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Absence of Diffusively Free Radical Cation Intermediates in Reactions of *β*-(Phosphatoxy)alkyl Radicals

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The chemistry of β-(phosphatoxy)alkyl radicals (or β-phosphate ester radicals) is a subject of considerable interest.[1] They are intermediates in the degradation of DNA effected by hydroxyl radical in DNA footprinting studies,[2] γ-irradiation,[3] and antitumor agents such as the iron−bleomycin complex[4] and the enediyne antibiotics.[5] Typical reactions of these radicals are elimination of phosphoric acid, as in DNA-degrading reactions, substitution, and phosphate migration (Figure 1). Much of this chemistry can be explained by invoking an initial heterolytic fragmentation into radical cations and phosphate anions.[1,6] Alternatively, concerted elimination of phosphoric acid and bimolecular nucleophilic substitution were found to be low-energy pathways in computational studies by Zipse,[7] and a combination of concerted [1,2] and [3,2] shifts has been implicated for migration reactions in low-polarity media.[8]

Considerable circumstantial evidence supports the heterolytic fragmentation hypothesis, but most studies of β-(phosphatoxy)alkyl radicals did not provide direct evidence for formation of radical cations; for example, early kinetic studies of eliminations involved time-resolved conductivity measurements of phosphoric acid formation,[9] and a recent ESR study detected an allylic radical elimination product.[10] Electron-donating groups accelerate phosphate eliminations,[9] but this does not preclude concerted processes which should have some polar character. The most compelling evidence for heterolytic fragmentations are product studies where isomeric β-(phosphatoxy)alkyl radicals gave the same mixture of substitution products[11] and photochemical studies in which CIDNP signals were observed;[12] both require freely diffusing radical cations.

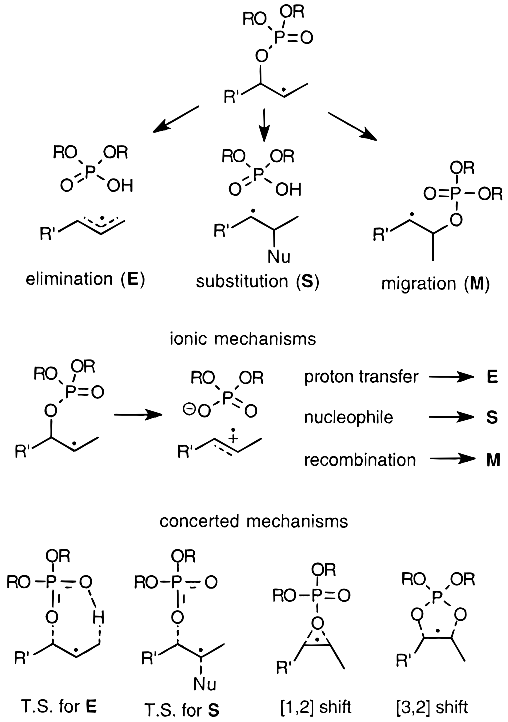
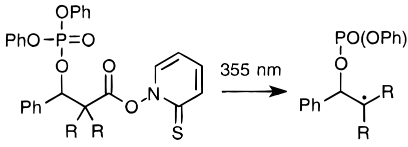


Figure 1. Reactions of β-(phosphatoxy)alkyl radicals.

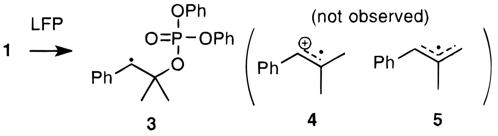
We report here laser flash photolysis (LFP) and product studies of β-(phosphatoxy)alkyl radicals **1** and **2**, produced from the



1: R = CH_3
1D: R = CD_3
2: R = CH_2Ph
2D: R = $CD_2C_6D_5$

corresponding PTOC esters,[13] which demonstrate the diversity of reaction pathways for these species. Specifically, we report examples of each type of reaction in Figure 1 which occur *without formation of diffusively free radical cation intermediates*.

Radical **1** rearranged mainly to the benzylic radical **3** as



determined by the UV spectrum that grew in with time (Figure 2A, Supporting Information). A weak absorbance at ca. 320 nm resembles those of other benzylic radicals.[14] One possible product, radical cation **4**, was excluded because styrene radical cations have a strong λ_{max} at ca. 350 nm and another strong absorbance in the visible region.[15] Another putative product, allyl radical **5**, was prepared independently from two precursors and displayed a strong absorbance at 305 nm but no peak at 320 nm

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(1) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, in press.

(2) Pogozelski, W. K.; Mcneese, T. J.; Tullius, T. D. *J. Am. Chem. Soc.* **1995**, *117*, 6428−6433.

(3) von Sonntag, C. *The Chemical Basis of Radiation Biology*; Taylor & Francis: London, 1987.

(4) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107−1136.

