Absolute Kinetics of Amidyl Radical Reactions

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Abstract: An absolute kinetic scale for amidyl radical reactions was established by a combination of direct laser flash photolysis (LFP) and indirect competition kinetic studies. Six amidyl radicals were studied by LFP. Arrhenius parameters were determined for 6-*exo* cyclizations of the *N*-butyl-6,6-diphenyl-5-hexenamidyl radical (**2**) and the *N*-butyl-6-(*trans*-2-phenylcyclopropyl)-5-hexenamidyl radical (**5**) and for 1,5-hydrogen transfer in the *N*-(6,6-diphenyl-5-hexenyl)acetamidyl radical (**3**); rate constants for these reactions at 20 °C are 3.0×10^7 s^{-1} (**2**), 5.5×10^6 s^{-1} (**3**), and 1×10^7 s^{-1} (**5**). Kinetic limits were established by LFP for the fast cyclizations of the *N*-methyl-5,5-diphenyl-4-pentenamidyl radical (**1**) and the *N*-methyl-5-(*trans*-2-phenylcyclopropyl)-4-pentenamidyl radical (**4**) ($k > 2 \times 10^8$ s^{-1} at ambient temperature) and for the slow fragmentation of the *N*-(2,2-diphenylethyl)acetamidyl radical (**6**) ($k = 2 \times 10^4$ s^{-1} at 48 °C). Rate constants for amidyl radical reactions with Bu_3SnH and PhSH were determined by competition kinetics; respective rate constants are 1.3×10^9 M^{-1} s^{-1} at 20 °C and 9×10^7 M^{-1} s^{-1} at 23 °C. Cyclizations of simple amidyl radicals were determined from competition kinetic studies by employing Bu_3SnH and *N*-(phenylthio)amide radical precursors using data from the literature and from studies in this work. Rate constants at 65 °C for 5-*exo* cyclizations of the *N*-butyl-4-pentenamidyl radical and the *N*-(4-pentenyl)butanamidyl radical and for 6-*exo* cyclization of the *N*-ethyl-5-hexenamidyl radical are 3×10^9 s^{-1}, 7×10^8 s^{-1}, and 1.0×10^7 s^{-1}, respectively. The kinetic values determined in this work can be employed in synthetic planning involving amidyl radicals, and the simple amidyl radical clocks can be used for measuring rate constants of bimolecular reactions. A compilation of the kinetics of nitrogen-centered radical cyclizations and bimolecular reactions of nitrogen radicals with Bu_3SnH and PhSH is presented.

Radical-based methods have become important components of the organic synthetic repertoire in recent years. Most of the methodology involves carbon-centered radicals where the utility of the methods is due to the facility of radical production in chain reactions, the fast rates of radical reactions in general and the ease of five-membered ring production in particular, and the stability of unprotected polar functional groups to the radical reaction conditions. Heteroatom-centered radicals have received considerably less attention than carbon-centered radicals in part because polar reactions of heteroatoms are so prevalent. In the case of nitrogen-centered radicals,[1] however, there exists a feature in addition to the typical advantages of radical-based methods that is attractive from the synthetic perspective. The more reactive and inherently more useful families of nitrogen-centered radicals are typically electrophilic in character and provide an Umpolung reactivity that complements the nucleophilic character of nitrogen in polar reactions.

Amidyl radicals are known to be highly reactive intermediates that display virtually exclusive reactivity at nitrogen[1] despite the fact that they apparently are π-type radicals.[2] Common reactions of amidyl radicals include remote functionalization of unactivated positions δ to nitrogen (similar to a Hofmann−Löffler−Freytag reaction), intermolecular additions, and cyclizations.[1] Given the wide occurrence of amides and lactams in natural products and the ease of removal of the acyl group of amides to provide amines, one might expect that these mildly electrophilic species[3] would have enjoyed a considerable amount of attention. This was the case years ago, and early reviews suggested the potential importance of amidyl radicals in synthesis. However, amidyl radical chemistry has not kept pace with carbon-centered radical chemistry in the intervening period, in part a result of two shortcomings. A major limitation was that the available precursors for amidyl radicals were highly reactive *N*-halo- or *N*-nitrosoamides that were produced under conditions that precluded many functional groups in the substrate and often were employed in nonchain reactions that gave high radical concentrations. In addition, the absolute kinetics of amidyl radical reactions were not well established.

In recent years, several new amidyl radical precursors have been reported that are available from mild reaction conditions and react cleanly in radical chain propagation steps. These include members of the PTOC[4] family of radical precursors[5,6] (see Figure 1 for examples), *N*-(phenylthio)amides,[7] and thiocarbazone derivatives.[8] Each of these amidyl radical precursors will react in chain propagation steps with stannyl (and one

(1) Reviews of nitrogen-centered radicals: Neale, R. S. *Synthesis* **1971**, *1*, 1−15. Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241−3260. Goosen, A. *S. Afr. J. Chem.* **1979**, *32*, 37−44. Stella, L. *Angew. Chem., Int. Ed. Eng.* **1983**, *22*, 337−350. Esker, J.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1993; Vol. 58, pp 1−45. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(2) Sutcliffe, R.; Griller, D.; Lessard, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 624−628.

(3) Caron, G.; Lessard, J. *Tetrahedron* **1993**, *49*, 8039−8058.

(4) The acronym PTOC is from pyridine-2-thioneoxycarbonyl. For a general overview of this family of radical precursors, see: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.

(5) (a) Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035−1038. (b) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933−4940.

(6) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1992**, *33*, 5913−5916. Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779−2786.

(7) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877−6880.

(8) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791−8794.

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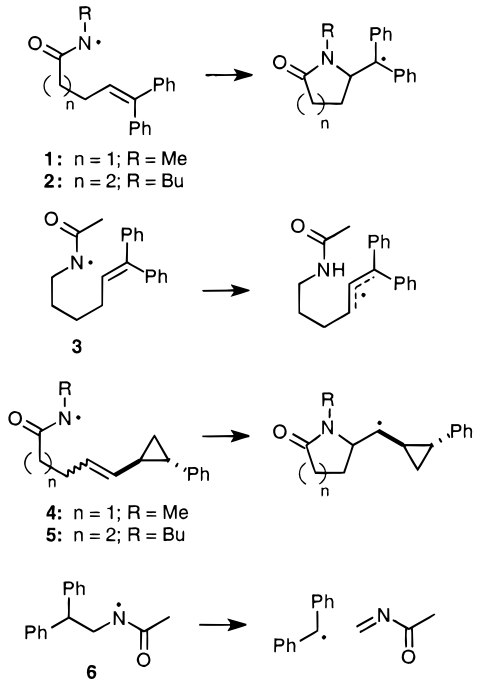


Figure 1. Radicals studied by LFP.

assumes also silyl) radicals, and the PTOC derivatives also will propagate chain reactions involving thiyl and selenyl radicals. In this work, we report the basis reactions for an amidyl radical kinetic scale that can be used for synthetic planning. Laser flash photolysis (LFP) methods were used to measure directly the kinetics of cyclizations of amidyl radicals which served as "radical clocks".[9] Rate constants for second-order trapping reactions of these radical clocks by the hydrogen atom donors Bu_3SnH and PhSH were then determined by indirect kinetic methods. Finally, the Bu_3SnH trapping reaction was combined with relative rate constants from the literature and from studies reported herein to determine rate constants for cyclizations of simple amidyl radicals that more closely resemble those that one would employ in synthesis.

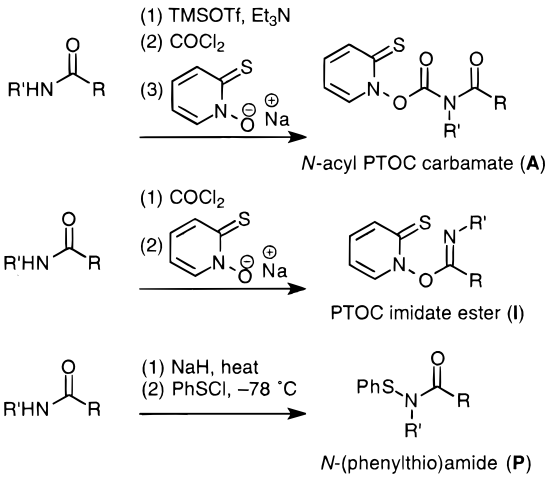
Results

Syntheses. Three types of amidyl radical precursors were used in this work, *N*-acyl PTOC carbamates[6] (**A**), PTOC imidate esters[5] (**I**), and *N*-(phenylthio)amides[7] (**P**). Each was prepared from the corresponding amide by literature methods as shown in Scheme 1. The preparations of the amides used in this work are provided in the Supporting Information, and the radical precursor preparations are given in the Experimental Section. As a general rule, members of the PTOC family of radical precursors are unstable with respect to reactions with nucleophiles and are decomposed by visible light. The *N*-acyl PTOC carbamates are somewhat more stable than the PTOC imidate esters and survive silica gel chromatography with partial decomposition. Synthetic intermediates were characterized spectroscopically and by HRMS. The PTOC carbamates and PTOC imidate ester radical precursors were characterized by NMR spectroscopy, and the more robust *N*-(phenylthio)amides were characterized NMR spectroscopy and by HRMS.

