A Kinetic Scale for Dialkylaminyl Radical Reactions

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Abstract: A kinetic scale for dialkylaminyl radicals was established by measuring unimolecular rate constants for a series of dialkylaminyl radical clocks that spans eight orders of magnitude and using clock reactions to measure the second order rate constants for reactions of several hydrogen atom donors. *N*-Hydroxypyridine-2-thione derivatives of carbamic acids (so-called PTOC carbamates) were used as radical precursors in direct, laser-flash kinetic measurements and in indirect, radical chain kinetic studies. The calibrated radical clocks are *N*-methyl-6,6-diphenyl-5-hexenaminyl, *N*-methyl-*trans*-5-phenyl-4-pentenaminyl, *N*-methyl-5,5-diphenyl-4-pentenaminyl, *N*-methyl-*trans*-2-phenylcyclobutanaminyl, and *N*-methyl-*trans*-2-phenylcyclopropanaminyl. Calibrated hydrogen atom donors are Bu_3SnH, *t*-BuSH, PhSH, and PhSeH. Whereas the tin hydride reactions with dialkylaminyl radicals are slower than reactions with alkyl radicals, the polarity-matched reactions of the electron-rich dialkylaminyl radicals with the electron-poor hydrogen donors *t*-BuSH, PhSH, and PhSeH have rate constants nearly equal to those for reactions of alkyl radicals with the same donor.

Radical-based synthetic sequences have increased in popularity tremendously in the past several years as methods for controlling radical chain reactions have been refined. By design, multiple reaction pathways must compete in a radical chain reaction, and some knowledge of the kinetics of the competing elementary processes is necessary for efficient planning. The kinetics of simple alkyl radical reactions are relatively well characterized, but analogous kinetic scales for heteroatom-centered radical reactions that might be used in synthesis are less well developed. For dialkylaminyl radical reactions, the only useful kinetic values derive from a kinetic ESR study[1] in which rate constants for one ring opening reaction were determined at low temperatures and from a recently reported laser flash photolysis (LFP) study[2] of a cyclization reaction (that of radical **4**• in this work) over the temperature range 0−59 °C. Quite recently, a limiting value at room temperature for another dialkylaminyl radical cyclization was determined by LFP.[3] Here, we report a kinetic scale for dialkylaminyl radical reactions. The kinetics of a series of unimolecular dialkylaminyl radical reactions were measured providing a set of "radical clocks"[4] that spans several orders of magnitude. More importantly for synthetic applications, the kinetics of second order reactions of dialkylaminyl radicals with commonly employed hydrogen transfer trapping agents, Bu_3SnH, *t*-BuSH, PhSH and PhSeH, also were measured.

Several types of nitrogen-centered radicals have been employed in synthetic conversions including neutral aminyl radicals.[5−7] Dialkylaminyl radicals are produced in chain reactions of *N*-chloroamines and *N*-bromoamines, and acceptable yields of 5-*exo* cyclization products from 4-pentenaminyl systems have been reported.[7] More recently developed methods for the production of dialkylaminyl radicals also are well suited for radical chain reactions. These include direct formation of aminyl radicals from reactions of *N*-hydroxypyridine-2(1H)-thione derivatives[8] (PTOC[9] carbamates, see below) and sulfenamides,[10−13] ring openings of radicals formed from α-(haloalkyl)aziridines,[14−16] and additions of carbon radicals to imines.[17−21] The PTOC carbamate precursors react in propagation steps with a variety of radicals ($R_3C^•$, $R_3Si^•$, $R_3Sn^•$, $RS^•$, $PhSe^•$). The other recent entries to aminyl radicals usually have employed tin hydride reagents for chain propagation, but in principle, radical chain reactions employing mixed hydride reagents such as the thiol−silane mixed reagent reported by Roberts[22] and the Bu_3SnH−PhSeH mixed reagent reported by Crich[23] also should be efficient.

Results

Materials and Methods. PTOC carbamates **1P**−**6P** (Figure 1) were employed as dialkylaminyl radical precursors both for direct LFP studies and for indirect competition studies. These radical precursors were prepared in good yield by reaction of

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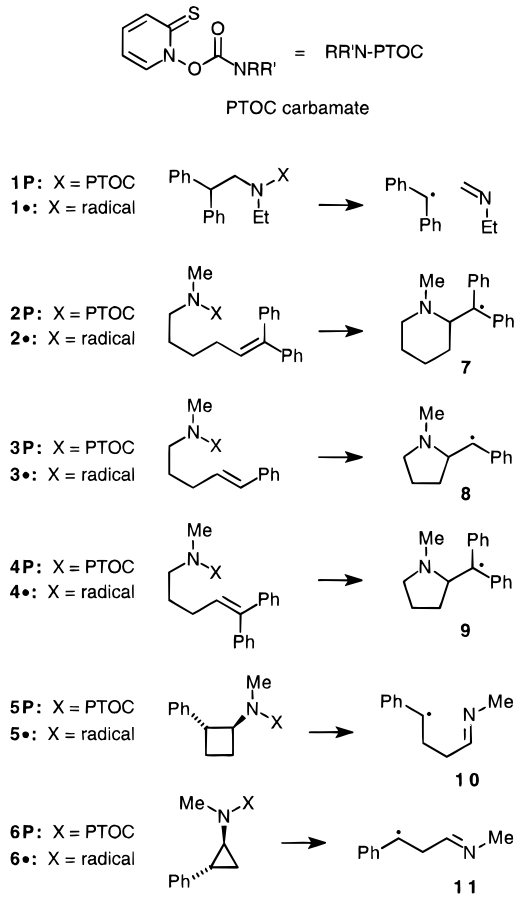


Figure 1. PTOC carbamate precursors, dialkylaminyl radicals, and the products of unimolecular dialkylaminyl radical reactions studied in this work.

the corresponding dialkylamine with 1-oxa-2-oxo-3-thiaindolizinium chloride[24] by a reported method.[8] PTOC carbamates from dialkylamines are thermally unstable and sensitive to visible light which requires handling precautions, but they usually can be purified by chromatography on silica gel. The dialkylamine precursors employed in this work were known or were characterized. The unstable PTOC carbamates were characterized by NMR spectroscopy. PTOC carbamates **1P**, **2P**, and **4P** were reported previously.[2,25]

All of the dialkylaminyl radicals studied in this work were designed such that unimolecular reactions, fragmentation of **1•**, cyclizations of **2•**, **3•**, and **4•**, and ring openings of **5•** and **6•**, would produce benzylic or diphenylalkyl radicals that have long wavelength λ_{max} values at ca. 315 and 325 nm, respectively. This feature permits direct LFP kinetic studies using UV detection.

