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Direct Measurements of Unimolecular Radical Kinetics Employing Ultrafast Radical Rearrangements as Reporters

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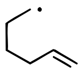
Organic radical chemistry has blossomed in recent years in part due to a greatly increased knowledge of radical reaction rate constants. Knowledge of absolute or relative rate constants is critically important for radical-based synthetic methods because most useful reactions are chain processes in which undesired pathways compete with the desired ones. In mechanistic studies, the availability of rate constants changes a qualitative mechanistic probe study into a more quantitative radical clock[1] study. The cyclization of the 5-hexenyl radical (**1**) and the ring opening of the cyclopropylcarbinyl radical (**2**) are archetypal radical rearrangements whose rate constants serve as the linchpins for an alkyl radical kinetic scale that spans 8 orders of magnitude,[2] but, ironically, the "best" kinetic values of these reactions at room temperature (and of many other radical processes employed as radical clocks) were determined from indirect competition kinetic studies in part because the educt and product radicals lack useful UV chromophores. Such rate constants contain (1) experimental uncertainties of the initially measured second-order trapping reactions employed as basis reactions, (2) uncertainties from the actual competition kinetic studies used to calibrate the clock, and (3) an unknown degree of uncertainty due to the necessary assumption that the rate constants for reactions of model radicals employed in the calibrations of the second-order basis reactions are equal to the rate constants for reactions of radicals of interest. For cases where the functionality is removed from the radical center by several intervening methylene groups, such as in **1**, there is little doubt that the latter assumption is reasonable, but this assumption is substantially less secure for radical **2** and its analogs.



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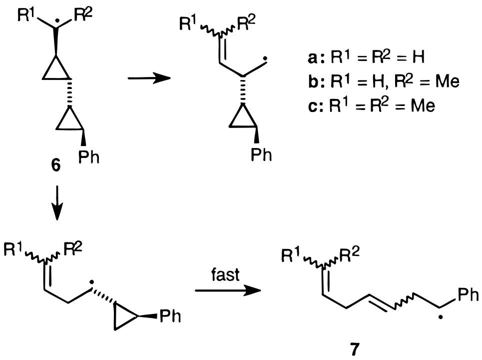
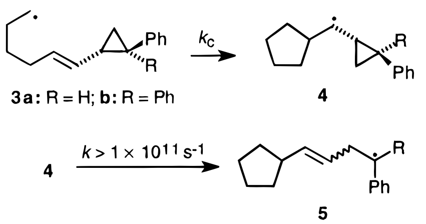
We discuss here a general method for direct laser flash photolysis (LFP) measurements of unimolecular radical kinetics employing ultrafast radical rearrangement reactions as UV detectable reporters. The reporter groups are installed synthetically via Wittig reactions, and the method can be applied to a wide range of radicals including those for which absolute basis kinetic values are not available.

The general concept is illustrated with radicals **3** which produce radicals **4** by 5-*exo* cyclizations. Radicals **4** are phenyl-substituted cyclopropylcarbinyl radicals that will ring open to radicals **5**, which are UV-detectable benzylic and diphenylalkyl radicals, with rate constants exceeding 1×10^{11} s^{-1} at room temperature.[3] Thus, in LFP experiments, the slow rate constants for cyclizations of radicals **3** are obtained by following the formation of radicals **5**.

Scheme 1





In practice, the observed rate constants for cyclizations of (*E*)-**3a** and **3b** (5:1, (*Z*):(*E*)), produced by LFP of the corresponding PTOC ester[4,5] precursors, at 25 °C were 8.3 and 5.0×10^{5} s^{-1}, respectively, and radicals **3** can now be used as radical clocks.[6] The observed rate constants for **3** also permit an evaluation of the kinetic effects of the arylcyclopropyl reporter groups which are "conjugated" with the double bond in radicals **3**. On the basis of calibration with Bu_3SnH trapping, the rate constant for cyclization of the 5-hexenyl radical (**1**) at 25 °C is 2.5×10^{5} s^{-1},[7] and 5-*exo* cyclization of the 5-heptenyl radical is slightly faster.[8] We conclude that the reporter groups in radicals **3** have relatively minor accelerating effects on the cyclizations.

