) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (b) Johnston, L. J.; Lusztyk, J.; Wagner, D. D. M.; Abeywickrema, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

(17) Values of k_6/k_2 (M) obtained as the reciprocals of the slopes of ([**10**] + [**12**])/[**11**] vs $[Bu_3SnH]_0$ plots (Figure 4) are as follows: 40 °C, 0.117 ± 0.004; 60 °C, 0.139 ± 0.008; 80 °C, 0.163 ± 0.005; 100 °C, 0.182 ± 0.009.

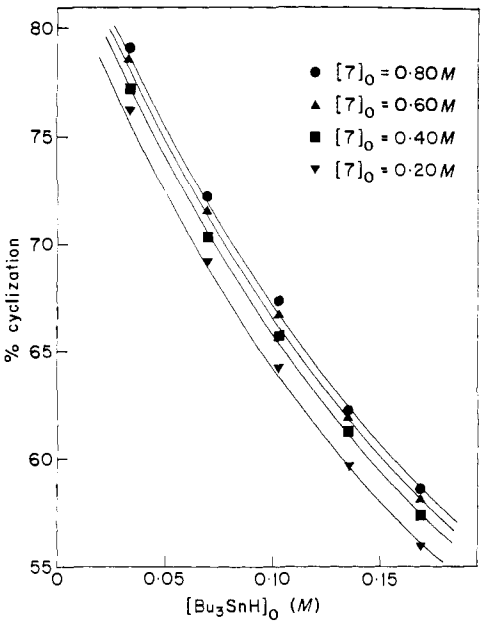


Figure 5. Plots of percentage of cyclization ($100 \times [\mathbf{11}]/[Bu_3SnH]_0$) vs $[Bu_3SnH]_0$ for reactions of $[\mathbf{7}]_0 = 0.20$, 0.40, 0.60, and 0.80 M with Bu_3SnH in benzene at 80 °C. Curves were generated with eq 6 (see text).

for 95–100% of the Bu_3SnH consumed. The results are presented as plots of percentage of cyclization ($100 \times [\mathbf{11}]/[Bu_3SnH]_0$) vs $[Bu_3SnH]_0$ in Figure 5. In addition to **10** and **11**, bromopentane was produced in amounts ranging from 2% of **11** ($[\mathbf{7}]_0 = 0.20$ M, $[Bu_3SnH]_0 = 0.170$ M) to 32% of **11** ($[\mathbf{7}]_0 = 0.80$ M, $[Bu_3SnH]_0 = 0.035$ M). The reduced aldehyde **12** and pentane were not detected. To account for the effect of $[\mathbf{7}]_0$ on the percentage of cyclization (Figure 5) and the presence of bromobutane, the first-order mechanism in Scheme IV was modified to give Scheme V.

Like the second-order reactions of **1** (vide supra), the extent of cyclization depends upon both $[Bu_3SnH]_0$ and $[\mathbf{7}]_0$. In the case of **1**, the dependence of the extent of cyclization upon the concentration of aldehyde was shown to be due to two factors: (i) reversible cyclization and (ii) the ability of the aldehyde to function as a selective H• donor. The fact that the yields of **11** are also dependent upon $[\text{aldehyde}]_0$, requires the cyclization of **8** to be reversible. This result is consistent with prior work demonstrating that **9** undergoes β-scission in the presence of 0.030 M Bu_3SnH in benzene at 80 °C.[18]

During the reactions of **1** under second-order conditions, butane was formed by the decarbonylation of acyl radicals derived from **4**. The results suggested that the majority of these acyl radicals arose from intramolecular H• abstraction in **2**. In the reactions of **7**, however, *n*-pentane is not detected, indicating that intramolecular 1,6 H• transfer is too slow to compete with other possible reactions of **8**. This observation is consistent with previous results demonstrating that 1,6 H• transfer in **8** is slower than 1,5 H• transfer in **2** due to the less favorable seven-membered transition state accompanying the 1,6 reaction.[11] Therefore, intramolecular H• transfer in **8** has not been included in Scheme V.