The PTOC carbamate radical precursors are especially useful for LFP studies for several reasons. A long-wavelength chromophore centered at about $\lambda_{max} = 360$ nm can be irradiated with the third harmonic of a Nd-YAG laser (355 nm). Due to the wavelength of the laser light employed and the fact that the kinetics of the reactions can be followed by UV at shorter wavelengths, light scattering and sample fluorescence do not interfere with the UV observations permitting kinetic studies to the temporal limit of the instrument which, in our case, is about 8×10^7 s^{-1}. The 2-pyridinethiyl radical produced by photolysis of a PTOC precursor has a long wavelength λ_{max} centered at about 490 nm[26−28] but is relatively transparent at

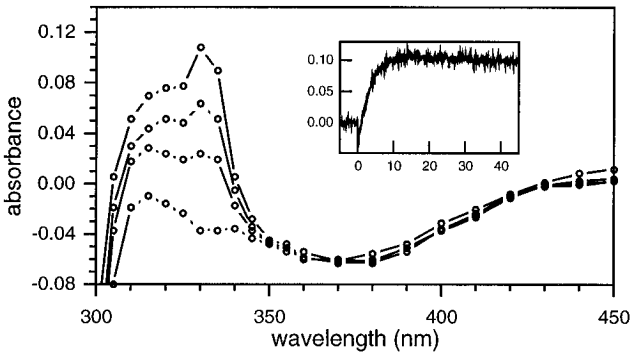
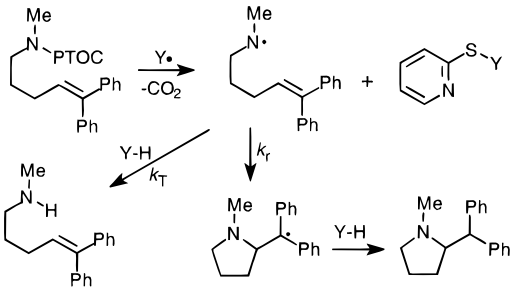


Figure 2. Time-resolved spectrum of radical **9** produced by cyclization of radical **4•** at 22 °C following laser irradiation of precursor **4P**. Initial bleaching is observed due to destruction of **4P**. From the bottom, the traces are taken 0.2, 2.2, 4.2, and 13.8 μs after the laser pulse. The inset shows the kinetic trace at 330 nm; the X axis is in μs, and the Y axis is in au.

Scheme 1



wavelengths useful for observing benzylic and diphenylalkyl radicals; in fact, net bleaching is observed in the region of 300−400 nm immediately following the laser pulse. Due to the relatively strong absorbance of the PTOC moiety and good efficiency in the photolysis,[29] dilute solutions must be employed in LFP studies with the sample flowing through the reaction cell. Figure 2 shows a time-resolved spectrum of the diphenylalkyl radical produced by cyclization of radical **4•**; the inset contains a typical kinetic trace.

Indirect kinetic studies were performed in a conventional manner (illustrated for **4•** in Scheme 1).[30] Radical chain reactions were initiated by visible light irradiation of THF solutions of the PTOC carbamates in the presence of hydrogen atom transfer trapping agents. The PTOC carbamates react in radical chain reactions by addition of radical Y• to the thione group and concomitant or subsequent N−O bond cleavage to give acyloxyl radicals which rapidly decarboxylate[31] to give the relatively stable dialkylaminyl radicals. Rearrangement of the dialkylaminyl radical competes with trapping by hydrogen atom donor Y−H. The rearranged radicals also react with Y−H, and the Y• radical produced in these reactions propagates the chain sequence. Following the radical reaction, the product mixtures were analyzed by NMR spectroscopy or GC to determine product yields. For the ring openings of the radicals **5•** and **6•**, the final rearranged products from trapping radicals **10•** and **11•**

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(31) Rate constants for decarboxylations of the acyloxyl precursors to dialkylaminyl radicals have not been measured. From our LFP results with PTOC precursor **5P**, the decarboxylation rate constant must be greater than 1×10^8 s^{-1} at 0 °C.

Table 1. Arrhenius Functions for Dialkylaminyl Radical Clock Rearrangement

radical	Arrhenius function[a]	$k_{(20)}$ (s^{-1})[b]	method
2•	$(10.1 \pm 0.4) - (8.0 \pm 0.5)/\theta$		direct[c]
	$(9.8 \pm 0.4) - (8.0 \pm 0.5)/\theta$	ca. 7×10^3	estimated[d]
3•	$(9.66 \pm 0.17) - (5.88 \pm 0.23)/\theta$	1.9×10^5	direct
4•	$(9.54 \pm 0.14) - (5.40 \pm 0.19)/\theta$	3.2×10^5	direct
5•	$(13.12 \pm 0.24) - (5.91 \pm 0.31)/\theta$	5.1×10^8	indirect
6•	$(14.53 \pm 0.26) - (3.58 \pm 0.33)/\theta$	7.2×10^{11}	indirect

[a] Errors are 2σ. $\theta = 2.3RT$ in kcal/mol. [b] Rate constant at 20 °C. [c] Value obtained from LFP observed rate constants. [d] Value obtained by multiplying LFP kinetic results by 0.5; see text.

were imines which were hydrolyzed to the corresponding aldehydes before GC analysis.