In most cases, preparative-scale reactions were conducted with the radicals studied by LFP. Products were either isolated and characterized or shown to be identical by GC to authentic samples prepared by alternative methods.

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

Scheme 1



Kinetic Methods. Direct kinetic studies were accomplished with a nanosecond-resolution kinetic spectrometer employing a Nd:YAG laser. Members of the PTOC family of radical precursors have a long wavelength λ_{max} centered at about 360 nm and are efficiently cleaved by the third harmonic of the Nd:YAG laser (355 nm);[10] all studies with *N*-acyl PTOC carbamates and PTOC imidate esters employed 355 nm light for radical production. The *N*-(phenylthio)amides do not absorb appreciably at 355 nm, and these precursors were cleaved with the fourth harmonic of the Nd:YAG laser (266 nm).

LFP reactions were performed with helium-sparged, dilute solutions of the precursors ($1-5 \times 10^{-5}$ M) that flowed through a cell in the kinetic spectrometer. Most of the LFP kinetic studies involved first-order processes that were measured with high precision because hundreds of data points were collected in a run. Each LFP kinetic value listed in this work results from a computer solution of averaged data collected in 5−15 experiments. The precision of the kinetic determinations was often better than the temperature control and is indicated for those cases where two "sets" of data are reported at a given temperature; in these cases, each set is completely independent.

LFP studies were conducted with radicals **1**−**6** (Figure 1). 5-*Exo* cyclization of amidyl radical **1** and 6-*exo* cyclization of radical **2** were expected to give diphenylalkyl radicals that are readily detected by UV spectroscopy. Radical **3** also might have cyclized, but the 1,5-hydrogen atom transfer reaction shown in Figure 1 occurred instead. Radicals **4** and **5** contain a "reporter group" [11] for use in direct LFP studies. Cyclizations of **4** and **5** initially produce the (2-phenylcyclopropyl)carbinyl radicals shown in Figure 1. These first-formed product radicals rapidly open to benzylic radicals that can be observed by UV spectroscopy; the ring opening is so fast that one only measures the kinetics of the initial cyclization reactions.[12] Radical **6** was expected to suffer a β-fragmentation reaction that gives the UV-detectable diphenylmethyl radical and an enamide.

Indirect kinetic studies were accomplished by standard competition kinetics methods.[13] Reactions were run with an

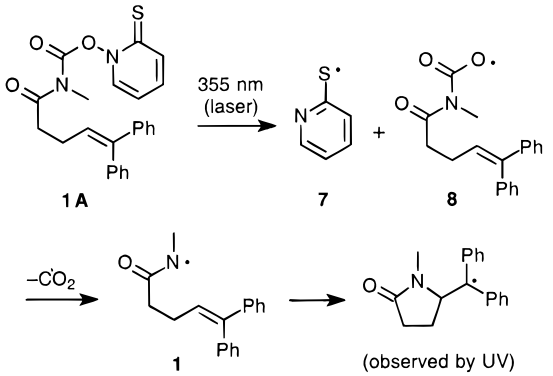
(10) For early LFP kinetic studies with PTOC dervatives, see: Bohne, C.; Boch, R.; Scaiano, J. C. *J. Org. Chem.* **1990**, *55*, 5414−5418. Ha, C.; Horner, J. H.; Newcomb, M.; Varick, T. R.; Arnold, B. R.; Lusztyk, J. *J. Org. Chem.* **1993**, *58*, 1194−1198.

(11) Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, J. H.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505−8506.

(12) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662−9663. Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915−10921.

(13) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

Scheme 2



excess of hydrogen atom transfer trapping agent, but true pseudo-first-order conditions could not be maintained in tin hydride reactions due to the high reactivity of this agent. Ratios of rate constants were determined from product mixtures according to eq 1 where U is unrearranged product, R is rearranged product, k_R is the first-order rate constant for rearrangement, k_T is the second-order rate constant for trapping, and $[YH]_m$ is the average concentration of trapping agent. For the amounts of Bu_3SnH employed in this work, the use of $[YH]_m$ in the pseudo-first-order form of eq 1 introduces an error of $<5\%$.[13]

$$[U]/[R] = (k_T/k_R)[YH]_m \quad (1)$$

LFP Kinetic Studies. The 5-*exo* cyclization of radical **1**, produced from the corresponding *N*-acyl PTOC carbamate **1A**, was initially studied. Scheme 2 illustrates the sequence of reactions which occur upon laser photolysis of precursor **1A**. Photochemical cleavage of the weak N−O bond gives the (2-pyridine)thiyl radical (**7**) and amidylacyloxyl radical **8**. Decarboxylation of **8** gives amidyl radical **1** which can cyclize to give the diphenylalkyl product radical that was expected to have λ_{max} at about 335 nm.[14]

The diphenylethenyl moiety accelerates the cyclization of radical **1**, and this reaction was expected to be the fastest amidyl radical reaction studied. In fact, it was so fast that it exceeded the dynamic resolution of our nanosecond kinetic unit. Because the PTOC precursors have a long wavelength λ_{max} at 360 nm and because radical **7** does not have a strong absorbance in the region of 300−350 nm,[15] the initial photochemical cleavage reaction should result in bleaching in the region of 330−335 nm where the diphenylalkyl radical product absorbs strongly. However, we observed an "instant" growth in signal in the 330−335 nm region following the laser flash and no further increase in signal intensity with time, indicating that the cyclization reaction of **1** was essentially complete within the 7-ns duration of the laser pulse. The rate constant for cyclization of **1** exceeded 2×10^8 s^{-1}.

Confirmation that cyclization of radical **1** occurred rapidly was obtained in a preparative scale reaction of PTOC carbamate **1A**. Tin hydride trapping of amidyl radicals is quite fast ($k = 1.3 \times 10^9$ M^{-1} s^{-1} at room temperature, see below), but reaction of **1A** in the presence of 0.05 M Bu_3SnH gave mainly the cyclic product *N*-methyl-5-(diphenylmethyl)-2-pyrrolidinone. Given that the acyclic amide product is ultimately produced by tin hydride trapping of both amidyl radical **1** and its immediate

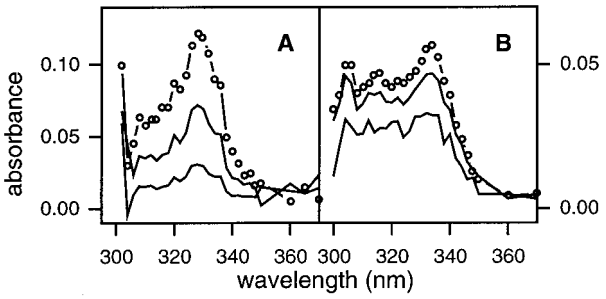
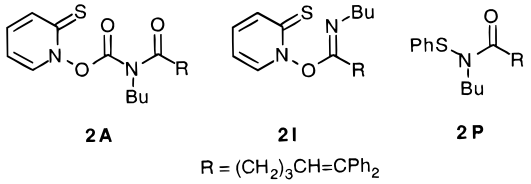


Figure 2. Time-resolved spectra from reactions of radical **2** from precursor **2A** (A) and from precursor **2P** (B). Spectra in A are at 34, 54, and 134 ns after the laser flash, with data at 24 ns subtracted to give a baseline. Spectra in B are at 51, 71, and 101 ns after the laser flash. Symbols for the late time spectrum in both A and B show the wavelengths that were monitored.

precursor acyloxyl radical **8**, the good yield of pyrrolidinone from this reaction requires that the rate constant for cyclization of **1** at room temperature exceeded 1×10^8 s^{-1}.