The reporter method can be applied to cyclopropylcarbinyl radical ring openings as demonstrated with the series of radicals **6**, produced by LFP of the corresponding PTOC esters (Scheme 1). Radicals **6** (two diastereomers in each case by virtue of the position of phenyl substitution) ring open by two channels, only one of which leads to the "reporting" products **7**. Nevertheless, k_{obs} for formation of **7** is the total rate constant for rearrangement of **6** by both channels. The rate constants for rearrangements of radicals **6** followed general expectations. Ring opening of the primary radical **6a** exceeded our instrumental capabilities ($k > 1 \times 10^{8}$ s^{-1})[9] at 0 °C, the secondary radical **6b** rearranged

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[1] Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.

[2] Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

[3] Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915−10921.

[4] The acronym PTOC derives from pyridine-2-thione-*N*-oxycarbonyl. PTOC esters are actually mixed anhydrides of the thiohydroxamic acid *N*-hydroxypyridine-2-thione and a carboxylic acid. Similarly, PTOC carbamates and *N*-acyl PTOC carbamates are anhydrides of the thiohydroxamic acid and a carbamic acid or *N*-acyl carbamic acid, respectively.

[5] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.

[6] For **3a**, $(\log k{\cdot}s) = (9.9 \pm 0.3) - (5.4 \pm 0.4)/\theta$, and for **3b**, $(\log k{\cdot}s) = (10.1 \pm 0.2) - (6.0 \pm 0.3)/\theta$, where $\theta = 2.3RT$ in kcal/mol and errors are at 2σ. These kinetic measurements were conducted with solutions that were $1-2 \times 10^{-5}$ M in precursor; increasing the precursor concentration by a factor of 5−10 gave the same rate constants showing that radical−radical reactions were not important.

[7] Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742.

[8] Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251−2254.

[9] The upper limit for the kinetics reported here represents the limit of the nanosecond kinetic spectrometer we employed. In principle, the method should be applicable to faster reactions when a picosecond laser unit is employed.

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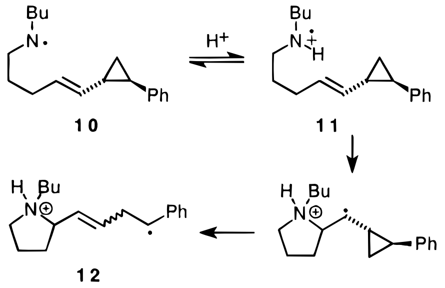
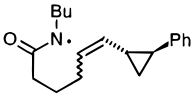
Scheme 2



with a rate constant of 5.6 × 10^7 s^{-1} at 11.0 °C, and the tertiary radical **6c** had $k_{obs} = 3.0 \times 10^7$ s^{-1} at 10.5 °C. For comparison, the rate constant for ring opening of the cyclopropylcarbinyl radical (**1**) at 0 °C is 3 × 10^7 s^{-1}.[10] The 1-methyl- and 1,1-dimethylcyclopropylcarbinyl radicals rearrange at 37 °C with rate constants of 7 and 9 × 10^7 s^{-1}, respectively, on the basis of nitroxyl trappings,[11] and approximate rate constants of 2 and 3 × 10^7 s^{-1} at 11 °C can be estimated with assumptions regarding log *A* for these reactions.[11] Again, the reporter groups in **6** appear to impart relatively small kinetic accelerations to the parent systems.

Radicals **8** demonstrate the reporter group method applied in a system for which little kinetic information is available. Amidyl radicals **8** (a 1.3:1 mixture of (*E*) and (*Z*) isomers), produced by LFP of the corresponding *N*-acyl PTOC carbamate,[4,12] cyclized in a 6-*exo* fashion with only a single observable rate constant at each temperature studied. The kinetics measured over the 2−49 °C range were described by (log k·s) = (9.60 ± 0.31) − (3.45 ± 0.41)/2.3RT (in kcal/mol, errors at 2σ) which gives $k = 1.2 \times 10^7$ s^{-1} at 25 °C. For comparison, amidyl radical **9** has been reported to cyclize in a 6-*exo* fashion with a rate constant at 25 °C of 1 × 10^6 s^{-1}, but this value derives from an approximate rate constant determined at −95 °C by kinetic ESR spectroscopy and an assumption that log *A* for the cyclization will be 10.4.[13] Radical clock **8** can now be used to calibrate second-order reactions of amidyl radicals; for example, from a conventional competition trapping study,[2] the rate constant for reaction of PhSH with **8** was (8.4 ± 0.8) × 10^7 M^{-1} s^{-1} at 23 °C (error at 2σ).



