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Rate Constants for Aminyl Radical Reactions

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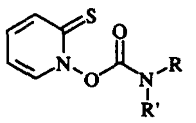
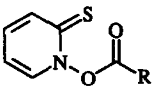
Abstract: Rate constants for cyclization of the *N*-methyl-5,5-diphenyl-4-pentenaminyl radical (4) and for reaction of this radical with *t*-BuSH were determined by direct methods.

Absolute and relative rate constants for radical reactions are critically important for synthetic planning and for mechanistic studies. Although rate constants for a number of unimolecular and bimolecular reactions of simple alkyl radicals are known,[1] kinetic data for reactions of stabilized carbon-centered radicals and of heteroatom-centered radicals is substantially more limited. We have initiated an effort to develop kinetic scales for several types of radicals. Here we report absolute rate constants for bimolecular reactions of *t*-butylthiol with a dialkylaminyl radical and for cyclizations of a dialkylaminyl radical clock. The kinetic values for reactions of *t*-BuSH are then combined with previously reported relative rate constants to calculate absolute rate constants for some dialkylaminyl radical reactions.

We have shown that PTOC carbamates (1), related in their chemistry to Barton's PTOC esters[2] (2), are useful sources of dialkylaminyl radicals for synthetic conversions[3] and for relative rate constant measurements by competition kinetic methods.[4] Members of the PTOC class of radical precursors contain a broad chromophore centered at about λ = 370 nm. The PTOC esters are known to be useful radical sources for direct kinetic studies using laser-flash methods,[5] and we have found that PTOC carbamates are also.



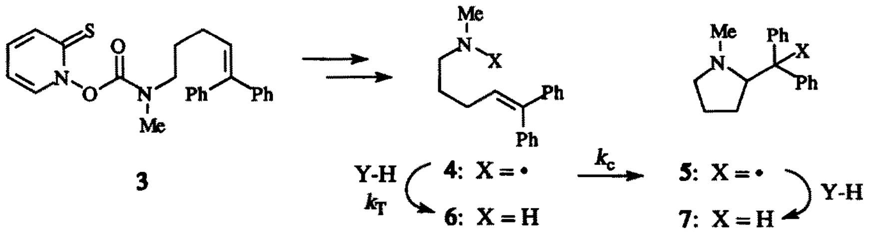
1 (PTOC carbamate)



2 (PTOC ester)

PTOC carbamate 3 was prepared from the corresponding dialkylamine by a standard method.[6] Reaction of 3 either in a radical chain propagation step or by direct photolysis produces a carbamoyloxyl radical that decarboxylates rapidly to give dialkylaminyl radical 4 (Scheme 1). A 5-*exo* cyclization of radical 4 produces radical 5 in which the diphenylalkyl radical center can be observed readily by its characteristic UV absorbance spectrum. A carbon radical analog of 4, the 6,6-diphenyl-5-hexenyl radical, cyclizes with a rate constant of 5×10^7 s^{-1} at 25 °C,[5b] and the rate constant for cyclization of radical 4 was expected to be smaller. In a competition study, trapping of radical 4 by an appropriately fast hydrogen atom transfer trapping agent gives acyclic amine 6, and trapping of radical 5 gives pyrrolidine 7. Preliminary competition studies showed that radical 4 cyclized efficiently in the presence of Bu_3SnH giving pyrrolidine 7 in yields of up to 95% by GC; however, radical 4 was partially trapped by *t*-BuSH.

Scheme 1



Absolute rate constants both for cyclization and for trapping of **4** by *t*-BuSH were determined by laser-flash kinetic methods.[7] As was the case with the PTOC ester precursors,[5] the pyridine-2-thiyl radical, with λ_{max} at 490 nm was produced "instantly". Radical **5** was observed to grow in with time. Figure 1 shows a portion of the time resolved spectrum of the reaction mixture; the signal from **5** with λ_{max} at ca. 330 nm is characteristic of a diphenylalkyl radical.[5b]

In the presence of radical trapping agent Y-H, the observed rate constants (k_{obs}) are given by eq 1 where k_T is the second order rate constant for trapping, k_c is the rate constant for cyclization and k_0 is the pseudo first order rate constant for other reactions of radical **4**. When reactions of precursor **3** were conducted in the presence of varying concentrations of *t*-BuSH at 10, 25 and 40 °C, the results shown graphically in Figure 2 were obtained.[7] The slopes of the lines gave $k_T = 4.8(12), 5.6(6)$ and $7.0(4) \times 10^6\ M^{-1}\ s^{-1}$, respectively.[8] The temperature dependent function for trapping (in kcal/mol) is given in eq 2, and the rate constants for trapping at 25 and 50 °C from eq 2 are 5.7 and $7.5 \times 10^6\ M^{-1}\ s^{-1}$, respectively. Direct studies of the cyclization of **4** in the absence of *t*-BuSH by a procedure[7] likely to introduce lower amounts of oxygen than in the thiol studies gave the temperature dependent function in eq 3. Because the values of ($k_c + k_0$) are on the order of 10^5 to $10^6\ s^{-1}$, one must estimate the significance of k_0 in order to extract k_c.