(5) Christner, D. F.; Frank, B. L.; Kozarich, J. W.; Stubbe, J.; Golik, J.; Doyle, T. W.; Rosenberg, I. E.; Krishnan, B. *J. Am. Chem. Soc.* **1992**, *114*, 8763−8767. Hangeland, J. J.; De voss, J. J.; Heath, J. A.; Townsend, C. A.; Ding, W.-d.; Ashcroft, J. S.; Ellestad, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 9200−9202.

(6) See Chapter 7 in ref 3.

(7) Zipse, H. *J. Am. Chem. Soc.*, **1994**, *116*, 10773−10774. Zipse, H. *J. Am. Chem. Soc.* **1997**, *119*, 2889−2893.

(8) Crich, D.; Yao, Q.; Filzen, G. F. *J. Am. Chem. Soc.* **1995**, *117*, 11455−11470. Crich, D.; Jiao, X. Y. *J. Am. Chem. Soc.* **1996**, *118*, 6666−6670.

(9) Behrens, G.; Koltzenburg, G.; Ritter, A.; Schulte-Frohlinde, D. *Int. J. Radiat. Biol.* **1978**, *33*, 163−171. Koltzenburg, G.; Behrens, G.; Schulte-Frohlinde, D. *J. Am. Chem. Soc.* **1982**, *104*, 7311−7312.

(10) Peukert, S.; Batra, R.; Giese, B. *Tetrahedron Lett.* **1997**, *38*, 3507−3510.

(11) Peukert, S.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 4365−4368.

(12) Gugger, A.; Batra, R.; Rzadek, P.; Rist, G.; Giese, B. *J. Am. Chem. Soc.* **1997**, *119*, 8740−8741.

(13) The acronym PTOC is from pyridine-2-thioneoxycarbonyl. Synthetic applications: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924. LFP applications: 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.

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

(15) Johnston, L. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1993**, *115*, 6564−6571.

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Table 1. Rate Constants for Reactions of Radicals **1** and **2**

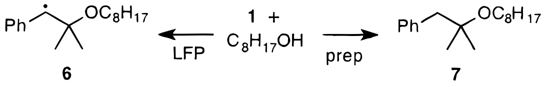
	solvent	Arrhenius function[a]	k_{obs} (s^{-1})[b]
1	benzene		1.2×10^6
1	THF	$(10.9 \pm 0.3) - (6.2 \pm 0.5)/\theta$	1.5×10^6
1D	THF		1.5×10^6
1	CH_3CN	$(11.0 \pm 0.5) - (5.0 \pm 0.7)/\theta$	1.8×10^7
1D	CH_3CN	$(11.0 \pm 0.3) - (5.0 \pm 0.4)/\theta$	1.8×10^7 [c]
2	hexane		$<1 \times 10^4$ [d,e]
2	benzene		2×10^4 [e]
2	THF	$(13 \pm 1) - (11 \pm 1)/\theta$	3.4×10^4 [e]
2	CH_3CN	$(11.6 \pm 0.3) - (8.0 \pm 0.4)/\theta$	5.2×10^5
2D	CH_3CN	$(12.4 \pm 0.5) - (9.0 \pm 0.7)/\theta$	5.0×10^5
2	CH_3CN/H_2O[f]		3×10^6

[a] Listed errors in activation parameters are at 2σ; $\theta = 2.3RT$ (kcal/mol). [b] Observed rate constant at 20 ± 1 °C unless stated; errors are <10%. [c] 18 °C. [d] 50 °C. [e] Maximum value; when $k_{obs} < 1 \times 10^5$ s^{-1}, the kinetic value contains a component from radical−radical and radical−oxygen reactions. [f] Acetonitrile−water, 1:1 (v:v).

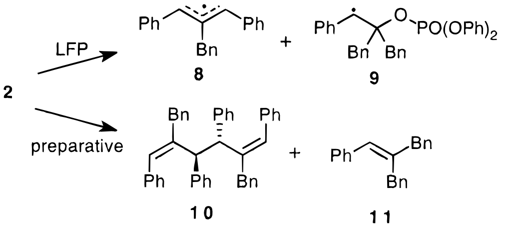
(Figure 2B). Radical **5** could only be a minor product from **1** (<10%) on the basis of the signal intensity observed at 305 nm.