6-*Exo* radical cyclizations are typically 2 orders of magnitude less rapid than 5-*exo* cyclizations of analogous radicals, and this generalization holds for several pairs of radicals that contain the terminal diphenylethenyl moiety present in radicals **1**−**3**.[16] Amidyl radical **2** reacted slowly enough such that kinetics could be measured with a nanosecond-resolution unit.

Preliminary studies of radical **2** indicated that it reacted with a rate constant in the low 10^7 s^{-1} range at ambient temperature, which is optimal for radical kinetic studies by LFP because radical self-reactions and radical reactions with residual oxygen are too slow to compete. The potential problems with LFP studies using various amidyl radical precursors are discussed later. Because of these experimental uncertainties, we employed three precursors to radical **2**, *N*-acyl PTOC carbamate **2A**, PTOC imidate ester **2I**, and *N*-(phenylthio)amide **2P**, in order to provide



assurance that the observed kinetics resulted from the cyclization reaction of **2**. Figure 2 shows time-resolved spectra of the product formed upon the irradiation of precursors **2A** and **2P**. The amount of radical **2** produced by 266-nm irradiation of **2P** was considerably less than that formed from **2A**, but the major feature at 335 nm is the same in both spectra. The spectrum observed to grow in following irradiation of **2I** was similar to that observed from **2A**. The absorbance with λ_{max} at about 335 nm is characteristic of diphenylalkyl radicals,[14] indicating that radical **2** cyclizes in a 6-*exo* fashion.

An analogue of radical **2** lacking the phenyl groups has been reported to react by an internal hydrogen atom abstraction to give an allylic radical in competition with a 6-*exo* cyclization,[17] and radical **3** also reacts by an intramolecular hydrogen

(14) Chatgilialoglu, C. In *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. 2, pp 3−11.

(15) Alam, M. M.; Watanabe, A.; Ito, O. *J. Org. Chem.* **1995**, *60*, 3440−3444.

(16) (a) Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684−1687. (b) Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S. U. *J. Am. Chem. Soc.* **1995**, *117*, 3674−3684. (c) Horner, J. H.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 11124−11133. (d) Ha, C.; Musa, O. M.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 2704−2710.

(17) Sutcliffe, R.; Ingold, K. U. *J. Am. Chem. Soc.* **1982**, *104*, 6071−6075.

Table 1. Arrhenius Parameters for Radical Reactions[a]

radical	source	log *A*	E_a (kcal/mol)	k_{20}[b] (s^{-1})
2	**2A**	9.30 ± 0.13	2.46 ± 0.16	2.9×10^7
	2I	9.03 ± 0.35	2.09 ± 0.57	2.9×10^7
	2P	9.35 ± 0.06	2.49 ± 0.07	3.1×10^7
	WA[c]	9.33 ± 0.05	2.48 ± 0.07	3.0×10^7
3	**3A** (312)[d]	9.89 ± 0.20	4.22 ± 0.27	5.5×10^6
	3A (330)[d]	9.67 ± 0.59	3.89 ± 0.80	5.8×10^6
	WA[c]	9.86 ± 0.18	4.18 ± 0.26	5.5×10^6
5	*cis,trans*-**5A**[e]	9.60 ± 0.31	3.45 ± 0.41	10.6×10^6
	trans-**5A**	8.89 ± 0.08	2.64 ± 0.12	8.3×10^6

[a] Stated errors are at 2σ. [b] Rate constant at 20 °C calculated from Arrhenius function. [c] Weighted average. [d] Monitoring wavelength in nanometers. [e] A ca. 1:1 mixture of diastereomers was employed.

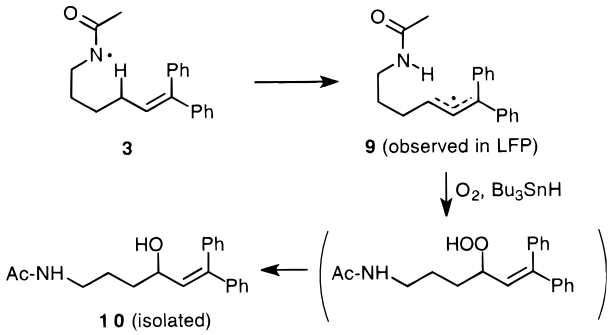
abstraction (see below). Because we incorporated the kinetics of reaction of amidyl radical **2** into tin hydride trapping kinetics discussed later, it was necessary that we determine the extent of hydrogen abstraction in this species. In preparative scale reactions and in competition kinetic studies with Bu_3SnH employing precursor **2P**, the cyclic product *N*-butyl-6-(diphenylmethyl)piperidin-2-one was obtained. More importantly, a preparative reaction with the *N*-(phenylthio)amide precursor **2P** was conducted in the presence of Bu_3SnD at a concentration of trapping agent small enough such that the ratio of acyclic to cyclic product was ca. 2:1. If intramolecular hydrogen abstraction occurred in competition with cyclization of radical **2** and the allylic radical thus formed reacted with the tin deuteride, the ultimate *acyclic* amide product would contain deuterium. The acyclic amide isolated from this reaction was analyzed by ^1H, ^2H, and ^{13}C NMR spectroscopy, and the NMR results indicated no detectable amount of deuterium at the allylic position (<1%).

It is possible in principle that the putative diphenylallylic radical formed via translocation in radical **2** was unreactive with Bu_3SnD, as apparently was the case for a related species discussed below, and ultimately coupled with other radicals or reacted with oxygen. In the Bu_3SnH-mediated reactions of **2P** discussed below, the total yields of products were high, comparable to those obtained in reactions of related *N*-(thiophenyl)amides lacking the aryl groups. Nevertheless, we make the conservative estimate that errors introduced in the tin hydride kinetics due to intramolecular hydrogen abstraction in **2** are less than 10%.

Table S1 in the Supporting Information contains the variable temperature kinetic results for radical **2** produced from the three precursors, and Table 1 contains the Arrhenius parameters for the reaction. Because the PTOC imidate derivatives are especially unstable, the sample of **2I** could not be purified by chromatography, and kinetic studies with this precursor were conducted over a limited temperature range with a crude sample. Studies with the *N*-acyl PTOC carbamate were conducted over such a broad temperature range that the Arrhenius function should be highly reliable. The agreement in the kinetics from the different precursors is excellent, and the Arrhenius parameters for **2** from each of the precursors are within 2σ of the weighted average values.

Radical **3** mainly reacted by an intramolecular hydrogen abstraction, a 1,5-translocation (Scheme 3). LFP studies with precursor **3A** showed fast growth of a species with a UV signal following laser irradiation, but a broad spectrum was observed with λ_{max} at about 313 nm rather than at 335 nm that would correspond to the absorbance for a diphenylalkyl radical (Figure 3A). We conclude that the spectrum is that of the diphenylallylic radical **9** (Scheme 3) because a similar spectrum was observed when the 1,1-diphenyl-3-methylallyl radical (**12**) was produced from PTOC ester precursor **11** (Figure 3B).[18] In addition, the reported spectrum of the 2-methyl-1-phenylallyl radical has λ_{max} at 305 nm.[19] The identity of the intermediate was also indicated by the fact that, in preparative reactions of *N*-acyl PTOC carbamate **3A** in the presence of Bu_3SnH, we obtained alcohol **10** (Scheme 3) but no *N*-acylpiperidine product. We assume that alcohol **10** arose from reduction of a hydroperoxide formed by initial oxygen trapping of the persistent radical **9** which, apparently, reacts only slowly with tin hydride.

Scheme 3



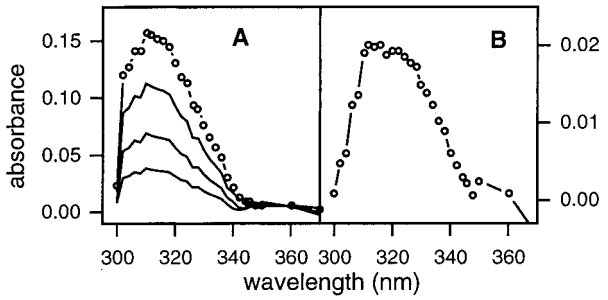
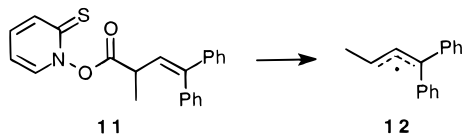


Figure 3. (A) Time-resolved growth spectrum of product from radical **3**. The traces are for 68, 108, 188, and 348 ns after the laser flash, with the data at 28 ns subtracted to give a baseline; the 348 ns data contains symbols showing the wavelengths monitored. (B) Spectrum of radical **12**; the radical was produced "instantly" from the PTOC ester precursor **11** in nonsparged THF, and the residual spectrum after 45 μs was subtracted from the spectrum observed at 1.5 μs.



