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Approximate Rate Constants for Cyclizations of Alkyl Radicals onto Benzyl Oxime Ethers

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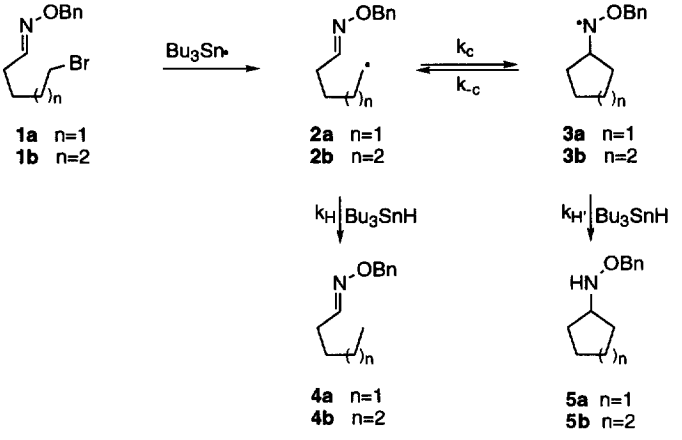
Abstract: *The approximate rate constants for 5-exo and 6-exo cyclizations of alkyl radicals onto oxime ethers have been kinetically determined to be $4.2x10^7$ s^{-1} and $2.4x10^6$ s^{-1} at 80 °C, respectively. The competition studies gave similar results, confirming the effectiveness of rate constants obtained from kinetic studies.* © 1997 Elsevier Science Ltd.

Radical cyclizations of alkyl radicals onto C=N bonds have received much less attention synthetically and mechanistically, as compared with radical cyclizations onto C=C and C=O bonds.[1] Alkyl radical additions to imines,[2] oxime ethers,[3] and hydrazones[4] have been recently reported and their synthetic usefulness has proven increasingly important. Among three different types of C=N bonds, oxime ethers seemed to be most widely used as radical acceptors. Cyclization rates of alkyl radicals onto C=N bonds have been recently studied. The rate constants for the cyclization of alkyl radicals onto *N,N*-diphenylhydrazones[5] and onto *N*-aziridinyl imines[6] were reported and showed that C=N bonds of hydrazones were much better radical acceptors than C=C and C=O bonds. Kinetic studies of aryl[7] and alkyl radical[8] additions onto imines also showed the similar results. In connection with our ongoing research on radical-mediated acylation approach,[9] we were very much interested in the efficiency of an oxime ether group as a radical acceptor. Furthermore, we were curious to know the dependence of the rate constants on the nature of C=N bonds. Among three different types of C=N bonds such as an imine, an oxime ether, and a hydrazone, we wanted to know which C=N bond would be the most efficient radical acceptor.

		$H_3CCH{=}N{-}CH_3$	$H_3CCH{=}N{-}OCH_3$	$H_3CCH{=}N{-}NMe_2$
C- Electron density	AM1-UHF	-4.075	-4.141	-4.177
	PM3-UHF	-4.092	-4.096	-4.127

Before we began our kinetic studies to answer this question, we studied the possibility of the dependence of the electron density at the iminyl carbon atom on the cyclization rate. We predicted that the larger the electron density in an iminyl carbon was, the better the radical acceptor would be. Thus, we calculated the electron densities of three different types of the iminyl carbon atoms using semi empirical calculation (MOPAC). According to the results obtained from the calculations, if our hypothesis would be correct, cyclizations of oxime ethers would be faster than those of imines but slower than those of hydrazones.



Scheme 1

$$\frac{[4]}{[5]} = \frac{k_H}{k_c}[Bu_3SnH]_o + \frac{k_H\, k_{-c}}{k_{H'}\, k_c} \qquad (1)$$

Application of the steady state approximation to the kinetic analysis consistent with the mechanism shown in Scheme 1 leads to the approximate rate eq 1, where k_H and $k_{H'}$ are the second order rate constants for reactions of alkyl and aminyl radicals with Bu_3SnH. Also, k_c and k_{-c} are the first order rate constants for cyclizations and ring opening reactions, and $[Bu_3SnH]_o$ represents the initial Bu_3SnH concentration. From eq 1, the ratio of rate constants (k_H/k_c) is found as the slope of a plot of **[4]**/**[5]** as a function of $[Bu_3SnH]_o$ under pseudo-first order conditions. Since k_H was previously known,[10] k_c can be easily calculated from its slope. Similarly, k_{-c} would be calculated from the intercept.