The kinetics of rearrangement of **1** (Table 1) were strictly first-order and preclude dissociation to phosphate anion and radical cation followed by bimolecular recombination. The reaction was accelerated by an increased solvent dielectric constant[16] as expected for a reaction occurring with a polarized transition state. The log *A* values of 11 are similar to those found in migration reactions of related β-acetoxy radicals which are believed to be concerted.[17] The $\Delta S^{\ddagger}$ value of −3 to −5 eu is not consistent with the positive $\Delta S^{\ddagger}$ expected[18] for heterolysis or rapid equilibration to an ion pair followed by rate-limiting recombination.[19] The deuterated analogue **1D** displayed no kinetic isotope effect. A concerted migration mechanism for **1** agrees with previous mechanistic studies.[8]

When radical **1** was studied in THF in the presence of 1-octanol,[16] the rate constant for formation of benzylic radical products (i.e., the sum of all rate constants) accelerated with a first-order dependence on octanol concentration. The new reaction was a *bimolecular* nucleophilic substitution of alcohol on **1**, giving radical **6**, a radical analogue of an S_N2' reaction (see Figure 1) that has not been observed previously but was predicted.[7] The rate constant at 20 °C was 2×10^6 M^{-1} s^{-1}. Octyl ether **7** was obtained in 60% yield from a preparative-scale reaction of **1** in 1-octanol containing *t*-BuSH.



Radical **2** displayed another reaction. Time-resolved spectra in benzene, THF, acetonitrile, and acetonitrile/water (1:1) showed the formation of the allylic radical **8** and a benzylic radical which we assume is radical **9** from a migration reaction. Spectra of products from **2** and **2D** (Figure 2C,D) are superpositions of the spectrum of radical **8** (Figure 2E) and another absorbance in the region of 320 nm. Difference spectra obtained by normalizing λ_{max} in the spectrum of **8** to that from **2** and subtraction show the underlying benzylic radical signal (Figure 2F). We estimate that the radical **9** predominates over **8** for the 0.1-ms time course of the LFP experiments, but it is possible that **9** eventually channels through radical **8** in secondary reactions. Preparative-scale reactions conducted in the presence of thiol gave coupling product **10** and its isomers and trapping product **11** in 64% and 13% yields, respectively.



LFP kinetic studies of radical **2** were conducted in several solvents (Table 1). Again, the kinetics were strictly first-order precluding fragmentation to radical cations and phosphate anions that subsequently reacted bimolecularly. Radicals **8** and **9** are produced in reactions that are quite closely related or are formed from a single process involving a bifurcation after the rate-limiting step because the ratios of **8**:**9** estimated from time-resolved spectra were the same in THF at 19 °C and in acetonitrile at 20 and 43 °C (**8**:**9** = 40:60). Further, the deuterated analogue **2D** reacted with about the same overall rate constants as found for **2** but gave a slightly different product distribution (**8**:**9** = 30:70 in THF at 20 °C). That is, an isotope effect was observed in the product-forming step but not the rate-limiting step.

The reactions of radical **2** are complex but show all the hallmarks of concerted processes. Diffusively free radical cations are excluded by the absence of second-order kinetic behavior and the absence of a radical cation UV spectrum. The log *A* values of 12−13 and the relatively small kinetic response to changes in solvent dielectric constant suggest a modestly polarized, concerted transition state as opposed to a highly polarized transition state expected for initial fragmentation to a radical cation−anion pair that subsequently reacts before diffusional escape.[20]

Diffusively free cation radicals are excluded as first-formed intermediates in reactions of **1** and **2**, but fragmentation to a radical cation−phosphate anion pair that reacts "instantly" on the nanosecond time scale remains as a possible reaction course. Multiple heterolytic and concerted reactions of β-(phosphatoxy)-alkyl radicals are possible, but it is clear that the reactions of these species are poorly characterized. The phosphate migration reaction has only been known for a few years.[21] The present work has demonstrated a bimolecular nucleophilic substitution reaction and implicated a concerted [1,3]-elimination reaction, neither of which were previously known even if computationally predicted.[7] Given the importance of β-phosphate radicals in DNA degradation by anticancer agents, one expects that other methods will be brought to bear on the mechanisms of their reactions.

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Supporting Information Available: Experimental procedures for preparation of the precusors for **1** and **2**, preparative reactions, and LFP experiments, X-ray structural data for **10**, and Figure 2 (15 pages). See any current masthead page for ordering and Internet access instructions.

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(16) Dielectric constants: hexane, 1.88; benzene, 2.27; THF, 7.58; acetonitrile, 35.9; water, 78.4; 1-octanol, 10.3. See: Riddick, J. A.; Bunger, W. B.; Sakano, T. K. *Organic Solvents Physical Properties and Methods of Purification*, 4th ed.; Wiley: New York, 1986.

(17) Barclay, L. R. C.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 1793−1796.

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

(19) For a prior equilibrium followed by a rate-limiting reaction, the overall log *A* term is the sum of the log *A* values of the elementary reactions. For a dissociation−recombination equilibrium followed by a rate-limiting recombination or abstraction step, log A_{obs} will be approximately equal to log *A* of the initial dissociative step, i.e. log $A \approx 15$ would be expected for the cases discussed here.

(20) Swain, C. G.; Swain, M. S.; Powell, A. L.; Alunni, S. *J. Am. Chem. Soc.* **1983**, *105*, 502−513.

(21) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **1993**, *115*, 1165−1166. Koch, A.; Giese, B. *Helv. Chim. Acta* **1993**, *76*, 1687−1701.