Scheme V is the minimum mechanism required to account for the product distributions under second-order conditions. Further support for this mechanism can be obtained by demonstrating its ability to quantitatively predict the percentage of cyclization as a function of $[\mathbf{7}]_0$ and $[Bu_3SnH]_0$. In accord with Scheme V, [**11**] is related to the initial concentrations of the starting materials by the differential equation, eq 6.[19] This equation was used to

$$\frac{-d[\mathbf{11}]}{d[Bu_3SnH]} = \frac{k_6}{k_2}\left(\frac{k_{-6}}{k_3}([\mathbf{7}]_0 - [\mathbf{11}]) + [Bu_3SnH]\right) \Big/ \left([Bu_3SnH]^2 + \left(\frac{k_6}{k_2} + \frac{k_{-6}}{k_3} + \frac{k_7}{k_3}([\mathbf{7}]_0 - [\mathbf{11}])\right)[Bu_3SnH] + \left(\frac{k_{-6}}{k_3} + \frac{k_6}{k_2}\right)\frac{k_7}{k_3}([\mathbf{7}]_0 - [\mathbf{11}])\right) \quad (6)$$

calculate theoretical yields of **11** by an iterative technique (Runge–Kutta method)[13] which could be compared with the observed yields of **13** given in Figure 5. The calculated yields of **11** were then adjusted to give the best fit to the observed yields of **11** by the variation of k_6/k_2, k_{-6}/k_3, and k_7/k_3 using the Simplex algorithm with χ^2 minimization.[14]

A good fit, shown as the curves in Figure 5, was obtained with $k_6/k_2 = 0.159 \pm 0.006$ M, $k_{-6}/k_3 = 0.0310 \pm 0.0016$ M, and $k_7/k_3 = 0.149 \pm 0.016$. The agreement between the second-order k_6/k_2 ratio and that obtained under first-order conditions, $k_6/k_2 = 0.163 \pm 0.005$ *M*,[17] supports the mechanism in Scheme V. Furthermore, the result of $(k_2/k_6)(k_{-6}/k_3) = 0.19$ is consistent with the first-order results which required that $0 \le (k_2/k_6)(k_{-6}/k_3) \le 0.35$ (vide supra). Given the reported values[6,16] at 80 °C of $k_2 = 6.4 \times 10^6$ M^{-1} s^{-1} and $k_3 = 3.7 \times 10^8$ M^{-1} s^{-1}, values of $k_6 = 1.0 \times 10^6$ s^{-1}, $k_{-6} = 1.1 \times 10^7$ s^{-1}, and $k_7 = 5.5 \times 10^7$ M^{-1} s^{-1} are obtained.

(v) Comparison of the Exo Cyclizations of 2 and 8. Our studies of the exo cyclizations of the unsubstituted ω-formyl alkyl radicals **2** and **8** have established that the reaction products and yields are qualitatively and quantitatively accounted for by the mechanisms presented in Schemes III and V. These reactions are more complex than the corresponding 5-hexenyl[16a] and 6-heptenyl[20] exo cyclizations due to the formation of reactive cycloalkoxy radical intermediates which readily undergo β-scission and H• abstraction from donors other than Bu_3SnH. In the case of **2**, the reaction is further complicated by intramolecular 1,5 H• transfer. The competing H• transfers are suppressed when the reactions are carried out in the presence of a large excess of Bu_3SnH and the mechanisms for 1,5 and 1,6 exo cyclization simplify to Schemes II and IV, respectively. However, in the presence of Bu_3SnH in excess, the reduction of aldehydes to alcohols occurs as a side reaction.

In agreement with prior studies,[5] we find that higher yields of cyclic alcohol are obtained from 1,6 cyclization of **8** than from 1,5 cyclization of **2** under identical conditions (the same $[Bu_3SnH]_0$, $[\omega\text{-bromoaldehyde}]_0$, temperature). The kinetic results reveal that the higher yields of 1,6 exo closure are to a small extent due to the relative rates of cyclization and to a large extent due to the relative rates of β-scission.

To illustrate this point, let us compare the two reactions at 80 °C under pseudo-first-order conditions (a large excess of Bu_3SnH). The rate constant for 1,6 closure of **8**, $k_6 = 1.0 \times 10^6$ s^{-1}, is slightly larger than the 1,5 closure of **2**, $k_1 = 8.7 \times 10^5$ s^{-1}. Once formed, the cycloalkoxy intermediates either abstract H• from Bu_3SnH, with a rate constant of $k_3 = 3.7 \times 10^8$ M^{-1} s^{-1},[6] or undergo β-scission. The rate constants for these β-scissions differ substantially, $k_{-6} = 1.1 \times 10^7$ s^{-1} while $k_{-1} = 4.7 \times 10^8$ s^{-1}. Thus, it can be seen that while both ω-formylalkyl radicals cyclize at roughly the same rate, a much larger percentange of the 1,6 cyclizations proceeds to cyclic alcohol because the reverse reaction, β-scission, is much slower in the 1,6 case. For example, at a $[Bu_3SnH]_0 = 0.10$ M the 80 °C rate constants predict that 77% of the 1,6 closures of **8** proceed to yield cyclohexanol while only 7.3% of the 1,5 closures of **2** proceed to yield cyclopentanol.