The ratios of products and the concentration of trapping agent employed in the indirect study provide relative rate constants for the unimolecular rearrangement and bimolecular trapping. In studies establishing the rate constants for the bimolecular reactions, where the unimolecular reaction rate constant is known for the radical clock employed, calculation of the absolute rate constant for the bimolecular process is direct. However, for studies in which unimolecular rate constants are determined using a trapping agent with known second order rate constants, one must assume that the rate constants for reaction of the trapping agent with the radical of interest and with the radical clock initially used to calibrate the trapping agent are equal. This common assumption of indirect radical kinetic studies[30] is reasonable for the work reported here for two reasons. (1) All of the radicals for which kinetics were measured are dialkylaminyl radicals and, more specifically, methylalkylaminyl radicals. (2) The thiophenol and benzeneselenol employed in the indirect calibrations of ring openings of **5•** and **6•** react with small activation energies in highly exothermic processes which, with early transition states, should be relatively insensitive to minor changes in the radical structures. In support of the latter statement, one notes that the rate constants for reactions of PhSH with primary, secondary, and tertiary alkyl radicals are nearly the same.[32]

Direct Unimolecular Kinetics. The dialkylaminyl radicals **1•** to **6•** represent a series with increasing unimolecular reactivity. LFP studies were attempted with all but the most reactive member, the cyclopropylaminyl radical **6•**. Fragmentation of radical **1•** was too slow to observe by LFP ($k < 1 \times 10^4$ s^{-1}). We note, however, that Bowman has reported that a dialkylaminyl radical closely related to **1•** fragments appreciably when generated in the presence of Bu_3SnH.[12] Ring opening of the cyclobutylaminyl radical **5•** was at the other extreme of our direct kinetic capabilities. Rapid growth in the benzylic radical signal from ring opened product **10•** could be observed, but even at 0 °C this reaction was too fast for accurate kinetic measurements ($k > 1 \times 10^8$ s^{-1}).

LFP kinetic studies of the 6-*exo* cyclization of radical **2•** and the 5-*exo* cyclizations of radicals **3•** and **4•** were performed at various temperatures. Our kinetic unit has a lower temperature limit of about 0 °C, and the thermal instability of the PTOC carbamates produces an upper limit. The kinetic results are listed in Table S1 of the supporting information. Arrhenius functions for the cyclization reactions are given in Table 1.

Although the 6-*exo* cyclization of aminyl radical **2•** could be studied by LFP, the observed rates were at the lower useful limit of the LFP method, specifically, in the range of 1×10^4 s^{-1}. With such slow reactions, a number of systematic errors can be important because the observed rate constants are the sums of all rate constants for reactions that consume the radical

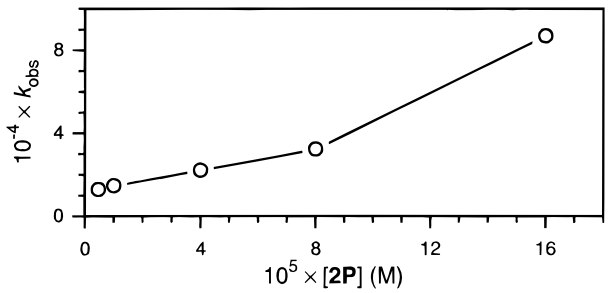

Figure 3. Effect of concentration of precursor **2P** on the observed rate constants at 20 °C for reactions of radical **2•**.

and any other reactions that give rise to a diphenylalkyl radical signal. Possible interfering reactions include pseudo-first-order reactions with residual oxygen, bimolecular radical−radical reactions, and bimolecular additions of the aminyl radical or the 2-pyridylthiyl radical to either the thione moiety or the diphenylethene moiety of a precursor molecule.[28,33] The effects of most of these interfering reactions on the kinetics of cyclization of radical **2•** could be estimated, and several could be minimized by appropriate experimental design.

Intermolecular addition reactions to the diphenylethene moiety of the PTOC carbamate were judged to be insignificant based upon the following study. A PTOC ester precursor to a simple alkyl radical was studied by LFP in the presence of 1,1-diphenyl-1-heptene; the photolysis produced an alkyl radical and the 2-pyridylthiyl radical. No appreciable signal for formation of a diphenylalkyl radical product was observed when the concentration of the alkene was less than 5×10^{-4} M, two orders of magnitude greater concentration than that employed for kinetic studies with PTOC carbamate **2P**. Because the dialkylaminyl radicals are demonstrated in this work to be less reactive than isostructural alkyl radicals in cyclizations onto the diphenylethene moiety,[27,34,35] we make the logical assumption that they are also less reactive in intermolecular additions to this group.

The occurrence of bimolecular radical−radical reactions in the kinetic studies of **2•** was apparent from the observed rate constants with varying concentrations of PTOC **2P**; a complex concentration effect on the observed kinetics was observed (Figure 3). The results in Figure 3 indicate that, at a precursor concentration of 5×10^{-6} M, the observed rate constant was nearly equal to that which would be observed at infinite dilution, and the kinetic studies of aminyl radical **2•** were conducted with this precursor concentration.

Pseudo-first-order reactions of **2•** with residual oxygen also affected the LFP kinetics. From a series of studies in which the diphenylmethyl radical was generated from its PTOC ester precursor[26] and using the known[36] rate constant for reaction of this radical with O_2, we determined that the residual O_2 concentration in our sparged solutions was $\leq 2 \times 10^{-5}$ M. An approximate rate constant for reaction of a dialkylaminyl radical with O_2 was determined by LFP studies of the rate of reaction of **4•** in oxygenated ($[O_2] = 0.002$ M) solution to be 2×10^8 M^{-1} s^{-1} at 20 °C. From these values, one estimates that the pseudo-first-order reaction of $R_2N^•$ with residual O_2 in sparged solutions was $\leq 4 \times 10^3$ s^{-1} at 20 °C.

