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Heterolytic Cleavage of a β-Phosphatoxyalkyl Radical Resulting in Phosphate Migration or Radical Cation Formation as a Function of Solvent Polarity

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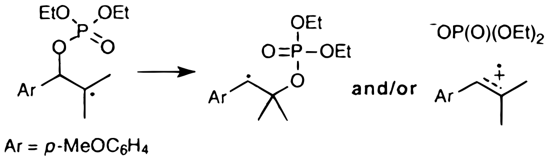
ABSTRACT



The 2-(diethylphosphatoxy)-2-(*p*-methoxyphenyl)-1,1-dimethylethyl radical (1) reacted to give the benzylic radical product from phosphate migration or a radical cation (or a mixture of the two) as a function of solvent. Smooth acceleration in rates of reactions of 1 in solvents of increasing polarity and consistent entropies of activation indicate that radical 1 reacts by common mechanism irrespective of the final products formed, specifically by initial heterolysis to a radical cation–phosphate anion pair.

The reactions of β-ester radicals in general are of interest due to their mechanistic diversity.[2] The β-phosphatoxyalkyl radicals, a subset of β-ester radicals, are of further interest because such radicals are intermediates in the cleavage of DNA effected by anticancer agents such as bleomycin.[3] β-Phosphatoxyalkyl radicals can react by phosphate migration, phosphoric acid elimination or nucleophilic substitution with loss of phosphate from the adjacent position, a radical equivalent of an S_N2 or S_N2' reaction depending upon the position of nucleophile attachment. The consensus views of the mechanisms of these reactions are that two distinct reaction manifolds are involved; migrations are concerted processes, whereas elimination and substitution reactions proceed through radical cations formed by initial heterolysis.[2]

Our groups have reported kinetic[4,5] and labeling[6,7] studies of β-phosphatoxyalkyl radical reactions that, we believed, were most consistent with concerted reactions. More recently, however, we reported detailed studies of a competing migration and elimination reaction of a β-phosphatoxyalkyl radical that are not consistent with our original conclusions; specifically, the results indicated that both products arose from a common intermediate, an ion pair produced by heterolysis, even in low polarity solvents.[8] Herein, we report

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[1] (a) Wayne State University. (b) University of Illinois at Chicago.

[2] Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. W. *Chem. Rev.* **1997**, *97*, 3273−3312.

[3] Pogozelski, W. K.; Tullius, T. D. *Chem. Rev.* **1998**, *98*, 1089−1107.

[4] Choi, S. Y.; Crich, D.; Horner, J. H.; Huang, X. H.; Martinez, F. N.; Newcomb, M.; Wink, D. J.; Yao, Q. W. *J. Am. Chem. Soc.* **1998**, *120*, 211−212.

[5] Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Newcomb, M.; Whitted, P. O. *Tetrahedron* **1999**, *55*, 3317−3326.

[6] Crich, D.; Yao, Q. W. *J. Am. Chem. Soc.* **1993**, *115*, 1165−1166.

[7] Crich, D.; Yao, Q. W.; Filzen, G. F. *J. Am. Chem. Soc.* **1995**, *117*, 11455−11470.

[8] Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H. Submitted for publication.

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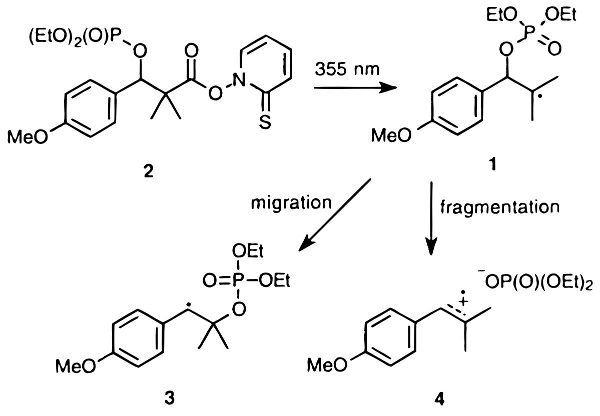
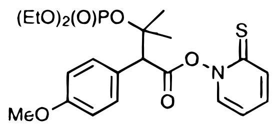
an example of a β-phosphatoxyalkyl radical that reacts by phosphate migration or fragmentation to a diffusively free radical cation in a solvent-dependent fashion. The results provide further evidence of a common pathway involving initial heterolytic cleavage for seemingly different reactions.

Radical **1** contains the elements necessary for nanosecond resolution kinetic studies in a variety of solvents employing laser flash photolysis (LFP) methods. Laser irradiation (Nd: YAG, 355 nm) of the PTOC ester precursor **2**[5] results in efficient cleavage of the N−O bond, giving the pyridine-2-thiyl radical and an acyloxyl radical that rapidly decarboxylates to give the desired radical **1** (Scheme 1). The pyridine-2-thiyl radical has a long wavelength absorbance with λ_{max} at 490 nm,[9] and UV spectra observed immediately after photolysis of PTOC precursors contain this absorbance and a bleaching centered at 360 nm from destruction of the precursor. As shown in Scheme 1, diethyl phosphate migration in **1** would give the benzylic radical **3**, whereas heterolytic fragmentation would give radical cation **4**.