$$k_{obs} = k_0 + k_c + k_T[\text{Y-H}] \qquad (1)$$

$$\log k_T = 8.3(5) - 2.1(6)/2.3RT \qquad (2)$$

$$\log (k_c + k_0) = 9.6(1) - 5.4(2)/2.3RT \qquad (3)$$

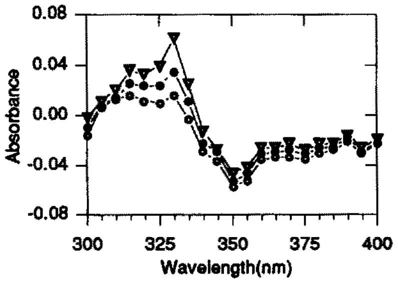


Figure 1. Time resolved spectrum following irradiation of 3. From the bottom, the signals were measured at 2.7, 4.7 and 9.7 μs.

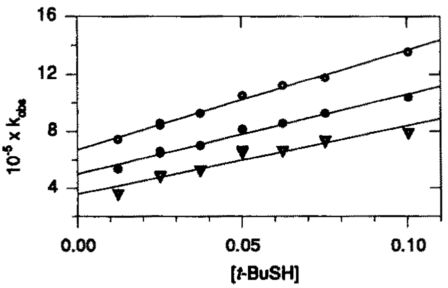


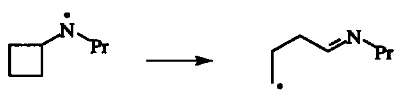
Figure 2. Observed rate constants in the presence of *t*-BuSH. From the bottom, the temperatures were 10, 25 and 40 °C.

In principle, indirect studies of cyclization of **4** in the presence of *t*-BuSH could provide an accurate measure of k_C when combined with the trapping kinetics in eq 2. However, these experiments were complicated by the fact that cyclic radical **5** was not trapped efficiently by *t*-BuSH resulting in disproportionation products from **5**. Therefore, indirect studies[9] over the temperature range -22 to 49 °C with varying concentrations of *t*-BuSH were conducted in the presence of 0.1 M Bu_3SnH which trapped **5** efficiently. The temperature dependent function for the competition reactions is given in eq 4. Addition of eq 2 to eq 4 gives the Arrhenius function for cyclization of **4** in eq 5. Eqs 3 and 5 are essentially equivalent, and, given the large errors in eq 5, we recommend the use of the more precise eq 3 to calculate k_C; i.e. we assume that k_O in eq 3 is negligible. Therefore, the rate constant for cyclization of **4** at 25 °C is 4×10^5 s^{-1}.

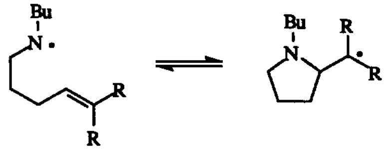
$$\log (k_C/k_T) = 1.4(7) - 3.8(9)/2.3RT \qquad (4)$$

$$\log k_C = 9.7(9) - 5.9(11)/2.3RT \qquad (5)$$

Only limited kinetic studies of dialkylaminyl radicals are available with which our results can be compared, and we are aware of only one previous study in which rate constants for reaction of a dialkylaminyl radical clock were measured directly. In that work,[10] Maeda and Ingold employed kinetic ESR methods to study the ring opening of the *N*-cyclobutylpropylaminyl radical (**8**). Extrapolation of their results to 50 °C gave a lower limit for the rate constant for ring opening of **8** of 5×10^5 s^{-1} which was later combined with the results of competition studies of ring opening of **8** and trapping by *t*-BuSH to give a lower limit for the rate constant for thiol trapping of the dialkylaminyl radical of 2-3 × 10^6 M^{-1} s^{-1} at 50 °C.[4a] Given the large error limits in the Maeda and Ingold study and the relatively large extrapolation that was required to obtain the rate constant for the reaction at 50 °C, this value is acceptably close to the value of 7.5×10^6 M^{-1} s^{-1} found in this work. As is common for the kinetics of hydrogen atom transfers to simple carbon radicals,[1] we assume that all secondary aminyl radicals will react with a given hydrogen atom transfer agent with the same rate constant.



