Photochemistry of Phosphate Esters: An Efficient Method for the Generation of Electrophiles[1]

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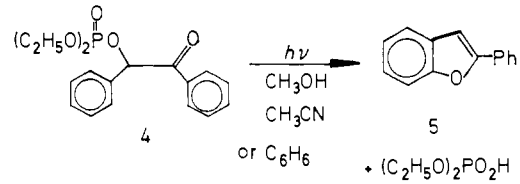
We have recently determined that for excited arylmethyl phosphates, the dialkyl phosphate anion is a surprisingly efficacious leaving group.[2,3] For example, upon irradiation of a variety of esters possessing an aryl or a carbonyl chromophore adjacent to the phosphate moiety, e.g., esters **1**–**3**,[4] the phosphate anion departs as the nucleofuge in a highly efficient photochemical process and leaves behind a reactive electrophile. In most instances the fate of that electrophile is solvent dependent as illustrated in Scheme I. For each arylmethyl ester, the major product[4] arises from electrophilic attack on the solvent by the photochemically generated "benzylic" carbocation through nucleophilic substitution (in alcohol or acetonitrile) or by electrophilic aromatic substitution (in benzene). These products are often accompanied by formation of lesser amounts of the corresponding ethyl ether and radical-derived coupling products, the former arising from loss of the elements of ethyl metaphosphate.[5]

Among the variety of arylmethyl phosphate esters examined, the naphthylmethyl phosphates **2** and **3** undergo especially efficient and clean photofragmentations. The ester disappearance and the substitution product appearance efficiencies are practically equal (Table I) with only traces of detectable side products. Attempts to sensitize the reactions of these two phosphates with acetophenone or benzophenone were not successful implicating the singlet as the reactive excited state for naphthyl esters.

Benzoin diethyl phosphate (**4**), on the other hand, gives exclusively the intramolecular rearrangement product 2-phenylbenzo[b]furan (**5**),[6] regardless of the nature of the medium (eq 1). In contrast to the naphthylmethyl phosphate esters, the



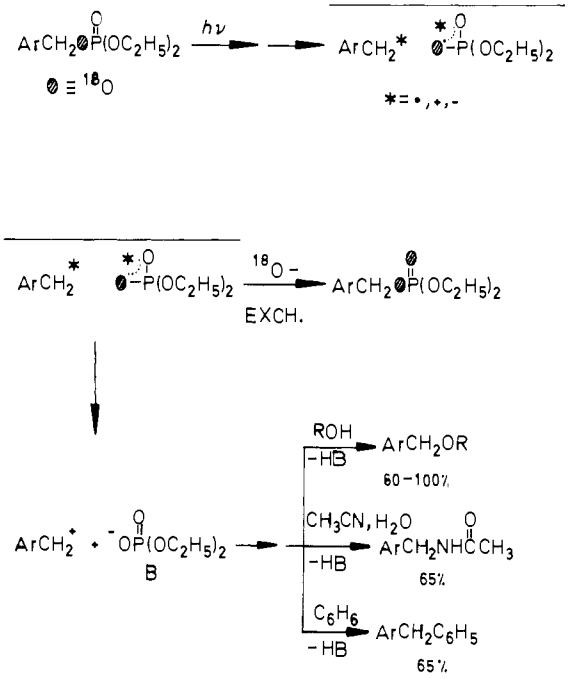
(1)

photolysis of benzoin diethyl phosphate occurs via the triplet manifold, as evidenced by efficient quenching of product appearance with either piperylene or naphthalene (Stern–Volmer slopes of 56 and 43 M^{-1}, respectively) along with equally efficient quenching of the ester disappearance. This photoreaction thus provides an entry into the α-keto carbocation[7] from **4** as well as serving as a potential photoprotection group for the phosphate moiety.[8]

A mechanistic rationale for the arylmethyl phosphate ester photolysis, outlined in Scheme I, is supported by oxygen-18 labeling, stereochemical, and substituent effect studies. The oxygen-18 labeling and stereochemical studies suggest the intervention of an equilibrating intermediate, possibly an ion pair, capable of exchanging the benzylic and phosphoryl oxygens. The quantum efficiencies (Table I) for the oxygen-label exchange, which are half of the efficiencies for an ion-pair return mechanism, clearly illustrate the importance of the recombination pathway as an energy wastage outlet for the excited ester. Furthermore, the sum of the quantum efficiencies for all of the photochemical reactions establishes the near unit efficiency for this bond-dissociation process.

