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Enol Ether Radical Cation Reaction Kinetics. Laser Flash Photolysis Calibration of Radical Cation Clocks

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Synthetic applications of radical reactions in organic chemistry increased rapidly in the past two decades largely due to the mild conditions of many radical conversions and a growing understanding of radical kinetics, much of which was obtained with radical clocks that permit one to "time" reactions.[1] Although not widely applied in synthesis as yet, radical cations offer attractive features that include enhanced radical reactivity and attenuated cation reactivity. The development of radical cations as routine synthetic tools will require both specific methods for their production and kinetic information. In regard to the former, recent advances in the production of radical cations under non-oxidative conditions by heterolytic fragmentation of radicals are especially noteworthy.[2] In this work, we report the calibration of enol ether radical cation clocks[3] using laser flash photolysis (LFP) methods and kinetic information about the heterolysis of β-phosphate radicals and the evolution of diffusively free enol ether radical cations from the initially formed ion pairs.

The reaction sequence we studied is shown in Scheme 1. Photolysis of PTOC esters **1**[4] (Nd:YAG, 355 nm) gives the 2-pyridinethiyl radical and acyloxyl radicals that decarboxylate to give α-methoxy-β-(diethylphosphatoxy)alkyl radicals (**2**). Heterolytic cleavage of radicals **2** (loss of diethyl phosphate) gives the target enol ether radical cations **3** that cyclize to the distonic radical cations **4**. The cyclizations of **3** to **4** are the "clock" reactions, but a UV-observable element was necessary for direct kinetic studies. Thus, we incorporated a reporter group, the 2,2-diphenylcyclopropylcarbinyl unit.[5] Ring openings of radicals **4** give diphenylalkyl radicals **5** that are readily detected by their characteristic UV absorbances. The photochemical cleavages and decarboxylation steps of precursors **1** are very fast, producing radicals **2** in less than 1 ns. Similarly, the ring-opening reactions of radicals **4** will occur on the picosecond time scale.[6] Thus, the measured kinetics are either for the heterolysis reactions of **2**, the cyclizations of **3**, or both. We note that the fast ring openings of radicals **4** to **5** preclude reversion of **4** to **3** that might occur with simple enol ether radical cations.

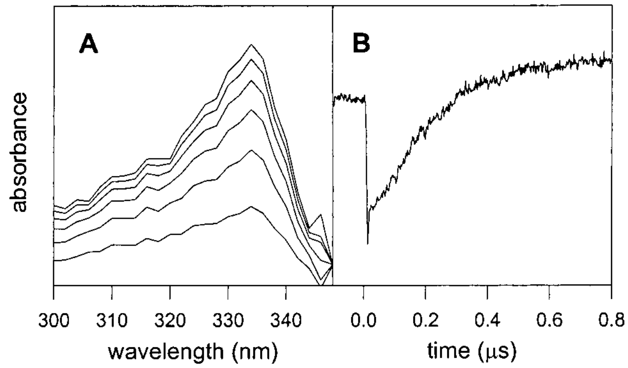

Figure 1. (A) Time-resolved growth spectrum at 20 ns intervals from 61 ns after photolysis of **1a** in acetonitrile at 21 °C. (B) Signal at 335 nm following photolysis of **1b** in acetonitrile at −20 °C. The initial bleaching is from destruction of the precursor.

Scheme 1

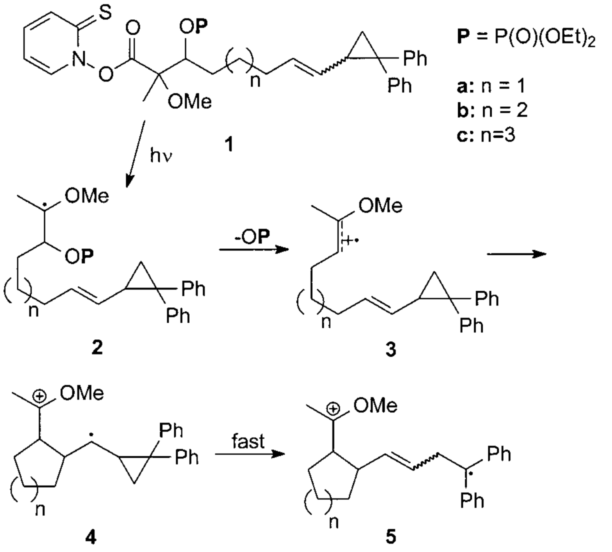

Table 1. Rate Constants and Yields for Enol Ether Radical Cation Reactions[a]

solvent[b]	**1a**	**1b**	**1c**[c]
0% TFE	3.0×10^7 (65)	1.7×10^7 (25)	
0.5% TFE	8.0×10^7 (80)	3.9×10^7 (80)	
1.0% TFE		4.5×10^7 (90)	2×10^5 (10)
2.5% TFE	$>2 \times 10^{8d}$ (95)	5.5×10^7 (100)	1×10^5 (20)