Kinetic studies for radical **3** were obtained using *N*-acyl PTOC carbamate **3A**. Table S2 in the Supporting Information contains kinetic results at two monitoring wavelengths, 312 and 330 nm, and the Arrhenius parameters are in Table 1. Signal growth at 312 nm was a single exponential process, but the growth at 330 nm was better fit by a double exponential solution. The faster rate constant of the two values in the double exponential solution of the 330 nm data is listed in Table S2, and although the precision in the Arrhenius parameters for these data is only fair (Table 1), the values are within the 95% confidence interval of the data collected at 312 nm. Second-order processes (radical−radical and radical-oxygen reactions) cannot interfere with the kinetics of unimolecular reactions faster than 1×10^5 s^{-1} because the concentrations of radicals and

(18) Emanuel, C. J.; Newcomb, M. Unpublished results.

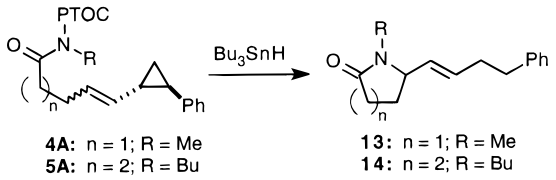
(19) Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Martinez, F. N.; Newcomb, M.; Wink, D. J.; Yao, Q. *J. Am. Chem. Soc.* **1998**, *120*, 211−212.

oxygen are so small in our experimental design that even diffusion-controlled bimolecular reactions have pseudo-first-order rate constants $< 1 \times 10^4$ s^{-1}.[20] We believe it is most likely that the "multiple processes" at 330 nm involved (1) initial production of allylic radical **9** in non-Boltzmann populations of conformers, (2) conformational relaxation (allyl radical bond rotation) with a rate constant on the order of 10^6 s^{-1}, and (3) slightly different UV spectra for the conformers of radical **9**. This type of behavior has been observed for the related 2-benzyl-1,3-diphenylallyl radical where the spectrum produced "instantly" displayed a 5-nm hypsochromic shift in the UV spectrum and a ca. 10% increase in absorbance at λ_{max}, with a rate constant of 2×10^6 s^{-1} at ambient temperature, in what was attributed to a conformational relaxation process.[19]

The use of the "reporter groups" in amidyl radicals **4** and **5** provides a means for measuring radical kinetics by LFP with UV detection without introducing a large kinetic acceleration that arises with aryl substitution directly on the alkene moiety. The reporter group in these radicals has a minor accelerating effect that, for the case of the 5-hexenyl radical cyclization, amounts to about a factor of 2 at ambient temperature.[11] Nevertheless, the 5-*exo* cyclization of radical **4** was too fast to measure. Upon irradiation of *N*-acyl PTOC carbamate precursor **4A** at 12 or 20 °C, we observed an "instant" growth in the region around 320 nm (λ_{max} for benzylic radicals)[14] as opposed to an initial bleaching, and there was no further signal growth with time. The cyclization reaction of **4** is faster than 2×10^8 s^{-1}.

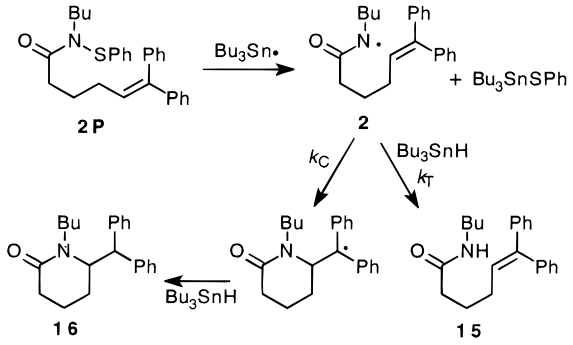
Radical **5** reacted in a 6-*exo* cyclization slowly enough to permit kinetic studies.[21] Irradiation of *N*-acyl PTOC carbamate precursor **5A** was followed by growth of a signal with λ_{max} at about 322 nm, consistent with a benzylic radical.[14] Kinetic studies of radical **5** were performed with two samples of **5A**, one that was a ca. 1:1 mixture of *cis* and *trans* isomers and one that was diastereomerically pure *trans*-**5A**. One can assume that LFP of the mixture of isomers of **5A** produced about a 1:1 mixture of isomeric radicals **5**, but the signal-to-noise ratio was not adequate to permit a meaningful double exponential solution of the data. Therefore, the data was solved for a single exponential process. The kinetic values are collected in Table S3 in the Supporting Information, and the Arrhenius parameters are in Table 1. From the differences in the kinetic values and Arrhenius parameters for *trans*-**5** and the *cis*,*trans*-**5** mixture, it seems apparent that *cis*-**5** reacted somewhat faster than *trans*-**5**, but rate constants for *cis*-**5** cannot be obtained because the exact composition of the mixture of radicals cannot be determined precisely.

Preparative scale reactions confirmed that cyclizations of **4** and **5** occurred. *N*-acyl PTOC carbamates **4A** and **5A** were



allowed to react in the presence of dilute Bu_3SnH. Pyrrolidinone **13** was obtained from **4A** in 43% yield, and piperidinone **14** was obtained from **5A** in 14% yield. The low yield of **14** is in part a reflection of the very fast trapping reaction of tin hydride

Scheme 4



(see below). Both **13** and **14** were obtained as the *trans* isomers as deduced by the observation that the ^{1}H NMR spectra obtained at 500 MHz contained vinyl proton signals only for *trans*-alkenes. In addition, GC analysis of products from reactions of **5A** with PhSH did not indicate the presence of a second cyclic isomer in detectable amounts.

Amidyl radical **6** also was evaluated as a potential radical clock. In this case, the fragmentation reaction shown in Figure 1 produces the diphenylmethyl radical. Irradiation of either *N*-acyl PTOC carbamate **6A** or PTOC imidate ester **6I** at ambient temperature resulted in no appreciable growth in signal intensity at 335 nm, indicating that the fragmentation reaction had a rate constant $< 1 \times 10^4$ s^{-1} and was slow with respect to bimolecular radical−radical and radical−oxygen reactions. At 48 °C, irradiation of **6A** was followed by growth of a weak signal with $\lambda_{max} = 330$ nm and with a rate constant of $k_{obs} = 2.3 \times 10^4$ s^{-1}. These results are self-consistent because fragmentation reactions typically have large, positive entropies of activation (log *A* terms of about 15).[22] Accordingly, the unimolecular fragmentation process will be increasingly competitive with bimolecular reactions (log *A* of ca. 10) as the temperature is increased. If the fragmentation of **6** does have log $A = 15$, then the 48 °C kinetic results give a calculated rate constant for fragmentation of **6** at 20 °C of $k = 2 \times 10^3$ s^{-1}, a value too slow to measure with our LFP experimental design.[20]

Indirect Kinetic Studies. Second-order rate constants for intermolecular reactions of amidyl radicals are necessary for establishing a kinetic scale. One of the more common reagents used synthetically in radical-based methods is Bu_3SnH, and the *N*-(phenylthio)amides react with tin hydride in radical chain reactions.[7] We have used amidyl radical **2** as a radical clock for timing the tin hydride trapping reaction.

Precursor **2P** reacted in the presence of tin hydride in toluene by the sequence of reactions shown in Scheme 4 to give, ultimately, amide **15** and piperidinone **16**. Relative rate constants for trapping of the amidyl radical (k_T) and cyclization (k_C) were determined by eq 1, and the results are listed in Table 2. Because tin hydride reacts rapidly with the amidyl radical, on the order of 10^9 M^{-1} s^{-1}, only small concentrations of the trapping agent could be employed, and even then the amide product **15** predominated. The data in Table 2 provides the relative Arrhenius function in eq 2 where $\theta = 2.3RT$ in kcal/mol and the errors are at 2σ. Combination of the relative Arrhenius function in eq 2 with that for cyclization of radical **2** given in Table 1 gives the absolute Arrhenius function for reaction of tin hydride with the amidyl radical in eq 3 that can

(20) Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, *118*, 3862−3868.

(21) Preliminary results for radical **5** were reported in ref 11.

(22) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.