8



9: R = H
10: R = Me

11: R = H

A rate constant for reaction of a dialkylaminyl radical with Bu_3SnH can be estimated from our previous competition studies with radical **8**.[4a] Bu_3SnH reacted about 0.03 times as fast with **8** as did *t*-BuSH. This gives an approximate rate constant of 2×10^5 M^{-1} s^{-1} for reaction of the tin hydride at 50 °C. A rate constant of about 1×10^5 M^{-1} s^{-1} for reaction of Bu_3SnH with a dialkylaminyl radical at 25 °C is consistent with our observation that essentially no trapping of radical **4** occurred at 25 °C in the presence of 0.5 M tin hydride.

Using the approximate rate constant for reaction of a dialkylaminyl radical with Bu_3SnH at 50 °C calculated above, one can estimate the rate constant for cyclizations of the simple aminyl radical clocks **9** and **10** both of which were studied in competition with Bu_3SnH trapping.[4b,11] The rate constants for cyclizations at 50 °C for both **9** and **10** are 1×10^4 s^{-1}. Radicals **9** and **11** partially equilibrate in the presence of Bu_3SnH;[4b] from the rate constant for ring opening of **11** at 50 °C previously obtained[4b] and the rate constant for cyclization of **9**, the equilibrium constant for the reaction at 50 °C is 1 rather than the previously calculated 0.3.

With the direct measurement of rate constants for reactions of *t*-BuSH with aminyl radicals, the kinetics of secondary aminyl radical reactions are now positioned on an absolute scale. The key feature in the experimental design is the use of a radical clock that gives a product with a readily observed UV spectrum. We expect that similar methods can be applied to determine rate constants for reactions of other heteroatom-centered radicals and stabilized carbon-centered radicals.

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6. *N*-Methyl-5,5-diphenyl-4-pentenamine (**6**) was prepared from 5-bromopentanoic acid by conversion to the acid chloride ($SOCl_2$, 78%), reaction with PhMgBr to give the diphenyl alcohol (80%), TsOH catalyzed dehydration (100%) and reaction of the bromide with methylamine (89%). PTOC carbamate **3** (prepared from amine **6** by the method of Newcomb *et al.*[4b]) was obtained as a yellow, viscous oil in 80% yield after chromatography on silica gel. *N*-Methyl-2-(diphenylmethyl)pyrrolidine (**7**) was obtained as a yellow oil in 63% yield after chromatography on neutral alumina from a reaction of PTOC **3** in CH_3CN in the presence of PhSH and malonic acid. All intermediates and products were characterized by ^1H and ^{13}C NMR spectroscopy. Amine **6** and pyrrolidine **7** also were characterized by high resolution MS.
7. Kinetic studies were accomplished with an Applied Photophysics LK-50 kinetic spectrometer employing a Spectron Nd-YAG laser. For studies in the absence of thiol, solutions of precursor **3** in THF flowed from a temperature controlled addition funnel into a 10 × 10-mm flow cell contained in a temperature controlled well. The addition funnel contained a gas bubbler through which N_2 or He was passed. Temperatures were measured as the solutions exited the flow cell and are believed to be accurate to ± 1 °C. Solutions were irradiated with a 7 ns laser pulse at 355 nm. Twelve studies were performed over the temperature range 0 to 59 °C. PTOC carbamate **3** was not stable in the presence of *t*-BuSH; the half-life of **3** in the presence of 0.05 M *t*-BuSH at 25 °C was 450 s. Therefore, for studies with *t*-BuSH, solutions of **3** and of the thiol (sparged with N_2) in 50-mL gas-tight syringes were pumped with a syringe pump through stainless steel coils immersed in a temperature controlled bath and into a union immediately before the flow cell, and kinetic studies were performed within 10 s of mixing. Results of studies in the presence of *t*-BuSH are shown graphically in Figure 2. All directly measured rate constants had errors of <1% at 2σ.
8. All stated errors in parentheses are 2σ for the last significant figure.
9. Indirect kinetic studies were accomplished by standard methods.[1] Solutions of precursor **3**, *t*-BuSH, 0.1 M Bu_3SnH and pentadecane (internal standard) in THF in shielded reaction vessels were placed in temperature controlled baths. The shields were removed, and the solutions were irradiated with a 150 W tungsten-filament lamp at a distance of 0.3 m for several min. Solutions were analyzed by GC (thermal conductivity detector) on a 15 m SE-54 wide bore capillary column (Alltech). Thirteen kinetic runs were performed over the temperature range -22 to 49 °C.
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