The observation that the β-scission rates of **3** are faster than those of **9** is supported in the literature. Walling and Padwa have shown that the 1-methylcyclopentoxy radical undergoes β-scission at a rate 10 times faster than the (1-methylcyclohexyl)oxy radical at 80 °C.[21] These differences in rate can be attributed to the

(18) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415.
(19) Equation 6 was derived from Scheme V with the following assumptions: (i) that the steady-state approximation applies to [**9**] (ii) that $-d[Bu_3SnH] = d[\mathbf{10}] + d[\mathbf{11}]$, and (iii) $[\mathbf{7}] = [\mathbf{7}]_0 - [\mathbf{11}]$ (neglecting the minor yields of bromopentane).

(20) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472.
(21) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593.

Table III. Arrhenius Parameters for Selected Exo Radical Cyclizations

radical	log (A/s^{-1})	E_a, kcal/mol	k(at 25 °C), s^{-1}	ref
4-formylbutyl **2**	10.23 ± 0.31	6.88 ± 0.46	1.5×10^5	6
5-formylpentyl **8**	9.38 ± 0.20	5.43 ± 0.30	2.5×10^5	this work
5-hexenyl	10.42 ± 0.32	6.85 ± 0.42	2.5×10^5	16a
6-heptenyl	9.54 ± 0.35	7.91 ± 0.45	5.5×10^3	21

estimated 6.5 kcal/mol ring strain[22] associated with the cyclopentyl ring.

Activation parameters and rate constants at the 25 °C rate for the exo closures of **2** and **8** are compared with those of the analogous ω-alkenylalkyl exo closures in Table III. Unexpectedly, the results show that the 1,6 closure of **8** is faster than the 1,5 closure of **2**. This trend is opposite to that shown by the analogous ω-alkenylalkyl radicals, where 1,5 closure of the 5-hexenyl radical and related systems is generally faster than 1,6 closure of the 5-heptenyl radical and related systems.[2] Why do these ω-formylalkyl radicals deviate from this well-established reactivity pattern?

To answer this question we must first consider the reason why 1,5 cyclizations dominate in ω-alkenylalkyl systems. An hypothesis that appears to account satisfactorily for all the experimental data relating to the ring closures of 5-hexenyl radicals and related species rests upon the requirement for efficient overlap between SOMO and π* orbitals.[24] Essentially, this theory contends that the strain that accompanies the most favorable orientation of reactive centers is greater in the transition-state structure for 1,6 cyclization than that for the 1,5. MM2 force field calculations applied to transition-state models support this hypothesis, revealing the expected strain energy differences and successfully predicting the regio- and stereoselectivity in a large number of cyclizations.[25,26]

In light of these results, we postulate that in ω-formylalkyl cyclizations, the strain that develops in the 1,5 transition-state structure is greater than that in the 1,6. A possible reason for this reversal in kinetic preference is provided by a comparison of the transition-state geometries of the 5-hexenyl and 4-formylbutyl (**2**) exo cyclizations. The transition-state geometry for the 1,5 closure of the 5-hexenyl radical has been calculated by several methods, yielding values of 2.20 Å (MINDO/3),[27] 2.20 Å (MNDO),[25] and 2.34 Å (STO-3G)[26] for the distance from the radical carbon to the nearer end of the double bond. A significantly shorter distance of 1.92 Å (AM1) has been obtained for the 1,5 closure of **2**.[6] This result reveals that the cyclization of **2** has a later transition state than the 5-hexenyl radical, an observation consistent with the fact that the former reaction is endoergonic ($\Delta G°$ = 7.1 kcal/mol), while the latter reaction is exoergonic ($\Delta G°$ = −12.6 kcal/mol).[28] The 6.5 kcal/mol ring strain present in a ground-state cyclopentane ring[23] may have a greater contribution in the tighter ω-formylalkyl transition state than in the looser ω-alkenylalkyl one, giving rise to additional strain energy in the 1,5 closure of **2**.

Molecular mechanics calculations carried out on the reactions in Table I support this hypothesis. The forming C–C bond distance in the exo closure transition-state structures was fixed at 2.20 Å for the ω-alkenylalkyl radicals and at 1.92 Å for the ω-formylalkyl radicals.[29] All other atom positions were optimized by using MM2[30] yielding transition-state energies. The energies of the reactant molecules were subtracted from the transition-state energies to yield strain energies. For the ω-alkenylalkyl radicals, the method predicts 1,5 exo to be favored over 1,6 exo by 1.3 kcal/mol (observed difference in E_a is 1.06 kcal/mol). For the ω-formylalkyl radicals, the method predicts 1,6 exo to be favored over 1,5 exo by 0.6 kcal/mol (observed difference in E_a is 1.45 kcal/mol).