Table 2. Results of Bu_3SnH Trapping of Radical 2[a]

temp[b] (°C)	[Bu_3SnH][c] (M)	[U]/[R][d]	(k_T/k_C) (M^{-1})
50	0.097	3.27	34
	0.081	3.12	38
65	0.098	3.40	35
	0.082	2.80	34
76	0.210	6.89	33
	0.239	7.88	33
84	0.261	8.20	31
	0.193	6.13	32
92	0.167	5.08	30
	0.248	7.67	31

[a] Reactions run in toluene with AIBN initiation. [b] ±1 °C. [c] Mean concentration of tin hydride. [d] Observed ratio of acyclic to cyclic amide products. The total yields of products determined by GC ranged from 63% to 81%.

be used to predict rate constants for tin hydride trapping, such as $k = 1.3 \times 10^9$ M^{-1} s^{-1} at 20 °C.

$$\log((k_T/k_C) \times M) = (0.93 \pm 0.21) + (0.93 \pm 0.33)/\theta \quad (2)$$

$$\log((k_T) \times Ms) = (10.26 \pm 0.22) - (1.55 \pm 0.34)/\theta \quad (3)$$

The rate constants calculated from eq 3 will be reasonably accurate for temperatures close to those of the competition study, but the Arrhenius parameters in eq 3 are probably slightly in error due to partial diffusion control conditions. Using estimated radii[23] for tin hydride and amidyl radical **2** and the dynamic viscosity of toluene and assuming stick boundary conditions, the diffusional rate constant for tin hydride reaction with **2** at 20 °C is about 1.1×10^{10} M^{-1} s^{-1} or about 9 times faster than that for tin hydride trapping. Benzene and cyclohexane are more viscous than toluene, and the diffusional rate constants in these solvents estimated by the same method would be about 8 (benzene) and 5 (cyclohexane) times faster than that for tin hydride trapping at 20 °C. The diffusional rate constants are lower limits because stick boundary conditions were assumed, but they show that the tin hydride trapping reaction can become partially diffusion-controlled. The apparent activation energies for diffusional rate constants from an Arrhenius-type treatment are in the range of 2−3 kcal/mol, and partial diffusion control of tin hydride trapping of amidyl radicals will be increasingly important at lower temperatures. The net result of partial diffusion control in regard to eq 3 is that both the log A and E_a terms in the equation are likely to be slightly greater than the actual values for the chemical process as opposed to composite diffusional and chemical processes.

Thiophenol trapping of an amidyl radical also was studied, in this case with amidyl radical **5**. A number of experimental difficulties arise in attempting to calibrate the reaction of an amidyl radical with a thiol trapping agent as opposed to tin hydride. Some of these can give rise to systematic errors in the kinetic determinations, but the kinetic value appears to be reliable (see Discussion). *N*-Acyl PTOC carbamate **5A** was allowed to react in the presence of varying concentrations of PhSH at 23 °C in THF to give the results listed in Table 3. Analysis of the data via the linear form of eq 1 gave a slope, equal to k_T/k_C, of (7.5 ± 0.7) M^{-1} and an intercept of (0.0 ± 0.2) M^{-1}. Combining the slope with the rate constant for cyclization of radical **5** gives a rate constant for the PhSH trapping reaction of $k = (9 \pm 1) \times 10^7$ M^{-1} s^{-1} at 23 °C (stated errors at 2σ). With alkyl radicals, PhSH reacts 50 times faster than Bu_3SnH at ambient temperature,[13] but the "hydridic" tin hydride reacts with an "electrophilic" amidyl radical more than an order of magnitude faster than does PhSH.

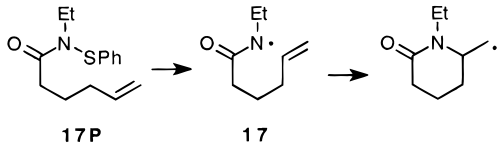
(23) Edward, J. T. *J. Chem. Educ.* **1970**, *47*, 261−270.

Table 3. Results of PhSH Trapping of Radical 5[a]

[PhSH][b] (M)	[U]/[R][c]	(k_T/k_C) (M^{-1})
0.09	0.70	7.8
0.16	1.23	7.7
0.24	1.87	7.8
0.32	2.24	7.0
0.53	4.06	7.7

[a] Reactions run in THF at 23 ± 1 °C. [b] Mean concentration of PhSH. [c] Observed ratio of acyclic to cyclic amide products. The total yields of products determined by GC ranged from 81% to 94%.

With the calibration of the rate constants for the reaction of tin hydride with an amidyl radical, it is possible to use ratios of rate constants for simple amidyl radical cyclizations in competition with tin hydride trapping to calculate rate constants for the cyclization reactions; the Discussion contains examples where rate constants for cyclizations were calculated from previously reported results. There was an obvious conflict between our data for 6-*exo* cyclization of radical **5** and results from ESR studies,[17] however, that required that we study the reactions of amidyl radical **17**. Whereas we observed that radical **5** reacted virtually exclusively via a 6-*exo* cyclization, Ingold's group reported that the closely related radical **17** reacted exclusively by an intramolecular hydrogen abstraction reaction that gives an allylic radical product.[17]



17P **17**

When radical **17** was generated by reaction of *N*-(thiophenyl)-amide **17P** in the presence of Bu_3SnH, we observed formation of *N*-ethyl-6-methyl-2-piperidinone, the ultimate product from 6-*exo* cyclization of radical **17**. The rate constant for cyclization of radical **17** at 65 °C, determined by competition between tin hydride trapping and cyclization, was $k = 1.0 \times 10^7$ s^{-1}. A more important result from the mechanistic standpoint was obtained when precursor **17P** was allowed to react in the presence of Bu_3SnD. The reaction was conducted with a concentration of tin deuteride small enough such that the cyclization reaction competed efficiently with trapping; the acyclic to cyclic product ratio was 2:1. Analysis of the mixture of products by ^2H NMR spectroscopy showed that the acyclic amide contained <2% deuterium at C4. Accordingly, the translocation reaction must be less than 4% as fast as the cyclization reaction, a result completely opposite that reported by Sutcliffe and Ingold.[17] A possible explanation of the difference in results for radical **17** is given below.

Discussion

The LFP-based approach to developing an amidyl radical scale employed in this work is similar to that we have used previously. The major difference between this approach and that commonly employed is that we used LFP for calibrations of unimolecular reactions, the kinetics of which can be determined with high precision, rather than for direct studies of bimolecular processes. The bimolecular rate constants necessary for developing a kinetic scale were obtained by indirect, competition kinetics using the calibrated radical clocks. Because the indirect studies typically are conducted over wide temperature ranges, the precisions in the rate constants and

Arrhenius parameters for bimolecular reactions determined by the composite method we employ is as good or better than those usually reported for direct LFP studies.

Few absolute rate constants for amidyl radical reactions were previously available. An early LFP study of *N*-nitrosoamides provided rate constants for decay of amidyl radicals and some second-order kinetic values.[24] Kinetic ESR studies by Ingold's group provided amidyl radical self-termination rate constants that were at or near diffusion control and a rate constant for hydrogen abstraction from cyclohexane by an amidyl radical.[25] Sutcliffe and Ingold also reported a kinetic ESR study aimed at the calibration of amidyl radical clocks that established some approximate rate constants and some kinetic limits.[17] The kinetic ESR method usually requires that reactions are conducted at low temperatures, and extrapolations of the results to ambient temperature can result in considerable errors.[26] The kinetics determined in this work for amidyl radical cyclizations are in fair to poor agreement with the results of the kinetic ESR studies as discussed later.

Reactions of Amidylacyloxyl Radicals. Among the three radical precursors employed for LFP studies in this work, the *N*-acyl PTOC carbamates are quite useful due to their ease in preparation, their relative stability, and their reactivity in chain reactions with thiyl radicals.[6] In addition, they are cleaved by 355-nm light which does not interfere with the observation of UV absorbances from benzylic and diphenylalkyl radicals that have λ_{max} values in the 320- and 335-nm range, respectively. However, the first-formed radicals from these precursors are amidylacyloxyl radicals **18** that can react by an intramolecular hydrogen atom transfer to give α-amide radicals **19** in addition to the desired decarboxylations that give amidyl radicals. In

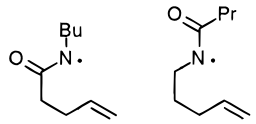
18 **19**

direct LFP studies, the competing radical translocation reaction might reduce sensitivity by diverting some of the reactant, but it has no affect on the kinetics. In *indirect* competition kinetic studies, however, the translocation reaction would result in the ultimate formation of unrearranged products and would introduce an error in the apparent rate constants for amidyl radical trapping reactions.