[a] Reactions conducted at (21 ± 1) °C. Observed rate constants in units of s^{-1}. Percent yields of products **5** (±5%) in parentheses. [b] Percentage of 2,2,2-trifluoroethanol in acetonitrile. [c] Rate constants for **1c** are upper limits; see text. [d] Instrument limit.

Photolyses of PTOC esters **1** in acetonitrile (ACN) or in solutions of ACN containing 2,2,2-trifluoroethanol (TFE) were followed by evolution of an absorbance centered at 335 nm from diphenylalkyl radicals **5** (Figure 1A). At 21 ± 1 °C, all traces displayed first-order growth; the kinetic results are listed in Table 1. Yields of radicals **5** given in Table 1 were determined by comparison of the ultimate intensity of the 335 nm signal from **5** to the initial intensity of the 490 nm signal from the byproduct of the photolysis, the 2-pyridinethiyl radical.[7] Reduced yields of **5a** and **5b** must result from reactions within the initially produced ion pair because these radicals were stable over several microseconds of the LFP experiments. We speculate that the destructive reaction is deprotonation of radical cation **3** by phosphate anion to give an allylic radical because recombination of **3** with phosphate would give radical **2** in a nondestructive process. Low yields of **5c** were due to reactions of the diffusively free radical cation (see below).

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(2) Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* **1999**, *1*, 225−227. Crich, D.; Huang, X.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 523−529. Bales, B. C.; Horner, J. H.; Huang, X.; Newcomb, M.; Crich, D.; Greenberg, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 3623−3629.

(3) Intramolecular cycloadditions that can serve as clocks for substituted styrene radical cations have been reported. See: Schepp, N. P.; Shukla, D.; Sarker, H.; Bauld, N. L.; Johnston, L. J. *J. Am. Chem. Soc.* **1997**, *119*, 10325−10334.

(4) Synthetic details will be reported. The acronym PTOC is for pyridine-2-thioneoxycarbonyl.

(5) 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.

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10.1021/ja015639x CCC: $20.00

Table 2. Arrhenius Parameters for Enol Ether Radical Cation Reactions

precursor	solvent[a]	Arrhenius function (log k, s)[b]
1a	0% TFE	$(9.71 \pm 0.10) - (2.94 \pm 0.12)/\theta$
	0.5% TFE	$(9.10 \pm 0.11) - (1.57 \pm 0.14)/\theta$
1b	0% TFE	$(10.47 \pm 0.17) - (4.23 \pm 0.21)/\theta$
	2.5% TFE	$(10.52 \pm 0.12) - (3.82 \pm 0.15)/\theta$

[a] Percent of TFE in ACN. [b] Errors are 2σ; $\theta = 2.313RT$ (kcal/mol).

The 6-*exo* cyclization of radical cation **3b** was readily characterized. In ACN at low temperatures, the kinetic traces clearly displayed a convolution of two processes with similar rate constants (Figure 1B), indicating that both the heterolysis and cyclization reactions were being monitored. Arrhenius functions for the **b** system were determined in the temperature range −30 to 50 °C in ACN and in ACN containing 2.5% TFE (Table 2). The log *A* term was unchanged in the two solvents and was consistent with that expected for a 6-*exo* cyclization.[8] The increased reactivity of the enol ether radical cation in comparison to an alkyl radical is a result of the considerably reduced activation energy; the rate constant for cyclization of the 6-heptenyl radical at ambient temperature is about 5×10^3 s^{-1}.[9] The slight reduction of E_a for cyclization of **3b** with increased solvent polarity, a feature not found in related radical cyclizations, reflects increasing concentration of charge in the transition state as radical cation **3** evolves to distonic radical cation **4**, a true oxonium ion.