An indirect kinetic study of the 6-*exo* cyclization of **2•** employing Bu_3SnH as a trapping agent also indicated that

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(33) Kinetic studies of addition reactions of the 2-pyridylthiyl radical to alkenes were recently reported; see ref 28.

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(36) Scaiano, J. C.; Tanner, M.; Weir, D. *J. Am. Chem. Soc.* **1985**, *107*, 4396−4403.

oxygen trapping interfered with the direct kinetic measurements. When PTOC precursor **2P** was allowed to react in the presence of Bu_3SnH at 25 °C, a mixture of acyclic amine and cyclized piperidine products were formed from trapping and cyclization, respectively. From the ratio of products (cycle/acycle = 0.27), the average concentration of tin hydride (0.075 M), and the rate constant for reaction of the aminyl radical with tin hydride at 25 °C (4.9×10^5 M^{-1} s^{-1}, see below), one calculates a cyclization rate constant for **2•** of 1.0×10^4 s^{-1} at 25 °C. The rate constant at 25 °C calculated from the Arrhenius function for cyclization of **2•** determined by LFP (see Table 1) is 1.7×10^4 s^{-1}. If one considers both kinetic values to be error free, oxygen trapping appears to account for about 40% of the total measured velocity in the LFP studies.

Other evidence led to a similar conclusion. When matched pairs (same temperature, concentrations equal) of LFP kinetic studies of precursors **2P** and **4P** were compared, the total signal growth for the diphenylalkyl radical product from **2•** was only about 40% as great as that for the product from **4•**. If the quantum efficiencies for cleavage of **2P** and **4P** are equal and the molar absorptivities of product radicals **7** and **9** are equal, then about 60% of radicals **2•** apparently reacted by extraneous pathways. Further, when the kinetics of cyclization of radicals **2•** and **4•** are compared with those of isostructural carbon radicals (see Discussion), the 5-*exo* cyclization of **4•** is a factor of 60 slower at 20 °C than the corresponding cyclization of its carbon analog, but the LFP rate constant for the 6-*exo* cyclization of **2•** is only a factor of 15 smaller than that of its carbon analog.

From these observations, we conclude that the LFP kinetics for **2•** are approximately twice the actual values for cyclization of **2•**. Because of the obvious systematic errors in the LFP cyclization kinetics of **2•**, we did not incorporate these kinetic values into other reactions by indirect methods. In Table 1, we estimate the rate constants for **2•** simply as one-half of the value of k_{obs} from the LFP studies. Because the LFP studies are direct kinetic measurements, the approximate rate constants for cyclization of **2•** that result from this estimate are likely to be as accurate as can be determined by an indirect study with compounded errors.

The 5-*exo* cyclizations of radicals **3•** and **4•** were faster than the 6-*exo* cyclization of **2•** as expected and, thus, were less problematical. The LFP kinetic values for these cyclizations were about two orders of magnitude larger than our estimated pseudo-first-order rate constant for reaction with residual oxygen. Similarly, because bimolecular reactions can only represent a minor amount of the total kinetics for reactions of **2•**, one can be confident that these potential interfering processes did not have significant effects in kinetic measurements of the 5-*exo* cyclizations.

The insignificance of bimolecular radical−radical reactions in kinetic studies of the cyclization of radical **4•** was demonstrated directly. A series of LFP studies was conducted at 20 °C with varying concentrations of PTOC carbamate (data in Table S2 of the supporting information). The concentration of radicals varied, but the observed rate constants were unchanged.

Indirect Unimolecular Kinetic Studies. The cyclobutylaminyl radical **5•** rearranged too fast for accurate LFP kinetic studies, and the cyclopropylaminyl radical **6•** was expected to rearrange even more rapidly. A cursory LFP study with PTOC precursor **6P** indicated that formation of benzylic radical **11** from ring opening of **6•** was "instantaneous". Both of these rearrangement reactions were studied by indirect kinetic methods using hydrogen atom transfer trapping reactions, the calibrations of which are discussed in the next section.

Ring opening of the cyclobutylaminyl radical **5•** was calibrated against trapping by PhSH. Table S3 (supporting information) contains the results from reactions run between −46 and 50 °C and the relative Arrhenius function for log (k_r/k_T) obtained from these data. Combination of this relative Arrhenius function with that for PhSH trapping (see below) gave the temperature-dependent function for rearrangement of **5•** in Table 1. At 20 °C, the ring opening has a rate constant of 5×10^8 s^{-1}. The calculated rate constant at 0 °C is 2.4×10^8 s^{-1}, consistent with our observation that this reaction was too fast for direct studies with our LFP unit.

The very fast ring opening of the cyclopropylaminyl radical **6•** could not be studied with PhSH trapping, but radical **6•** could be trapped in small amounts when benzeneselenol was employed at high concentrations. Reactions were conducted between −46 and 50 °C. The kinetic results are listed in Table S4 (supporting information) along with the relative Arrhenius function for log (k_r/k_T). The absolute temperature-dependent function is listed in Table 1. At 20 °C, the ring opening has a rate constant of 7×10^{11} s^{-1}.

A potential problem arises in the very fast apparent rate constants for ring opening of cyclopropylaminyl radical **6•**. Specifically, PhSeH has been reported to react with alkylacyloxyl radical intermediates in competition with the decarboxylation step.[37] In the case of indirect measurements of alkyl radical kinetics employing PTOC esters, this reaction is unimportant because the resulting product is a carboxylic acid. For dialkylaminyl radical studies, however, a similar reaction would produce a carbamic acid that would decarboxylate to give the same unrearranged amine product as obtained by PhSeH trapping of the dialkylaminyl radical. Hence, it is possible that the small amount of cyclopropylamine observed arose in part from this side reaction.