The translocation in radicals **18** competes with decarboxylation and is a function of the substitution at the center adjacent to the carbonyl group, with more highly alkyl-substituted positions demonstrating increased translocation.[6] In addition, its extent is influenced by the initial conformational population of radicals **18**, as demonstrated by a dramatic change in the amount of translocation as a function of the presence or absence of Mg^{2+}; this is consistent with the idea that the rotation about the C−N bond that interconverts conformations must be slower than decarboxylation.

The rate constants for decarboxylation of radicals **18** to give amidyl radicals are not known, but one can establish some limits. It is likely that the rate constants are smaller than those for decarboxylation of alkylacyloxyl radicals (ca. $10^{10}-10^{11}$ s^{-1} at ambient temperature)[27] due to the relative instability of amidyl radicals in comparison to alkyl radicals. If the rates of decarboxylation were too slow, however, LFP studies with these radicals would have been complicated, and it is clear that the rate constants for decarboxylation are greater than 2×10^8 s^{-1} at ambient temperature and did not affect the kinetics. The excellent agreement in the kinetics of cyclization of radical **2** (Table S1) produced from the three different precursors indicates that the same reaction was measured in each case. Importantly, even though we could not measure the rate constants for cyclizations of amidyl radicals **1** and **4**, the fact that the rate constants for cyclizations were greater than 2×10^8 s^{-1} requires that the decarboxylation reactions that produced these amidyl radicals were essentially complete within a few nanoseconds. We estimate, therefore, that decarboxylations of radicals **18** have rate constants in the 10^9-10^{10} s^{-1} range at ambient temperature.

Amidyl Radical Cyclizations. The LFP results provided lower kinetic limits for the 5-*exo* cyclizations of radicals **1** and **4** of 2×10^8 s^{-1} and rate constants and Arrhenius functions for the 6-*exo* cyclizations of radicals **2** and **5** (Table 1). By combining the Bu_3SnH trapping rate constants with extant competition kinetic results, one can also calculate rate constants for the 5-*exo* cyclizations of radicals **20** and **21**. These rate



20 **21**

constants are valuable for an amidyl radical kinetic scale not only because radicals **20** and **21** resemble those one would expect to see employed in synthetic applications but also because the absence of aryl and reporter groups in these species precludes any special substituent-derived kinetic effects that one might imagine for the electrophilic amidyl radicals.

The relative rate constants at 65 °C for cyclization (k_C) and tin hydride trapping (k_T) of radicals **20** and **21**, generated from the corresponding *N*-(phenylthio)amides, were (1.7 ± 0.1) M and (0.41 ± 0.01) M, respectively.[7] These values can be combined with the rate constant for tin hydride trapping at 65 °C determined in this work or directly converted to absolute rate constants because the ratio of rate constants (k_T/k_C) for radical **2** was determined to be 34.5 M^{-1} at 65 °C (Table 2). The rate constant at 65 °C for cyclization of **20** is $k_C = (3.1 \pm 0.2) \times 10^9$ s^{-1}, and that for cyclization of **21** is $k_C = (7.4 \pm 0.2) \times 10^8$ s^{-1}. One notes that at 65 °C the 5-*exo* cyclization of **20** is 300 times as fast as the 6-*exo* cyclization of **17**, consistent with the established pattern for related pairs of radicals. For example, the 5-hexenyl radical cyclizes about 2 orders of magnitude faster than the 6-heptenyl radical.[28]

The Arrhenius log *A* terms for the 6-*exo* cyclizations of radicals **2** and **5** were typical for such reactions, and it is reasonable to assume that the log *A* values for the 5-*exo* cyclizations of radicals **20** and **21** and the 6-*exo* cyclization of radical **17** also will be typical with log *A* in the range of 10. With this assumption, one would estimate rate constants for cyclization at 20 °C of 2×10^9 s^{-1} (**20**), 5×10^8 s^{-1} (**21**), and

(24) Tam, J. N. S.; Yip, R. W.; Chow, Y. L. *J. Am. Chem. Soc.* **1974**, *96*, 4543−4549.

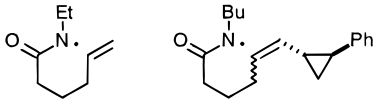
(25) Sutcliffe, R.; Anpo, M.; Stolow, A.; Ingold, K. U. *J. Am. Chem. Soc.* **1982**, *104*, 6064−6070.

(26) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 193−200.

(27) Falvey, D. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 7419−7420. Hilborn, J. W.; Pincock, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 2683−2686. Bockman, T. M.; Hubig, S. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4502−4503.

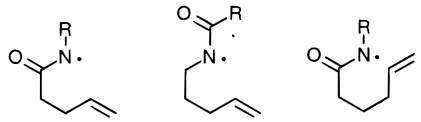
(28) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472−473.

4×10^6 s^{-1} (**17**).[29] For comparison, radical *trans*-**5** cyclizes with a rate constant of 8×10^6 s^{-1} at 20 °C.



17 **5**

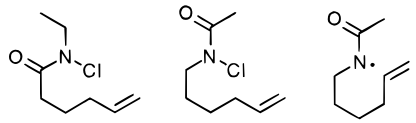
The rate constants for cyclizations of the simple amidyl radicals **5**, **17**, **20**, and **21** are in fair to poor agreement with values for related reactions obtained by kinetic ESR studies.[17] In that work, rate constants at ambient temperature were estimated from low-temperature ESR results and assumed log *A* values. The reported rate constants for cyclizations at 300 K were $k > 1 \times 10^7$ s^{-1} for radicals **22**, $k = 5 \times 10^4$ s^{-1} for **23**, and $k = 1 \times 10^6$ s^{-1} for **24**.[17] The 4 orders of magnitude



22 (R = Me, Et, *i*-Pr) **23**: R = Me **21**: R = Pr **24**: R = Me **17**: R = Et

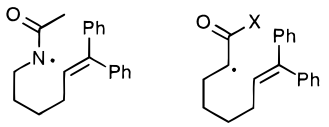
difference in rate constants for cyclization of **21** determined in this work and for **23** is especially glaring and cannot be attributed to an error due to extrapolation. The ESR-based rate constant for **23** was actually an estimate resulting from the fact that no spectrum of a cyclic product radical could be observed at low temperature.[17] We have previously noted that the absence of the expected ESR spectrum for the product from **23** probably was due to a translocation reaction following the cyclization reaction, a sequence that gives an α-amide radical that might not be observed in the ESR spectrum due to line broadening. Such a reaction was previously implicated by product studies of radical **21**.[5] Those who might wish to employ amidyl radical cyclizations for the synthesis of *N*-acyl pyrrolidines and piperidines should be aware of this possible complicating process. The factor of 4 difference in rate constants at ambient temperature for cyclization of **17** determined in this work and for **24** probably is a result of the extrapolation from low-temperature results in the ESR study. This conclusion is supported by the observation that at 20 °C radical *trans*-**5** cyclizes twice as fast as radical **17** and the previous observation that the same reporter group used in **5** gives a 2-fold acceleration in the cyclization of the 5-hexenyl radical.[11]

The situation with radical **17** deserves special comment. Sutcliffe and Ingold reported that whereas **24** cyclized, radical **17** reacted at low temperature by a 1,5-hydrogen atom transfer reaction.[17] We found that at 65 °C radical **17** cyclized in a 6-*exo* fashion and that the translocation reaction must represent <4% of the total reaction. Because the translocation and cyclization reactions should have similar log *A* values, these results are completely at odds with one another. From the description in the account of the ESR studies, there seems to be little doubt that an allylic radical was produced; the ESR signal was described as strong, and the reported hyperfine coupling values are clearly consistent with those expected for a monosubstituted allyl radical.[17] However, the radical precursors used by Sutcliffe and Ingold were *N*-chloroamides provided to them by Lessard's group, and no characterization data was in the report.[17] Our best guess as to the origin of the conflicting results is that the reactant claimed to be chloramide **25** actually was chloramide **26**, the precursor to radical **27** that was the species that reacted to give an allylic radical product. This proposal is consistent with our observation of translocation as the major reaction for radical **3**.