Scheme 1



Benzylic radical **3** was expected to have an absorbance at about 320 nm.[10] An authentic spectrum of radical **3** (Figure 1A) was obtained in the following manner. The PTOC ester precursor[11] **5** was photolyzed in He-sparged acetonitrile solution and in acetonitrile solution containing oxygen, and the UV spectra were monitored over several microseconds.



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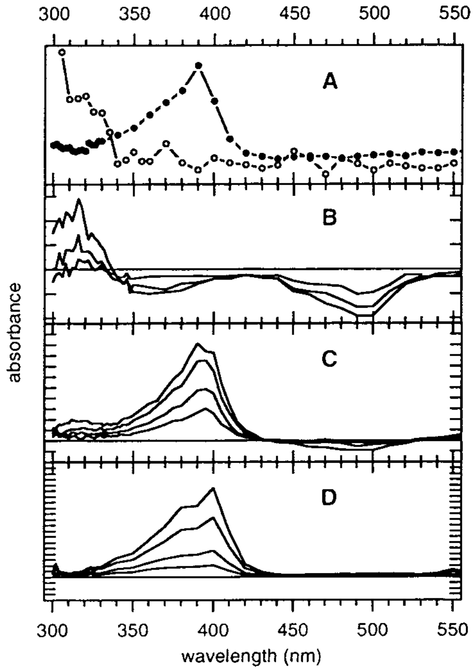

Figure 1. (A) Authentic spectra of benzyl radical **3** (open circles) and radical cation **4** (filled circles); the spectra are not on the same scale, see text for description of the methods used. (B−D) Time-resolved spectra from reactions of radical **1** at 22 °C: (B) growth in THF between 0.5 and 25.5 μs; (C) growth in acetonitrile between 0.3 and 2.5 μs; and (D) decay from products formed in water/acetonitrile (10:90, v:v). The tick marks on the *y* axes of spectra B−D are spaced at 0.01 AU.

Radical **3** was formed "instantly" in both cases. The benzylic radical was persistent over 4.5 μs in the He-sparged solution, but decayed in the oxygen-containing solution over this period. Subtraction of the nonsparged spectrum from the He-sparged spectrum gave the residual spectrum that contains only signals from **3**.[12] In passing, we note that the observation of radical **3** in acetonitrile over 4.5 μs without detection of radical cation **4** demonstrates that **3** is not a kinetically competent intermediate for formation of **4** in this solvent (see below).

An authentic spectrum of radical cation **4** was obtained by photoejection from 1-(*p*-methoxyphenyl)-2-methylpropene in acetonitrile upon 266 nm irradiation as described previously by Johnston.[13] The UV spectrum of **4** is also shown in Figure 1A; the absorbance centered at 390 nm is at slightly longer wavelength than the absorbances reported for the radical cations from *p*-methoxystyrene and anethole as expected due to the additional methyl group(s) in **4**.[13,14] One should note that the superimposed spectra of **3** and **4** in

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(9) Alam, M. M.; Watanabe, A.; Ito, O. *J. Org. Chem.* **1995**, *60*, 3440−3444.

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

(11) The acid precursor to PTOC ester **5** was prepared by a reaction sequence similar to that employed previously for production of the normethoxy analogue (see ref 8). The synthetic intermediates and the carboxylic acid had appropriate NMR spectra and elemental analyses, and PTOC ester **5** had appropriate NMR spectra.

(12) This procedure was used previously to obtain a UV spectrum of a benzylic radical from a PTOC ester precursor and is described in more detail in ref 8.

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

(14) Radical cation **4** also displayed an expected (ref 13) broad absorbance at longer wavelengths; spectra to 700 nm are in Supporting Information.

Figure 1A are not on the same scale; the molar absorption coefficient of radical cation **4** is ~1 order of magnitude greater than that of **3**.