Using radical cyclization kinetics as a model, one expects a 5-*exo* cyclization to be about 50 times faster than a 6-*exo* cyclization,[8] and the rate constant for cyclization of **3a** should be about 1×10^9 s^{-1} at ambient temperature on the basis of the rate constants found for **3b**. The measured rate constants for the 5-*exo* system must be those for the heterolysis of **2a**.[10] This conclusion is consistent with the large kinetic acceleration associated with increased solvent polarity. In addition, the log *A* terms found in ACN and 0.5% TFE in ACN (Table 2) are too small for a 5-*exo* cyclization and apparently are associated with an entropic penalty of solvent reorganization in the heterolysis.

The observed rate constants for the 7-*exo* cyclization of enol ether radical cation **3c** in Table 1 are upper limits. The cyclization reactions were so slow that other reactions of diffusively free **3c** were important as indicated both by the low yields of **5c** and by an observed reduction in the rate constants when increasingly dilute solutions of PTOC ester **1c** were studied. The kinetic values for **3c** are about 2 orders of magnitude smaller than those for the 6-*exo* cyclization of **3b**, and they are consistent with that expected from radical kinetics. The rate constant for reaction of the 7-octenyl radical is only about 100 s^{-1}.[9]

Semiquantitative information about the rates of conversion of the first-formed ion pairs to diffusively free ions is provided by the yields of **5a** and **5b**. In the more highly polar solvent mixtures, 2.5% TFE in ACN, ion pair escape was faster than reaction of diethyl phosphate anion with radical cations **3**. The yields of **5** in the 0.5% TFE solutions indicate that escape was about 4 times faster than deprotonation in this reduced polarity mixture. In ACN, the higher yield of **5a** (65%) compared to **5b** (25%) suggests that the cyclization of **3a** was competitive with the deprotonation reaction. Using the estimate (see above) that cyclization of **3a** has a rate constant of about 1×10^9 s^{-1}, the rate constant for deprotonation of **3a** by diethyl phosphate anion is also about 1×10^9 s^{-1}. From the yield of **5b**, ion pair escape in ACN is about 1/3 as fast as the deprotonation reaction, or about 3×10^8 s^{-1}.

The construction of functionalized cyclic products via enol ether radical cations has been demonstrated by Moeller and co-workers,[12] and one of the objectives of this work was to provide kinetic information about enol ether radical cation reactions that is useful for synthetic applications. Some general observations in that regard are possible. If the radical heterolysis entry to enol ether radical cations from β-phosphatoxyalkyl radicals is being used, the solvent polarity should be great enough to permit efficient escape of the radical cation from the first-formed ion pair. The measured $E_T(30)$ value for 2.5% TFE in ACN is about 56, similar in polarity to methanol,[13] and solvents or mixtures with this $E_T(30)$ value or greater should permit efficient ion pair escape.[14] Because the reporter group employed in this study was previously shown to have only a minor effect on radical kinetics, comparable to that of an alkyl group,[5,16] the results with **3** should apply to simpler systems. To a first approximation, one should expect that an enol ether radical cation will cyclize or add to an alkene that does not contain polar groups about 3 orders of magnitude faster than the corresponding radical, but we caution that enol ether radical cation additions to unsubstituted alkene groups might be reversible. An interesting observation, especially in regard to potential cascade reaction sequences, is that the distonic radical cation formed upon reaction of the enol ether radical cation has both substantially reduced radical reactivity and substantially increased cation reactivity.[15]

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Supporting Information Available: Tables of rate constants for the functions in Table 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] The "heterolysis reaction" is a complex sequence of reactions involving bond breaking to give a contact ion pair (CIP), solvation to the solvent-separated ion pair (SSIP), and escape of free ions. Heterolyses of related α-methoxy-β-(diethylphosphatoxy) radical have rate constants similar to that found for **2a**.[11]

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[14] Methanol should be an excellent solvent because it will react "slowly" with an enol ether radical cation.[15] In addition, rapid reaction of methanol with the distonic radical cation products could prevent reversible conversions.

[15] Rate constants at ambient temperature for enol ether radical cation reactions with water are in the 1×10^5 to 1×10^6 M^{-1} s^{-1} range; see: Newcomb, M.; Miranda, N.; Mousumi, S.; Huang, X.; Crich, D. Submitted for publication.

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