25 **26** **27**

Intramolecular Hydrogen Abstractions. Amidyl radical **3** reacted mainly by a 1,5-hydrogen atom transfer instead of a 6-*exo* cyclization. The rate constants for the translocation reaction (e.g., 5.5×10^6 s^{-1} at 20 °C) are of the same order of magnitude as that one might have expected for a 6-*exo* cyclization reaction, given that the 5-*exo* cyclization of radical **20** was only 4 times as fast as the 5-*exo* cyclization of radical **21** and the rate constant for 6-*exo* cyclization of **2** is 3×10^7 s^{-1} at 20 °C. Thus, the observation of the hydrogen atom transfer in radical **3** and our failure to isolate a piperidine product from preparative reactions of **3** indicate that the 6-*exo* cyclization reaction is disfavored. That is, some special steric effects appear to be at play in the transition structure of the 6-*exo* cyclization reaction that appreciably slow this process. It is of interest to note that a similar phenomenon was observed in a related carbon−radical system. Specifically, the 6-*exo* cyclization of the α-amide radical **28** was found to be only 0.03 times as fast as the cyclization of α-ester radical **29** even though 5-*exo* cyclizations of secondary α-amide and α-ester radicals have about the same rate constants.[30] Although the resemblance between **3** and **28** might be superficial, the results in total suggest that the transition states for 6-*exo* cyclizations of radicals are considerably more sensitive to steric effects than those of 5-*exo* cyclizations.



3 **28**: X = NEt_2 **29**: X = OEt

Bimolecular Hydrogen Transfer Reactions. The rate constants for bimolecular reactions of amidyl radicals with Bu_3SnH and PhSH provide the essential data for expanding an amidyl radical kinetic scale. With these values, others can readily calibrate amidyl radical reactions by competition kinetic methods that require no special apparatus.[13] To determine the rate constants for reactions of amidyl radicals with hydrogen atom transfer agents, we needed sources of amidyl radicals that reacted cleanly in radical chain reactions with the byproduct radical produced from the hydrogen atom donor. The *N*-(phenylthio)amides clearly meet this requirement when the donor is Bu_3SnH.[7] The reactions appeared to proceed within minutes, indicating that the rate-controlling step of the chain reaction

(29) We note that a competition study performed at 20 °C with Bu_3SnH trapping of radical **20** from the PTOC imidate ester precursor (ref 5b) gives an apparently small rate constant of 1.1×10^9 s^{-1} for cyclization of **20**. If this rate constant is accurate, then the log *A* value for cyclization of radical **20** would be 12.4, which appears to be too large. The PTOC imidate esters are readily hydrolyzed, and we believe it is possible that small amounts of hydrolysis of the precursor, giving the acyclic amide product, resulted in an apparently small rate constant for cyclization.

(30) Musa, O. M.; Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 786−793.

sequence, the relatively slow step that one assumes is reaction of the stannyl radical with the amide derivative, was quite rapid. The internal consistency of the kinetics of cyclization of radicals **20** and **21**, determined via tin hydride trapping using *N*-(phenylthio)amide precursors, with the cyclization kinetics measured by LFP in this work further indicates that the reactions were uncomplicated.

The reaction of Bu_3SnH with amidyl radical **2** was very fast, indicative of the high exothermicity of the reaction. The bond dissociation energy (BDE) of the N−H bond in a secondary amide is comparable to the N−H BDE of ammonia[31] or about 107 kcal/mol, whereas an R_3Sn−H BDE is only about 74 kcal/mol.[32] In addition, an electrophilic character of the radical, or at least a lack of nucleophilic character, is suggested by the fact that the reaction with tin hydride is about 3 orders of magnitude faster than reaction of a primary alkyl radical with Bu_3SnH.[33] Specifically, the $\Delta G°$ values for tin hydride reacting with an amidyl radical (−34 kcal/mol) and with an alkyl radical (−26 kcal/mol)[32] are large enough such that the transition states should be quite early, yet $\Delta G^{‡}$ for the amidyl radical reaction is about 4 kcal/mol smaller than that for the alkyl radical reaction, suggesting polar stabilization in the transition state for the amidyl radical reaction. That the amidyl radical reaction with thiophenol is slower than reaction with Bu_3SnH, whereas a nucleophilic carbon radical reacts with PhSH more rapidly[34] than it reacts with Bu_3SnH,[33] further indicates the electrophilic character of an amidyl radical.

The studies of thiophenol trapping were considerably more complicated than the tin hydride studies. In a manner similar to alkyl halides and pseudohalides, the *N*-(phenylthio)amides will not react with thiyl radicals in chain propagation steps. In studies of carbon-centered radicals reacting with thiols or benzeneselenol, it is possible to use a silane or tin hydride as a sacrificial reductant which reacts with the chalcogen-centered radical to give a Group 14 radical that will propagate a chain reaction with an alkyl halide,[35] but this approach is impractical for amidyl radicals which react more rapidly with tin hydride than with a thiol. The *N*-acyl PTOC carbamates and PTOC imidate esters do react in chain propagation steps with thiyl radicals, but problems exist in the applications of either of these types of precursors for indirect studies. The more robust *N*-acyl PTOC carbamates present the potential problems that the first-formed amidylacyloxyl radicals **18** could react with the donor intermolecularly or by intramolecular translocation to give an α-amide radical; both processes will introduce an error by leading ultimately to an unrearranged amide product. The PTOC imidate esters do not have this potential problem, but these compounds cannot be purified readily nor handled without some hydrolysis which, again, gives the unrearranged amide product and will introduce an error in the kinetics. Further, in an attempt to use a PTOC imidate ester in a competition kinetic study with a thiol, it appeared as if the activated acyl precursor reacted with the thiol by a polar addition reaction. The kinetic study of the reaction of thiophenol with radical **5** employed the *N*-acyl PTOC carbamate **5A**, but we believe the rate constant we obtained is reasonably reliable.

The potential translocation reaction in the amidylacyloxyl radical precursor to radical **5** is demonstrably insignificant. If it occurred, then this unimolecular process, which competes with unimolecular decarboxylation, would have introduced a constant amount of unrearranged amide product irrespective of PhSH concentration. The manifestations of this phenomenon would be (1) the individual values of (k_T/k_C) calculated for each concentration of PhSH would differ and (2) a plot of the ratio of unrearranged to rearranged products versus PhSH concentration would have a nonzero intercept reflecting the amount of translocation. In fact, the individual values of (k_T/k_C) at all concentrations of PhSH agree (Table 3), and the least-squares fit of that data has an intercept of (0.0 ± 0.2) M at 2σ. Any translocation that occurred would introduce a percentage error in (k_T/k_C) equal to the percentage of translocation, that is, 20% translocation would give a 20% error in the ratio and in the calculated value of k_T. However, for the data in Table 3 with a slope of $(k_T/k_C) = 7.5$ M, 20% translocation would give an intercept of 0.25 M which is outside the 95% confidence interval for the intercept we measured.

The potential for reaction of the amidylacyloxyl radical from **5A** with PhSH before decarboxylation is more difficult to evaluate. The rate constant for decarboxylation of the amidylacyloxyl radicals must be greater than 2×10^8 s^{-1} at ambient temperature because the cyclizations of radicals **1** and **4** were found to occur faster than this, and we estimated that the rate constant is in the 10^9-10^{10} s^{-1} range at room temperature. It is known that PhSH at up to 2 M concentrations does not react with alkylacyloxyl radicals faster than decarboxylation,[36] which occurs with rate constants in the $10^{10}-10^{11}$ s^{-1} range. If one assumes that PhSH reacts with these two types of acyloxyl radicals with about the same rate constants, then PhSH trapping of the amidylacyloxyl radicals would not be a major reaction in the studies conducted here where the PhSH concentrations were 0.1−0.5 M. Nevertheless, we caution that the rate constant for reaction of PhSH with an amidyl radical should be considered as an upper limit.