Conclusion

The kinetic studies described above delineate the similarities and the differences between the behavior of the formylalkyl radicals, **2** and **8**, and their alkenyl radical analogues. Both types of radicals preferentially undergo cyclization in the exo mode; the reaction is essentially irreversible for alkenyl radicals, but for the formylalkyl species it is rapidly reversible and the equilibrium lies in favor of the open-chain forms, especially for the lower homologue **2**.

The reactions of the bromoaldehydes, **1** and **7**, with tributylstananne are more complex that those of analogous alkenyl halides because of the propensity of the former to undergo abstraction of formyl hydrogen atoms by alkoxy radicals. In the case of the radical **2**, intramolecular hydrogen atom transfer also occurs. The rates and Arrhenius parameters for cyclization of **2** are similar to those for 5-hexenyl radical cyclization, but 1,6 ring closure of **8** is considerably faster that of 6-heptenyl radical. This depature from established reactivity patterns in radical cyclization is explicable in terms of the "tighter" transition states that accompany the formation of cycloalkoxy radicals. The results indicate that cyclization of the formylpentyl radical, **8**, and related systems should provide the most efficient method for formation of six-membered rings by radical cyclization and should have considerable synthetic potential.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian XL-200 spectrometer. Analysis by gas chromatography was performed on a Varian 3400 with a 25-m phenyl methyl silicone capillary column; the response of the flame ionization detector was calibrated with authentic compounds. The starting materials **1** and **7** were prepared by a literature method.[31] The activity of Bu_3SnH (Aldrich) and Bu_3SnD[32] was determined by hydrogen evolution from dichloroacetic acid. If below 95%, these reagents were purified by vacuum distillation.

Reactions of 1 and 7 with Bu_3SnH. It was discovered in the early stages of this work that the reaction of **1** or **7** with Bu_3SnH would sometimes occur immediately after mixing at room temperature. Therefore, these reagents were combined at the desired reaction temperature. This was accomplished by performing the reactions in glass vials sealed with Teflon-surfaced rubber septa. In a typical first-order experiment, a vial was charged with 1.00 mL of a benzene solution of Bu_3SnH. It was then sealed, the contents frozen with liquid N_2, evacuated, and filled wth argon via a needle through the septum. The sample was then immersed in a thermostated bath (±1 °C). After 15 min, the desired amount of a benzene solution containing **1** or **7** and 0.05 molar equiv (with respect to Bu_3SnH) of AIBN was injected to start the reaction. Two-hour reaction times were used for the reactions of **1** at 80 °C (it was subsequenily discovered that shorter times, e.g., 30 min, would also effect complete reaction). The reaction times for **7** were as follows 100 °C, 30 min; 80 °C, 30 min; 60 °C, 1 h; 40 °C, 2 h.

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(29) This approach is a simplified version of the one employed by Beckwith and Schiesser.[25] Here only the forming C–C bond distance is fixed. The values of 2.20 Å (MNDO)[25] and 1.92 Å (AM1)[6] were chosen because both were obtained by similar methods (AM1 is an updated version of MNDO) and can be directly compared to one another. For the ω-formylalkyl cyclizations, only the 1,5 exo closure transition-state structure has been calculated and it is assumed that the 1,6 exo closure has the same distance of 1.92 Å. This assumption is based on the fact that for the ω-alkenylakyl closures, MNDO yields the value of 2.20 Å for both the 1,5 exo and 1,6 exo cases.[25]
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In a typical second-order experiment, a vial was charged with 1.00 mL of a benzene solution containing **1** or **7** and 0.05 molar equiv (with respect to Bu_3SnH) of AIBN. The vial was sealed and deoxygenated as described above and placed in a bath at 80 °C. After 15 min, the reaction was started by injecting the desired amount of Bu_3SnH. Reaction times of 1 h were used for both **1** and **7** at 80 °C.

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Note Added in Proof. In a private communication, Dr. J. Lusztyk has provided the following experimental Arrhenius parameters for the reaction of *tert*-butoxy radicals with Bu_3SnH: $E_a = 1.1 \pm 0.1$ kcal/mol, $\log (A/s^{-1}) = 9.5 \pm 0.1$. Although these values are in reasonable agreement with our earlier estimates of $E_a = 1.83 \pm 0.54$ kcal/mol and $\log (A/s^{-1}) = 9.70 \pm 0.40$,[6] they suggest that the value of $k_3 = 6.6 \times 10^8$ M^{-1} s^{-1} at 80 °C would be more correct than that (3.7×10^8 M^{-1} s^{-1}) used in the paper. In this case the values of k_{-1}, k_4, and k_{-6} at 80 °C should be increased correspondingly by a factor of 1.8.