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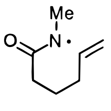

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In another application for a class of radicals that is poorly calibrated kinetically, the cyclization of dialkylaminium cation radical **11** was studied (Scheme 2). LFP of the PTOC carbamate[4,14] precursor in CH_3CN gave the dialkylaminyl radical (*E*)-**10**, which, in the presence of a carboxylic acid, was protonated reversibly to give the cation radical **11**. Cyclization of **11** followed by reporter group ring opening gave **12** which was monitored. As expected, saturation kinetics (with respect to acid concentration) was followed (Figure 1). Using previously measured protonation equilibrium constants for dialkylaminyl radicals by oxalic acid and CF_3CO_2H,[15] the saturation kinetic data was solved by regression analysis[15] to give rate constants for cyclization of **11** of 1.1 × 10^8 s^{-1} (13 °C, oxalic acid) and 1.0 × 10^8 s^{-1} (10 °C, CF_3CO_2H).[16]

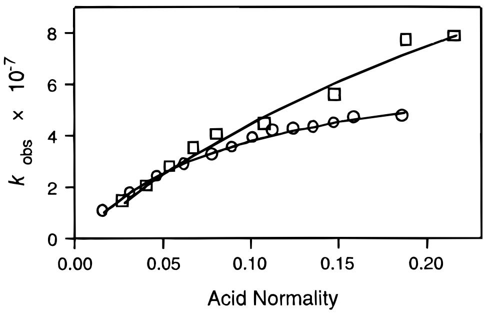

Figure 1. Observed rate constants for formation of radical **12** in CH_3CN in the presence of oxalic acid (circles) at 13 °C and CF_3CO_2H (squares) at 10 °C. The lines are fits for k_{obs} from regression analyses obtained by using protonation equilibrium constants from ref 15 for the respective acids and varying k_c.

The reporter group approach provides directly measured unimolecular kinetics that can be applied as radical clocks for a wide range of radical types. By employing the approach, one avoids most of the uncertainties in the kinetic measurements of the clock reactions (kinetics at a given temperature typically can be measured with <5% error, and often <2% error, at 95% CI) as well as the assumption that the basis reaction used for the clock calibration is an appropriate model. The method will be most useful when little absolute kinetic data is available for a class of radicals such as the nitrogen-centered radicals **8** and **11**.

Acknowledgment. We thank the National Science Foundation (CHE-9117929) for financial support.

Supporting Information Available: Synthetic schemes and experimental procedures for preparation of the PTOC precursors for all radicals and tables of kinetic results (24 pages). See any current masthead page for ordering and Internet access instructions.

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(10) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275−277.

(11) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687−5698.

(12) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779−2786.

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

(14) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163−3165.

(15) Horner, J. H.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 11124−11133.

(16) Wagner, Ruel and Lusztyk estimated that 5-*exo* cyclizations of dialkylaminium cation radicals similar to **11** occurred with rate constants of less than 1 × 10^6 s^{-1} on the basis of differences in rates of signal decays observed for saturated dialkylaminium cation radicals and *N*-alkyl-4-pentenaminium cation radicals.[17] On the basis of the rate constants for cyclization of **11** obtained in this work, it is possible that the cyclization reactions they studied were "instantaneous" on the nanosecond time scale and that the signal decays observed were from the distonic cyclic radical cation products. The rate constants for cyclization of **11** obtained in the present work are consistent with other reported data. Specifically, the *N*-butyl-4-pentenaminium cation radical cyclized in competition with trapping by Bu_3SnH with relative rate constants of $k_c/k_T = 0.34$ M at 25 °C.[18] One can estimate the rate constant for tin hydride trapping (k_T) of a dialkylaminium cation radical to be ca. 1−2 × 10^8 M^{-1} s^{-1} at 25 °C on the basis of the reported rate constant for Ph_3SnH trapping of these species of 2.4 × 10^8 M^{-1} s^{-1}.[15] From the observed relative rate constants and the estimated trapping rate constant, the rate constant for cyclization of the *N*-butyl-4-pentenaminium cation radical at 25 °C would be 3−7 × 10^7 s^{-1}, in general agreement with the kinetic values for **11** at 10−13 °C given the rate accelerating effects of the reporter group expected on the basis of the kinetic behavior observed for radicals **3**. We thank Dr. Janusz Lusztyk for a helpful discussion of the conflicting data.

(17) Wagner, B. D.; Ruel, G.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 13−19.

(18) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317−2328.