The relatively large log *A* value in the Arrhenius function for ring opening of radical **6•** reinforces the caveat concerning the measured kinetics. Specifically, the measured value is between that expected for a unimolecular ring opening and that for a unimolecular fragmentation reaction and is greater than those found for aryl-substituted cyclopropylcarbinyl radical ring opening reactions determined against the same trapping agent (PhSeH) as used for calibration of **6•**.[38−40] Therefore, we conclude that the kinetic values for ring opening of radical **6•** should be considered with some caution and regarded as possible lower limits until alternative methods for measuring the kinetics of this reaction are available.

Kinetics of Bimolecular Reactions. The kinetics of second order reactions of radicals with simple trapping agents, most commonly hydrogen atom transfer agents, provide the fundamental information necessary for developing a kinetic scale. In this work, rate constants for reactions of *t*-BuSH with a dialkylaminyl radical were measured directly by LFP, and rate constants for reactions of Bu_3SnH, PhSH, and PhSeH were determined indirectly using dialkylaminyl radical rearrangements as "radical clocks".[4]

Because *t*-BuSH is transparent at 330 nm, the 5-*exo* cyclization of radical **4•** could be employed in LFP studies of the kinetics of *t*-BuSH reactions. However, when a dilute solution of PTOC precursor **4P** in the presence of the thiol at 25 °C was monitored by UV spectroscopy, the characteristic long wavelength band of **4P** was lost with a half-life of several minutes

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Table 2. Arrhenius Functions for Hydrogen Transfer Reactions to Dialkylaminyl Radicals

donor	Arrhenius function[a]	$k_{(20)}$ (M^{-1} s^{-1})[b]
Bu_3SnH	$(9.11 \pm 0.21) - (4.66 \pm 0.28)/\theta$	4.3×10^5
t-BuSH	$(8.4 \pm 0.4) - (2.2 \pm 0.5)/\theta$	6×10^6
PhSH (versus **3•**)	$(10.66 \pm 0.19) - (3.45 \pm 0.25)/\theta$	
PhSH (versus **4•**)	$(10.60 \pm 0.27) - (3.56 \pm 0.34)/\theta$	
PhSH (av)[c]	$(10.64 \pm 0.15) - (3.49 \pm 0.20)/\theta$	1.1×10^8
PhSeH	$(11.82 \pm 0.26) - (3.37 \pm 0.33)/\theta$	2.0×10^9

[a] Errors are 2σ. $\theta = 2.3RT$ in kcal/mol. [b] Rate constant at 20 °C. [c] Statistically weighted average of results versus 3• and 4•.

indicating a reaction of the thiol with **4P** which we presume involves nucleophilic addition to the activated carbonyl group of the PTOC precursor.[41] Therefore, a double syringe pump was employed to deliver solutions of **4P** and thiol that were mixed immediately before entering the flow cell of the LFP unit. Kinetic measurements were made within 5 s of mixing.

Reactions of **4•** were studied in the presence of varying concentrations of *t*-BuSH (0.01 to 0.10 M) at 10, 25, and 40 °C (Table S5 in supporting information). In these reactions, k_{obs} is described by eq 1 where k_0 is the pseudo-first-order rate constant for all background reactions, k_r is the rate constant for the cyclization of radical **4•**, and k_T is the rate constant for the trapping reaction. As long as all first order and pseudo-first-order reactions ($k_0 + k_r$) remain constant, the trapping rate constant k_T can be determined from the slopes of plots of k_{obs} versus [RSH]. These plots gave values for k_T for *t*-BuSH of (4.8 ± 1.2), (5.6 ± 0.6), and $(7.0 \pm 0.4) \times 10^6$ M^{-1} s^{-1} at 10, 25, and 40 °C, respectively, where errors are at 2σ.

$$k_{obs} = (k_0 + k_r) + k_T[RSH] \quad (1)$$

An Arrhenius function for *t*-BuSH trapping calculated from all of the individual kinetic runs is given in Table 2. Whereas the kinetic values at each temperature seem to be reliable, the narrow temperature range employed for the temperature-dependent function appears to have introduced considerable error. A series of indirect kinetic studies of *t*-BuSH trapping of radical **4•** were performed in an attempt to confirm the results from the direct studies, but the kinetics from the indirect measurements contained even larger random errors. One problem was the instability of the PTOC precursor in the presence of *t*-BuSH (see above). A second problem was that the thiol does not react efficiently with diphenylalkyl radicals resulting in radical disproportionation reactions.[27] In order to avoid radical disproportionation products, the reactions were conducted with varying concentrations of *t*-BuSH and with 0.1 M Bu_3SnH added to trap the cyclic radical; trapping studies with the tin hydride (see below) assure that 0.1 M Bu_3SnH reacts with only a small amount of radical **4•**. We attempted to minimize the effect of the instability of the PTOC precursor in the presence of the thiol by adding the PTOC carbamate immediately before the competition reaction was initiated by visible light irradiation. Despite the experimental precautions, the random errors in the relative Arrhenius function from these indirect studies were so large (± 0.7 in log *A* and ± 0.9 in E_a) that these data were of little use other than to confirm the order of magnitude of the thiol trapping rate constant found in the direct studies. For example, the rate constant for *t*-BuSH trapping at 25 °C found indirectly was approximately 1×10^7 M^{-1} s^{-1}.

Bu_3SnH reacts so slowly with dialkylaminyl radicals that very high concentrations of the tin hydride would be required in direct LFP studies with radicals **3•** or **4•**, and the UV absorbances of both PhSH and PhSeH precluded LFP studies. These three hydrogen transfer agents were calibrated by conventional indirect kinetic studies. Radical **4•** was employed for Bu_3SnH and both **3•** and **4•** were used for PhSH. Because the kinetics of the dialkylaminyl radicals were measured directly, good precision could be obtained in the indirect kinetics. PhSeH reacted rapidly with dialkylaminyl radicals, and it was calibrated against the ring opening of the cyclobutylaminyl radical **5•** which, in turn, was calibrated indirectly (see above). We note that, unlike the case with *t*-BuSH discussed above, diphenylalkyl radicals have been shown to be trapped efficiently by Bu_3SnH and PhSH,[27] and one assumes that the highly reactive PhSeH also traps these radicals efficiently.