Registry No. **1**, 1191-30-6; **2**, 78939-50-1; **3**, 53578-06-6; **4**, 110-62-3; **5**, 96-41-3; **6**, 71-41-0; **7**, 57978-00-4; **8**, 59282-49-4; **9**, 3384-35-8; **10**, 66-25-1; **11**, 108-93-0; **12**, 111-27-3; Bu_3SnH, 688-73-3; nonanal, 124-19-6; 5-hexenyl radical, 16183-00-9; cyclopentylcarbinyl radical, 119009-89-1.

D-Talose Anomerization: NMR Methods To Evaluate the Reaction Kinetics

Joseph R. Snyder,[†] Eric R. Johnston,[‡] and Anthony S. Serianni*,[†]

Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556, and Department of Chemistry, Haverford College, Haverford, Pennsylvania 19041. *Received July 16, 1987*

Abstract: The kinetics of anomerization of the aldohexose, D-talose, have been studied by several NMR methods in order to evaluate their limitations, complementarity, and internal consistency and to further explore the effect of monosaccharide structure on reactivity. By use of D-[1-^{13}C]talose and ^{13}C NMR spectroscopy, six tautomeric forms were detected and quantitated in aqueous solution: α- and β-talofuranoses, α- and β-talopyranoses, hydrate (1,1-*gem*-diol), and aldehyde. The ^{13}C (75-MHz) and ^{1}H (620-MHz) NMR spectra of D-talose have been interpreted, yielding chemical shifts and coupling constants (J_{HH}, J_{CC}, J_{CH}) that have been evaluated in terms of ring configuration and conformation. By use of ^{13}C saturation-transfer NMR (ST-NMR), ring-opening rate constants (k_{open}) of the four cyclic forms were measured, and ring-closing rate constants (k_{close}) were calculated from k_{open} and equilibrium constants. NMR-derived rates of tautomer equilibration obtained after dissolving α-D-[1-^{13}C]talopyranose in aqueous solution were predicted accurately from a computer treatment of the unidirectional rate constants determined by ST-NMR under similar solution conditions. Two-dimensional ^{13}C exchange spectroscopy was applied to obtain overall rate constants of tautomer interconversion; rate constants obtained in this fashion compared favorably with those calculated from the ST-derived unidirectional rate constants using the steady-state approximation. Kinetic results show that anomeric configuration and ring size significantly affect ring-opening and ring-closing rates of monosaccharides.

Aldohexoses have the potential to exist in six monomeric forms (tautomers) in aqueous solution [α- and β-furanose, α- and β-pyranose, hydrate (1,1-*gem*-diol), and aldehyde].[1,2] The spontaneous interconversion between the cyclic forms, known as anomerization, appears to involve the aldehyde as an obligatory intermediate,[3,4] although its conformation has been the subject of debate.[5,6a,7] This characteristic reaction of reducing sugars plays an important role in organic chemistry and biochemistry. From the chemical standpoint, anomerization is an ideal reaction to assess the effects of structure, configuration, and conformation on ring-forming and ring-opening reactions in general, especially since many stereoisomers of the monosaccharides are available for study. In the biological sense, Benkovic and co-workers[6b] have shown that enzymes often act on specific tautomers of biologically important reducing sugars (e.g., D-fructose 6-phosphate). In some instances, therefore, the kinetics of tautomer interconversion can be a potential factor in regulating flux through certain pathways in cells.

Many studies[7-11] have examined the effect of carbohydrate and solvent structure on anomerization rates using various sugars, reaction conditions, and experimental protocols, producing a body of information that has established the general features of the reaction. Despite this considerable effort, however, little is known about the component ring-opening and ring-closing rate constants and their dependence on experimental conditions. This latter problem has been the focus of attention in this laboratory in recent years. With the aid of ^{13}C enrichment, we have shown that minor tautomers (e.g., hydrate and carbonyl forms) of monosaccharides can be detected and quantified in solution by ^{13}C NMR.[3b,4,12,13] Without enrichment, their detection is difficult. We have used ^{1}H and ^{13}C saturation-transfer NMR (ST-NMR)[3b,4,13,14] and

[†] University of Notre Dame.
[‡] Haverford College.

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