Time-resolved UV growth spectra from reactions of radical **1** were obtained in THF and acetonitrile. The spectra were produced by subtracting a short time spectrum from those obtained at later times which removes the features present immediately after photolysis. Positive signals are from species forming with time, and negative signals are from decaying species. The spectrum in THF (Figure 1B)[5] shows the growth of benzylic radical **3** and decay of the pyridine-2-thiyl radical; no signal from radical cation **4** is apparent. In acetonitrile solution, however, a strong signal from radical cation **4** grew in (Figure 1C), and comparison of the 300−320-nm regions in parts A and C of Figure 1 indicates that benzylic radical **3** also was formed in acetonitrile. We calculate an ~35% yield of radical cation **4** from reaction of **1** in CH_3CN from a comparison of the ultimate intensity of the 390-nm signal from the radical cation against the instantaneous intensity of the 490-nm signal from pyridine-2-thiyl and the known and measured extinction coefficients of the two radicals.[15]

Radical **1** reacted rapidly in aqueous acetonitrile solutions, precluding useful growth spectra, but Figure 1D shows the time-resolved *decay* spectrum of radical cation **4** produced from reaction of **1** in a 10% water solution. Radical cation **4** appears to be the only product formed in the aqueous acetonitrile reactions on the basis of the small 320-nm signal in Figure 1D; in addition, the ratio of the intensities at 390 and 490 nm in aqueous acetonitrile solutions was about 4 times as great as that in acetonitrile, in qualitative agreement with a high yield of **4** although the extinction coefficients of the two radicals in these solvent mixtures are not known.

The kinetics of reactions of **1** were studied. PTOC ester **2** is stable in THF and in acetonitrile, and variable-temperature studies were possible; the Arrhenius functions for reactions in these solvents are given in eqs 1 and 2

$$\log(k/\mathrm{s}^{-1}) = (12.1 \pm 0.8) - (9.7 \pm 1.2)/2.3RT \qquad (1)$$

$$\log(k/\mathrm{s}^{-1}) = (10.6 \pm 0.7) - (6.1 \pm 0.9)/2.3RT \qquad (2)$$

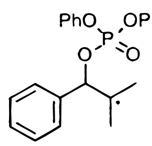
for THF and CH_3CN, respectively, where errors are at 2σ and the E_a values are in kilocalories/mole. For reactions in CH_3CN, the rate constants for signal formation in the 312−320- and 390−400-nm regions were comparable, suggesting that relatively slow secondary reactions were not involved in production of either product.[16] Because PTOC esters hydrolyze rapidly in aqueous solutions, studies in water/acetonitrile mixtures were more difficult, requiring mixing of a solution of **2** in acetonitrile and one of water/acetonitrile (or water only) via syringe pumps immediately before the LFP experiments were performed, and the kinetics in aqueous acetonitrile solutions were obtained only at ambient temperatures. Table 1 lists rate constants for reactions of **1** in various solvents at ambient temperature.

Table 1. Kinetics of Reactions of Radical **1** at (22 ± 2) °C

solvent	% **4**[a]	k (s^{-1})
THF	0	8×10^4
butanone[b]	25	1.2×10^6
CH_3CN	35	1.2×10^6
5% water[c]	95	7×10^6
10% water[c]	100[d]	1.7×10^7
50% water[c]	100[d]	8×10^7

[a] Percentage of product **4** estimated from the ratio of the ultimate intensity of the 390 nm signal from **4** to that of the pyridine-2-thiyl radical at 490 nm using the extinction coefficients in ref 15. [b] Despite drying, this solvent might have contained some water as deduced from the apparent hydrolysis of the PTOC ester upon standing. [c] Volume percent of water in water/acetonitrile. [d] No signal was observed at 320 nm from radical **3**.

The rate constants for reactions of **1** increase smoothly as the solvent polarity increases from THF to aqueous acetonitrile solutions, similar to the kinetic behavior observed in other β-ester radical reactions. For example, the 15-fold acceleration in reaction of **1** upon proceeding from THF to acetonitrile is comparable to the acceleration in reactions of radicals **6**−**8** in these solvents.[4,5,8] The obvious difference between radicals **6**−**8** and **1** is that the reactions of **6**−**8** do not give different products in the different solvents; **6** and **7** react by diphenyl phosphate and trifluoroacetate migrations, respectively, and radical **8** reacts in both solvents by a combination of diphenyl phosphate migration and diphenylphosphoric acid elimination reactions.[4,5,8] The log A terms in the Arrhenius functions (the entropic terms) for reactions of radical **1** in THF and acetonitrile are similar to one another as well as to those for reactions of radicals **6**−**8** in the same solvents.[4,5,8]



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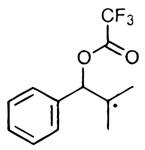
$k_{ACN} = 10 \times k_{THF}$



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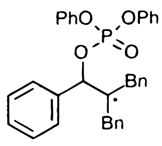
$k_{ACN} = 5 \times k_{THF}$



8

$k_{ACN} = 13 \times k_{THF}$

Both the kinetic solvent effects and the consistent entropies of activation indicate that the fundamental mechanism of the reaction of radical **1** does not change with solvent, even if the products ultimately formed do. This is dramatically illustrated by plotting the rate constants for reactions of **1**

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[15] The molar extinction coefficient for the 2-pyridinethiyl radical in acetonitrile is 3200 $\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$ (ref 9). That for **4** is approximately 30 000 $\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$ as determined from oxidation of the styrene with the chloranil triplet and comparison of the signal intensities for **4** and the chloranil radical anion.