Tables S6−S8 (supporting information) contain the results of the indirect kinetic studies with Bu_3SnH, PhSH, and PhSeH. Relative rate constants for trapping and rearrangement (k_T/k_r) were determined and used to calculate relative Arrhenius functions. The relative Arrhenius functions were then added to those for the respective rearrangements to give the absolute Arrhenius functions for the trapping reactions listed in Table 2. For PhSH trapping, the absolute Arrhenius functions resulting from studies with **3•** and **4•** were combined to give a weighted average function.

The calibration of thiophenol is the linchpin kinetic result of this work. Because the indirect kinetic method was used, the excellent agreement between the two Arrhenius functions resulting from PhSH trapping with radicals **3•** and **4•** is important in that it provides some assurance that systematic errors from unanticipated sources are small. The error limits in the log *A* and E_a terms in the weighted average function for PhSH trapping are actually smaller than those obtained in direct studies of Bu_3SnH reactions with alkyl radicals,[42,43] perhaps the most important set of radical kinetics from the synthetic perspective.

Discussion

The radical clocks **2•** through **6•** provide an overlapping series of calibrated unimolecular dialkylaminyl radical reactions that span a range of eight orders of magnitude, from 7×10^3 to 7×10^{11} s^{-1} at 20 °C. Given that modern analytical methods readily permit quantitation of 10:1 ratios of products and often allow accurate measurements of 100:1 ratios, this series should permit kinetic measurements for a wide range of reactions.

Few calibrated unimolecular dialkylaminyl radical reactions are available for direct comparisons. Maeda and Ingold reported rate constants for ring opening of the cyclobutylaminyl radical **12** at low temperatures, and an extrapolation of their results to 50 °C gives a rate constant for ring opening of 5×10^5 s^{-1},[1] but due to experimental difficulties, this value might be a lower limit.[44] Later, Newcomb *et al.* found that, at 50 °C, the ratio of rate constants for rearrangement of **12** and trapping by *t*-BuSH was 0.2 M.[45] Using the value for thiol trapping determined in this work and the ratio of rate constants, one calculates a rate constant for ring opening of **12** at 50 °C of 1.6×10^6 s^{-1}, which confirms that the reported[1] rate constant was a lower limit. Unfortunately, because **12** was the only dialkylaminyl radical for which primary kinetic data were available, the error in kinetics was propagated into rate constants for

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(44) See notes in ref 45.

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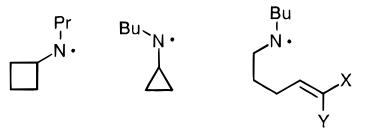
dialkylaminyl radical reactions determined by indirect methods (see below).



12 **13** **14**: X = Y = H; **15**: X = Y = Me; **16**: X = Ph, Y = H

Ring opening of cyclopropylaminyl radical **13** was reported to be about 50 times faster than ring opening of **12** at 50 °C as determined by *t*-BuSH trapping although this value was approximate.[45] From the results of the present work, however, cyclopropylaminyl radicals should ring open about three orders of magnitude faster than cyclobutylaminyl radicals. We conclude that in the previous study of the radical **13**, *t*-BuSH trapping was too slow to be useful, and the experimental ratio $k_r/k_T = 10$ M was only a lower limit. A PTOC carbamate was the radical precursor employed in the earlier study,[45] and given the observation in this work that the thiol reacts with PTOC carbamates, it is possible that unrearranged amine in the previous study resulted from ionic reactions.

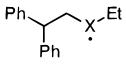
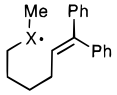
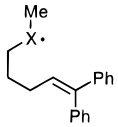
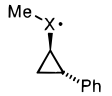
The relative kinetics for cyclizations of radicals **14** and **15** versus trapping of these radicals by Bu_3SnH at 50 °C were reported to be $k_T/k_c = (23 \pm 2)$ and (24.3 ± 0.6) M^{-1}, respectively, and these relative rate values were combined with an approximate rate constant at 50 °C for reaction of Bu_3SnH with a dialkylaminyl radical to give rate constants for cyclization of **14** and **15** at 50 °C of about 3×10^3 s^{-1}.[8,46] Using the rate constant for reaction of Bu_3SnH with a dialkylaminyl radical determined in this work, 9×10^5 M^{-1} s^{-1} at 50 °C, one calculates rate constants for cyclization of **14** and **15** at this temperature of 4×10^4 s^{-1}. It is noteworthy that an attempt to study the cyclization of radical **14** by kinetic ESR methods resulted in no observed cyclic radical at low temperatures and an estimate that the cyclization rate constant at 25 °C was ≤ 5 s^{-1};[1] it was noted previously that such a small value was not consistent with the observed yields of cyclic products from **14**.[8]

Quite recently, Lusztyk and co-workers, in a study of the kinetics of dialkylaminium cation radical reactions, reported that the upper limit for the rate constant for 5-*exo* cyclization of dialkylaminyl radical **16** at ambient temperature was 3.8×10^5 s^{-1}.[3] This upper limit compares favorably with the rate constant for cyclization of **3•** at 20 °C determined in this work of 1.9×10^5 s^{-1}.

The kinetics of reactions of several carbon radicals that are isostructural with the dialkylaminyl radicals studied here are available,[35,38,39,47] as are some for reactions of dialkylaminium cation radicals produced by protonation of the dialkylaminyl radicals.[25] A comparison between these demonstrates interesting properties of the dialkylaminyl radicals (Table 3). On the basis of the low N−H bond energy of a dialkylamine,[48] one would conclude that dialkylaminyl radicals are relatively stable, and it is widely appreciated that aminyl radical reactions are much slower than those of their aminium cation radical counterparts.[7] For the three cases where direct comparisons are available, the dialkylaminium cation radical reactions are several orders of magnitude faster than the corresponding dialkylaminyl reactions.