Conclusion

Rate constants for amidyl reactions measured directly by LFP methods provide the absolute kinetic values necessary for establishing an amidyl radical kinetic scale. These have been incorporated into rate constants for bimolecular reactions of amidyl radicals and cyclizations of simple amidyl radicals to give kinetic values that can be used in synthetic planning or for timing other amidyl radical reactions. Cyclizations of amidyl radicals are much faster than those of carbon-centered radicals, indicating that 5-*exo* cyclizations leading to either *N*-acylpyrrolidine or γ-butyrolactam products and 6-*exo* cyclizations leading to δ-valerolactam products can be incorporated into synthetic schemes, but 6-*exo* cyclizations that ultimately give *N*-acylpiperidine products are slow relative to competing 1,5-hydrogen atom transfer reactions. The development of nitrogen-centered radical kinetic scales has been an objective of our group for some time, and Table 4 contains an overview of the kinetic results from this work and previously reported studies.[16,20,37]

Experimental Section

General Methods. Commercially available reagents were purchased from either Sigma or Aldrich Chemical Co. and were used as received. Tetrahydrofuran (THF) and diethyl ether were distilled under a nitrogen

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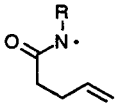
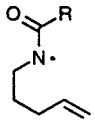
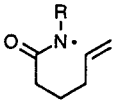
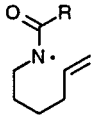
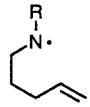
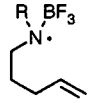
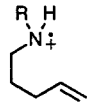
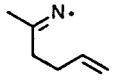
Table 4. Radical Rate Constants at 20 °C

Radical	k_C[a] (s^{-1})	k_T (Bu_3SnH)[b] (M^{-1} s^{-1})	k_T (PhSH)[c] (M^{-1} s^{-1})
	2×10^5 (ref 13)	2×10^6 (ref 37a)	1×10^8 (ref 37b)
	2×10^9	1.3×10^9	1×10^8
	5×10^8	1.3×10^9	1×10^8
	1×10^7	1.3×10^9	1×10^8
	translocation[d]	1.3×10^9	1×10^8
	2×10^4 (ref 20)	5×10^5 (ref 20)	1.2×10^8 (ref 20)
	7×10^5 (ref 16d)		
	1×10^8 (ref 11, 16d)	ca. 1×10^8 (ref 16c)	4×10^7 (ref 16c)
	ca. 1×10^4 (ref 37d)[e]	ca. 3×10^3 (ref 37d)	6×10^6 (ref 37d)

[a] Rate constant for 5-*exo* or 6-*exo* cyclization. [b] Rate constant for reaction with Bu_3SnH. [c] Rate constant for reaction with PhSH. [d] Translocation (1,5-hydrogen transfer) to give the allylic radical occurs; see text. [e] Estimated from results with the terminal diphenyl-substituted analogue.

atmosphere from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from phosphorus pentoxide. Dimethyl formamide (DMF) was distilled under reduced pressure from calcium hydride. The sodium salt of *N*-hydroxypyridine-2-thione was purified as described previously.[5b] ^1H NMR spectra were obtained at 300 or 500 MHz on Varian Gemini 300 or Unity 500 spectrometers, respectively. ^{13}C NMR spectra (75 or 125 MHz) were obtained on the same instruments. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. High-resolution mass spectral analyses were performed by the Central Instrumentation Facility at Wayne State University. GC analyses were performed on Varian model 3400 FID-equipped chromatographs unless otherwise noted.

The methods employed in this work are described here. The specific preparations of the radical precursors used in this work and the amide precursors to these compounds are presented in the Supporting Information.

Preparation of *N*-Acyl PTOC Carbamates (Method A). To 1 equiv of the amide in Et_2O (15 mL) were added 1.1 equiv of TEA and 1.1 equiv of TMSOTf. The mixture was stirred at ambient temperature for 12 h, and ammonium triflate was removed via syringe. Phosgene in toluene (1.5 equiv, 1.9 M solution) was added via syringe at ca. 5 °C, and the mixture was stirred for 3−4 h while warming to ambient temperature. After addition of benzene (10 mL), the solution was concentrated to ca. 10 mL at reduced pressure on a rotary evaporator containing a trap for the excess phosgene and TMSCl. 2-Mercaptopyridine-*N*-oxide sodium salt (1.2 equiv) was added to the flask, which was shielded from light with aluminum foil, and the mixture was stirred for 12 h. Filtration of the salts and dilution of the filtrate in benzene gave an organic phase which was washed with saturated aqueous $NaHCO_3$ solution (3 × 10 mL) and saturated aqueous NaCl solution (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield the crude *N*-acyl PTOC carbamate which was purified by column chromatography on silica gel (eluent, hexanes:EtOAc).

Preparation of PTOC Imidate Esters (Method B). To a 0.1 M solution of a secondary amide in benzene containing a catalytic amount of DMF at ca. 5 °C was transferred phosgene (1.5 equiv, 1.9 M solution in toluene). The solution was allowed to warm slowly to ambient temperature with stirring. The slow evolution of CO_2 was monitored via a mineral oil bubbler. After gas evolution was complete, excess phosgene and solvent were removed under reduced pressure to give the corresponding imidoyl chloride as a clear liquid. Dry Et_2O was added to the imidoyl chloride to form a 0.1 M solution. The flask was wrapped in aluminum foil, and anhydrous 2-mercaptopyridine-*N*-oxide sodium salt (1.2 equiv) was added via a solids addition tube under nitrogen. The mixture was stirred for 4−8 h. Residual salts were removed by filtration under N_2 and were rinsed with dry Et_2O. Concentration of the combined organic phase under vacuum gave the imidate esters as yellow oils. These products were not further purified.

Preparation of *N*-(Phenylthio)alkenylamides (Method C). To NaH (2.75 mmol, 60% in oil) in dry THF (15 mL) was added a secondary amide (2.50 mmol), and the mixture was heated at reflux for 4 h. The mixture was cooled to −78 °C, and 0.30 mL of phenylsulfenyl chloride, prepared by the method of Brower and Douglass,[38] was added dropwise until the yellow color of the sulfenyl chloride was persistent. The solvent was removed under reduced pressure, and the residue was partitioned between Et_2O (30 mL) and H_2O (10 mL). The ether layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent, hexanes:EtOAc) to give the *N*-(phenylthio)amides as colorless oils.

Photolysis of *N*-Hydroxypyridine-2-thione Derivatives (Method D). A 0.025−0.05 M solution of the *N*-acyl PTOC carbamate in dry benzene or dry THF was degassed under N_2 for 15−30 min in the dark. Trapping agents were added via syringe from a 0.05−0.5 M stock solution in the same solvent. The sample was irradiated with visible light from a 150 W tungsten filament flood lamp at a distance of 2−3 ft until disappearance of the PTOC carbamate (followed by TLC). Removal of the solvent at reduced pressure was followed by separation of the products using radial chromatography (silica gel, hexanes:EtOAc elution).

LFP kinetic studies were performed on a modified Applied Photophysics LK-50 kinetic spectrometer using the Applied Photophysics software for instrument control and data analysis. A Spectron Nd:YAG laser operating at a nominal power rating of 40 mJ (355 nm) or 45 mJ (266 nm) was used for photolysis. Hammamatsu 1P28 photomultiplier tubes and a Hewlett-Packard 54522 oscilloscope were employed. Solutions of the desired precursor in THF with an absorbance of 0.4−0.5 at the laser wavelength were sparged with helium and thermally equilibrated in a jacketed addition funnel by circulation

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of a water/ethylene glycol solution from a thermally regulated bath. For reactions conducted below 0 °C, the flow cell was positioned in a nitrogen-filled box fitted with quartz windows. The solutions were allowed to flow through a quartz flow cell with an 8 mm × 8 mm i.d. Temperatures were measured with a thermocouple placed in the flowing stream approximately 1 cm above the irradiation zone. Multiple runs (5−15) at a given temperature were averaged. The observed temperature variation over the course of multiple runs was ±0.2 °C. Observed rate constants had standard errors of 1−5%.

Indirect kinetic studies of radical **2** were achieved by reactions of *N*-(phenylthio)amide **2P** with different concentrations of Bu_3SnH in toluene. Stock solutions of amide **2P** (0.024 M), Bu_3SnH (0.50 M), and AIBN (0.01 M) were prepared under N_2. Appropriate volumes of these solutions were combined in tubes that were sealed under vacuum. After heating for 5 h at the temperatures indicated in Table 2, the tubes were opened, hexadecane was added as a standard, and the yields of **15** and **16** were determined by GC analysis (DB-17 column, TCD detector GC). Indirect kinetic studies of radical **17** were conducted in a similar manner using precursor **17P** at 65 °C.

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Supporting Information Available: Tables of LFP kinetic results for radicals **2**, **3**, and **5**, synthetic details for the preparation of radical precursors, synthetic details for preparation of the requisite amides, and NMR spectra of new compounds (58 pages, print/PDF). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. See any current masthead page for ordering information and Web access instructions.

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