[16] We note, however, that this behavior only excludes a relatively slow secondary reaction as the source of one product. It does not exclude the possibility that two distinct reactions give rise to products **3** and **4** because the kinetics are only reporting the total rate of loss of reactant radical **1**, irrespective of the number of reaction channels available.

[17] Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319−2358. Skwierczynski, R. D.; Connors, K. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 467−472.

against the $E_T(30)$ solvent polarity scale[17] (Figure 2). Although the products change from exclusively **3** in THF to exclusively **4** in 10% water in acetonitrile, the linear behavior of the plot indicates that the mechanism is unaltered to the point of the rate-determining step.

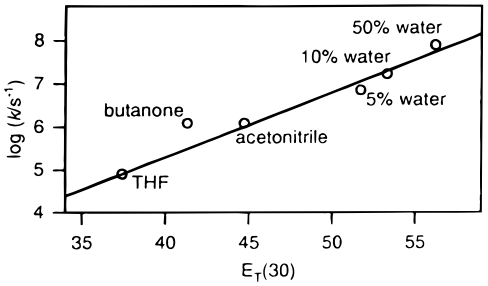
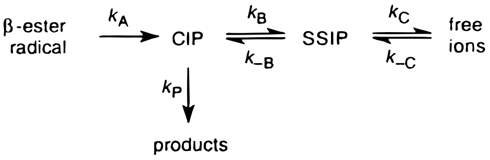


Figure 2. Rate constants for reactions of radical **1** plotted against the $E_T(30)$ solvent polarity scale. The butanone value was not used in the regression line; see note in Table 1.

Our recent studies of radical **8** indicated that the reaction proceeded as shown in Scheme 2.[8] Initial heterolysis gives a contact ion pair (CIP) of the radical cation and phosphate anion. Rapid collapse of the CIP competes with (possibly diffusion-controlled) evolution to a solvent-separated ion pair (SSIP), and the SSIP partitions back to the CIP or further separates to give diffusively free ions. In the case of radical **8**, a short-lived diffusively free radical cation was detected as a minor product in aqueous acetonitrile solutions but not in acetonitrile.

Scheme 2



Radical **1** appears to react by the same scheme. In THF, collapse to the migration product is the major secondary process. In acetonitrile, either (1) the rate constant for solvation of the CIP to give the SSIP is comparable to that for collapse to products or (2) further solvation of the SSIP to give free ions is competitive with return of the SSIP to the CIP. Diffusively free radical cation was not formed in the reactions of radical **8** in acetonitrile, but the methoxy-substituted styrene radical cation **4** is appreciably more stable than the radical cation from β,β-dimethylstyrene as judged by comparison of the oxidation potentials of styrenes[18] and the fact that radical **1** reacts in CH_3CN at ambient temperature about 20 times faster than its nor-methoxy analogue, the 2-(diethylphosphatoxy)-2-phenyl-1,1-dimethylethyl radical.[5] Thus, either possibility (or both) appears reasonable, and a distinction between the two might require picosecond dynamic studies. The kinetic behavior of radical **8** led us to conclude, however, that the rate constant for evolution of the SSIP to free ions (k_C in Scheme 2) was likely to be highly sensitive to solvent polarity.[8]

The solvent-dependent behavior of radical **1** provides a striking confirmation that aryl-substituted β-phosphatoxyalkyl radicals (and, by analogy, other β-ester radicals[2]) can react by initial heterolysis even when the final products are those of ester group migration. On the basis of the similarities of the kinetic behaviors and log *A* terms for several β-aryl-β-ester radicals in solvents of widely different polarities,[2,4,5,8] we believe the mechanistic picture in Scheme 2 is likely to apply for all cases where the incipient radical cation is at least as stable as a styrene radical cation. This includes simple α-oxy-β-phosphatoxy radicals such as those formed by hydrogen-atom abstraction from the sugars in DNA.[19] The mechanisms of reactions of β-ester radicals containing no cation-stabilizing groups, for which concerted pathways have been found computationally,[20] remain an open question.

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Supporting Information Available: Spectra of radical cation **4** from 300 to 700 nm. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] The oxidation potential of *p*-methoxystyrene is ~0.4 V lower than that of styrene; see: Akbulut, U.; Toppare, L.; Türker, L. *Makromol. Chem.* **1983**, *184*, 1661−1667.

[19] For example, ethyl vinyl ether and styrene have the same oxidation potentials in acetontrile. See: Katz, M.; Riemenschneider, P.; Wendt, H. *Electrochim. Acta* **1972**, *17*, 1595−1607.

[20] Zipse, H. *J. Am. Chem. Soc.* **1997**, *119*, 2889−2893.