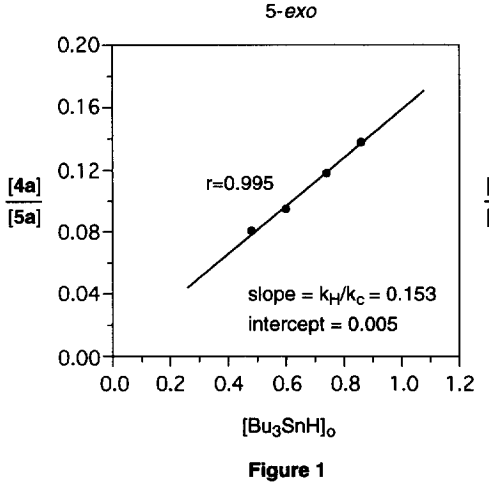


Figure 1

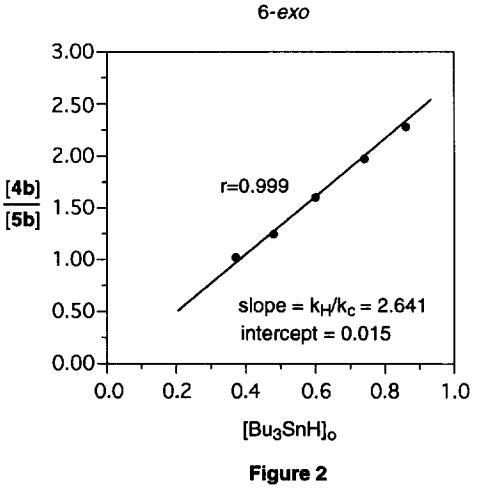
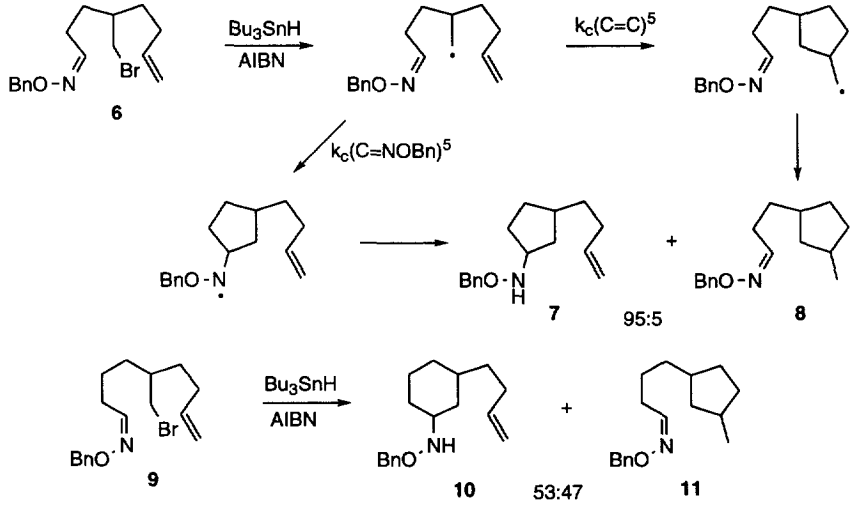


Figure 2

The substrates required for kinetic studies were easily prepared by routine operations and were obtained as inseparable mixtures of syn- and anti-isomers. Kinetic studies were carried out with **1** and an excess amount of Bu_3SnH (7~17 equiv)/AIBN (0.1 equiv) in benzene at 80 °C for 3 h and **4** and **5** were isolated in 90 -95% yield. Three experiments were carried out at each concentration of Bu_3SnH. The ratio of **4** and **5** were obtained by HPLC after chromatographic removal of an excess amount of Bu_3SnH. The products were synthesized independently, their response factors were determined and the ratio of **4** and **5** were finally calibrated. The experimental results for 5-*exo* and 6-*exo* cyclization are given in Figure 1 and Figure 2 as a plot of **4/5** vs $[Bu_3SnH]_0$. Since k_H is known to be $6.4x10^6\ M^{-1}s^{-1}$,[10] the rate constants (k_c) for 5-*exo* and 6-*exo* cyclization of alkyl radicals onto C=N bonds of oxime ethers can be calculated to be $k_c(C=N\text{-}OBn)^5=4.2x10^7\ s^{-1}$ and $k_c(C=N\text{-}OBn)^6=2.4x10^6\ s^{-1}$, respectively. Furthermore, the intercepts in Figure 1 and 2 were close to zero (0.005, 0.015), indicating that the cyclization steps were essentially irreversible.



Scheme 2

In order to confirm the rate constants derived from kinetic studies, we carried out a competition experiment involving 5-*exo* cyclization of an alkyl radical onto an oxime ether group *versus* onto an alkenyl group. Treatment of **6** in refluxing benzene with Bu_3SnH/AIBN under a highly diluted condition using a syringe pump for 3 h afforded a 95:5 mixture of **7** and **8**. Since the rate constant for 5-*exo* cyclization of α-alkyl substituted alkyl radicals to C=C bonds is known to be $3.6x10^6\ s^{-1}$ at 80 °C,[11] the rate constant, $k_c(C=N\text{-}OBn)^5$, for 5-*exo* cyclization of an alkyl radical to an oxime ether group can be calculated to be $6.8x10^7$ at 80 °C.

The rate constant for 6-*exo* cyclization of an alkyl radical onto an oxime ether was similarly determined with substrate **9.** When the radical reaction of **9** was carried out under the same condition, a 53:47 mixture of **10** and **11** was obtained. Thus, the rate constant for 6-*exo* cyclization of an alkyl radical to an oxime ether group would be $4.1x10^6\ s^{-1}$. The rate constants obtained from the competition studies are somewhat higher than the rate constants obtained from kinetic studies. Since the cyclization rates for α-substituted alkyl radicals must be larger than those for α-unsubstituted alkyl radicals, the competition data seem to be quite reasonable, confirming the effectiveness of rate constants obtained from kinetic studies.

In conclusion, the 5-*exo* and 6-*exo* cyclization rates of oxime ethers are larger than the corresponding imine cyclization rates(k_c^5=6.0 x 10^6 s^{-1}, k_c^6=6.7 x 10^5 s^{-1})[8] and comparable to the hydrazone cyclization rates.[12] The present results suggest that cyclization rates might be dependent on the electron density at the iminyl carbon atom, although further systematic studies are needed to clarify the correlation between the cyclization rate and the electron density at the iminyl carbon atom.

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References and Notes

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12. The reported kinetic data for the hydrazone cyclizations[5,6] were obtained with structurally different substrates. Thus, the direct comparison of the cyclization rate between the oxime ether and the hydrazone cyclization seems to be inappropriate. Further studies are needed for the direct comparison of the rate constants.

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