Comparison of the kinetics of the dialkylaminyl radicals and their isostructural carbon radical counterparts is perhaps more interesting. For the N−C versus C−C bond forming reactions, the 6-*exo* and 5-*exo* cyclization reactions, the carbon radicals react about 1.5 orders of magnitude more rapidly than the dialkylaminyl radicals, but the ring opening reaction of the cyclopropylaminyl radical **6•** is faster than that of its carbon radical analog. The influence of $\Delta G°$ on the kinetics of these reactions is apparent. For the σ-bond forming cyclization reactions, the C−C bond is stronger than the N−C bond, but this is not the case for the π-bond forming ring opening reactions of the cyclopropyl systems.

Table 3. Rate Constants for Radical Rearrangements[a]

structure	X = N	X = CH	X = HN^{+b}
	$< 1 \times 10^4$		2×10^7
	7×10^3	2×10^5	4×10^7
	3.2×10^5	2×10^7	1×10^{10}
	7.2×10^{11}	3×10^{11}[c]	

[a] Rate constants at 20 °C in units of s^{-1}. [b] The kinetics of aminium cation radicals are solvent dependent; the rate constants given are for reactions in THF. [c] Rate constant for the primary alkyl radical.

We predict that the kinetics of a wide range of dialkylaminyl radical reactions can be estimated with better than order-of-magnitude accuracy from the large body of carbon radical kinetics that are available as long as one considers the types of bonds that are being produced in the reactions. For example, 5-*exo* cyclizations of simple 5-hexenyl radicals occur with rate constants of about 6×10^5 s^{-1} at 50 °C.[30] From the comparison in Table 3 of the results with radicals **2•** and **4•** and their carbon analogs, one would estimate that carbon radicals cyclize about 30 times faster than the corresponding dialkylaminyl radical. Therefore, the 4-pentenaminyl radical **14** would be predicted to cyclize at 50 °C with a rate constant of approximately 2×10^4 s^{-1}, a good agreement with the value of $k_r = 4 \times 10^4$ s^{-1} calculated above.

The more important kinetic results of this work for synthetic applications are the second order rate constants for reactions of hydrogen atom transfer agents with dialkylaminyl radicals because these kinetic values can be incorporated into a variety of reactions by simple competition experiments. Previously, rate constants for reactions of *t*-BuSH and Bu_3SnH with dialkylaminyl radicals at one temperature were estimated using the ring opening of cyclobutylaminyl radical **12** as the clocking reaction.[45] However, it is now apparent that the kinetic value for reaction of **12** was a lower limit (see above), and the previous kinetic estimates for the hydrogen atom donors should not be used.

The kinetic results for reactions of the hydrogen atom transfer agents with dialkylaminyl radicals are compared to the rate constants for reactions of these agents with primary carbon radicals in Table 4. The noteworthy point from comparison of these values is that the overall energetics of the reactions are not the only feature influencing the kinetics. Because an N−H

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(47) Newcomb, M.; Filipkowski, M. A.; Johnson, C. C. *Tetrahedron Lett.* **1995**, *36*, 3643−3646.
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Table 4. Kinetics of Hydrogen Atom Transfer Reactions to Alkyl and Dialkylaminyl Radicals[a]

donor	$RCH_2^•$	$R_2N^•$
Bu_3SnH	2.4×10^6	4.9×10^5
t-BuSH	8×10^6	6×10^6
PhSH	1.4×10^8	1.2×10^8
PhSeH	2.1×10^9	2.2×10^9

[a] Rate constants at 25 °C in units of M^{-1} s^{-1}.

bond of a dialkylamine is weaker than a primary C−H bond in an alkane, one might expect that reactions of primary alkyl radicals with H-atom donors would be faster than reactions of dialkylaminyl radicals with the same donors. Whereas this is true for reactions of Bu_3SnH, the thiols and PhSeH react with the two types of radicals with nearly equal rate constants. The latter three hydrogen donors have element−hydrogen bonds that are polarized such that partial positive charge resides on hydrogen, whereas the opposite is the case for Bu_3SnH. Apparently, the transition states for hydrogen atom transfer from the "electron deficient" hydrides to the "nucleophilic" aminyl radicals are favorably polarized resulting in a lower energy of activation than one would predict solely on the basis of bond dissociation energies. The conclusion that the transition state energies for hydrogen transfers are reduced by favorable polarizations in reactions of "polarity matched" radicals and hydrogen donors was previously reached for reactions of electron rich (methoxy-substituted) radicals[47] and electron deficient (alkoxycarbonyl- and cyano-substituted and dialkylaminium cation) radicals.[25,35]

In conclusion, the results in this work establish a kinetic scale for dialkylaminyl radical reactions. The series of radical clocks **2•** through **6•** provide calibrated unimolecular reactions that span a range of eight orders of magnitude, and the hydrogen atom donors calibrated here react with dialkylaminyl radicals with rate constants that differ by nearly four orders of magnitude. With the rapidly evolving methodology for production of dialkylaminyl radicals in chain reactions and the increasing general interest in radical chemistry for organic synthesis, we expect that the dialkylaminyl radical kinetic scale will prove useful.

Experimental Section

General. NMR spectra were recorded at 300 (^{1}H) or 75 MHz (^{13}C). GC analyses were performed on flame ionization detector equipped GCs with low polarity, bonded phase, wide bore capillary columns. Tri-*n*-butyltin hydride was prepared by the method of Hayashi *et al.*[49] 2-Methylpropanethiol was distilled from CaH_2. Thiophenol was distilled from and stored over $CaSO_4$. Benzeneselenol was prepared and handled as previously described.[37]

PTOC carbamates **1P**, **2P**, and **4P** were prepared as previously reported.[25] The preparations of the secondary amines for PTOC carbamates **3P**, **5P**, and **6P** are given in the supporting information. The PTOC carbamates **3P**, **5P**, and **6P** were prepared by the method of Newcomb *et al.*[8] by reaction of the appropriate secondary amine with ca. 1.1 equiv of 1-oxa-2-oxo-3-thiaindolizinium chloride[24] and ca. 1.0 equiv of Et_3N in benzene. The crude PTOC carbamates were purified by chromatography on silica gel with hexanes−ethyl acetate elution. The isolated PTOC carbamates were >95% pure by NMR spectroscopy. NMR spectra of these products obtained at ambient temperature are complex due to slow bond rotations .

1-[(Methyl(*trans*-5-phenyl-4-pentenyl)carbamoyl)oxy]-2(1*H*)-pyridinethione (**3P**), prepared from 2.93 g (16.7 mmol) of the amine, was obtained as a yellow solid in 89% yield. Mp 84−86 °C. ^{1}H NMR: δ 1.82 (pentet, J = 7.2 Hz, 1.2 H), 1.95 (pentet, J = 7.4 Hz, 0.8 H), 2.3 (q, J = 7.2 Hz, 2 H), 3.06 (s, 1.3 H), 3.21 (s, 1.7 H), 3.44 (t, J = 7.1 Hz, 1.2 H), 3.59 (t, J = 7.5 Hz, 0.8 H), 6.21 (m, 1 H), 6.45 (dd, J = 15.6, 5.1 Hz, 1 H), 6.60 (t, J = 6.0 Hz, 1 H), 7.1−7.4 (m, 6 H), 7.5 (t, J = 7.5 Hz, 1 H), 7.6 (dd, J = 8.7, 1.8 Hz, 1 H). ^{13}C NMR: δ 26.655, 27.467, 30.092, 30.087, 34.613, 49.248, 50.256, 112.227, 125.974, 126.960, 127.038, 128.473, 129.201, 129.355, 130.640, 130.776, 133.506, 137.021, 138.670.

1-[(Methyl(*trans*-2-phenylcyclobutyl)carbamoyl)oxy]-2(1*H*)-pyridinethione (**5P**) was obtained as a gummy, yellow oil in 67% yield from reaction of 1.24 g (7.68 mmol) of *N*-methyl(*trans*-2-phenylcyclobutyl)amine. ^{1}H NMR: δ 2.2 (m, 3.7 H) , 2.6 (d, J = 7.2 Hz, 0.3 H), 3.07 (s, 0.9 H), 3.20 (s, 2.1 H), 3.7 (m, 0.7 H), 3.95 (m, 0.3 H), 4.9 (m, 0.7 H), 5.2 (q, J = 8.5 Hz, 0.3 H), 6.55 (m, 1 H), 7.1−7.3 (m, 7 H), 7.6 (m, 1 H); peaks are broadened extensively by exchange between rotamers. ^{13}C NMR: δ 21.857, 22.182, 23.310, 24.410, 30.288, 44.364, 45.354, 56.937, 58.200, 112.164, 112.276, 126.348, 126.527, 127.685, 128.335, 128.470, 133.463, 136.771, 138.371, 138.492, 141.953, 151.253, 175.948.

1-[(Methyl(*trans*-2-phenylcyclopropyl)carbamoyl)oxy]-2(1*H*)-pyridinethione (**6P**) was obtained as a gummy, yellow oil in 53% yield from reaction of 1.73 g (11.8 mmol) of *N*-methyl(*trans*-2-phenylcyclopropyl)amine. ^{1}H NMR: δ 1.3 (q, J = 6.7 Hz, 1 H), 1.4 (m, 0.5 H), 1.7 (m, 0.5 H), 2.9 (m, 1 H), 3.1 (broad s, 3 H), 3.2 (m, 1 H), 6.5 (t, J = 6.6 Hz, 1 H), 7.1−7.3 (m, 6 H), 7.6 (dd, J = 8.7, 1.8 Hz, 2 H); peaks are broadened extensively by exchange between rotamers. ^{13}C NMR: δ 15.692, 16.411, 25.454, 25.720, 35.411, 35.762, 39.240, 40.917, 112.296, 126.088, 126.221, 128.183, 133.450, 136.867, 138.411, 139.736, 176.014; one carbonyl signal not observed.

Direct Kinetics. The method was the same as previously described.[25] All kinetic studies were performed with flowing THF solutions the temperatures of which were measured with a thermocouple placed ca. 1 cm above the irradiation zone in the flow cell. For studies of the reactions of radical **4•** with *t*-BuSH, helium-sparged solutions of PTOC carbamate **4P** and the thiol in THF were placed in 50-mL gastight syringes that were mounted in a syringe pump. The solutions were pumped through 3-mm OD stainless steel tubing (ca. 2 m) placed in a temperature regulated bath and into a tee located immediately before the flow cell. Typical flow rates were 20 mL/min, and the delay between mixing and entering the reaction zone of the flow cell was <5 s.

Indirect kinetics were accomplished by conventional methods.[30] THF solutions of the appropriate PTOC carbamate (ca. 0.05 M), trapping agent, and a hydrocarbon internal standard were prepared at −78 °C in tubes shielded from light. The tubes were sealed under vacuum and placed in temperature-regulated baths. After equilibration for ca. 5 min, the shields were removed, and the tubes were irradiated with a 150-W tungsten-filament lamp. After 60 min, the tubes were cooled to −78 °C and opened. The reaction mixtures were analyzed by GC on low-polarity, bonded-phase, wide-bore capillary columns. GC response factors were determined with authentic compounds. Preparations of *N*-methyl-2-(diphenylmethyl)piperidine and *N*-methyl-2-(diphenylmethyl)pyrrolidine were reported previously;[25] preparations of other authentic samples of products are given in the supporting information.

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Supporting Information Available: Experimental procedures for preparation of the amine precursors to PTOC carbamates **3P**, **5P**, and **6P** and the products from rearrangement reactions of radicals **2•**, **5•**, and **6•** and kinetic results (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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