Support for an equilibrating ion-pair mechanism was also derived from examination of the photostereoisomerization of phenylethyl ester (*S*)-(−)-**6**. Upon irradiation, (S)-(−)-**6** undergoes substantial stereoequilibration in competition with substitution and elimination (eq 2). Furthermore, the ether substitution product from (*S*)-(−)-**6**, although also largely racemic, nevertheless

Scheme I. Photochemistry of Arylmethyl Phospate Esters[a]



[a] 1, Ar = phenyl; 2, Ar = 1-naphthyl; 3, Ar = 2-naphthyl.

Table I. Quantum Efficiencies[12] (ϕ) for Photolysis of Esters **1**–**4**, 6, and **8**.

ester	nucleophile	ϕ_{dis}[a]	ϕ_{exch}[b]	ϕ_{app}[c]
1[d]	methanol	0.39		0.19
	n-butyl alcohol	0.26	0.33	
	tert-butyl alcohol	0.16		0.08
	benzene	0.03	0.18	0.016
	acetone (sens), benzene	0.00		0.00
2[e]	methanol	0.08		0.08
	tert-butyl alcohol, benzophenone, or acetophenone	0.00		0.00
3[e]	methanol	0.3		0.25
	tert-butyl alcohol, benzophenone, or acetophenone	0.00		0.00
4[f]	benzene	0.28		0.26[g] (**5**)
6[d]	methanol	0.21		0.09[h] (**7**)
8[f]	methanol	0.038		0.014 (**9**)

[a] Disappearance quantum efficiency. [b] Quantum efficiency for the exchange of oxygen-18 label between the aryl methyl C–O and the phosphoryl oxygen. For an ion-pair return mechanism, these values must be doubled. [c] Appearance quantum efficiency. [d] At 254 nm. [e] At 300 nm. [f] At 350 nm. [g] In higher conversion runs, photodimer of the furan **5** appeared as a minor product at this wavelength (ϕ = 0.02). [h] Elimination also occurs. Efficiencies for styrene were not determined.

(1) Reported in part: Stoner, M. R.; Givens, R. S.; Matuszewski, B. *Abstr. Pap.—Am. Chem. Soc.* **1984**, *187th*, ORGN76. Givens, R. S.; Matuszewski, B. *Abstr. Pap.—Am. Chem. Soc.* **1984**, *187th*, ORGN77.

(2) Three earlier reports of benzyl phosphate ester photochemistry have appeared: (a) Arris, J.; Braddily, J.; Buchanan, J. G.; Thain, E. M. *J. Chem. Soc.* **1956**, 4968. (b) Clark, V. M.; Hobbs, J. B.; Hutchison, D. W. *J. Chem. Soc., Chem. Commun.* **1970**, 339. (c) Kaplan, J. H.; Forbush, B.; Hoffmann, J. F. *Biochemistry* **1978**, *17*, 1929.

(3) For quantitative comparisons with other photofragmentations see: (a) Givens, R. S.; Hrinczenko, B.; Liu, J. H.-S.; Matuszewski, B.; Tholen-Collison, J. *J. Am. Chem. Soc.* **1984**, *106*, 1779. (b) Givens, R. S. *Org. Photochem.* **1981**, *5*, 227. (c) Cristol, S. J.; Bindel, T. H. *Org. Photochem.* **1983**, *6*, 327.

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(6) (a) Sahm, W.; Schinzel, E.; Jurges, P. *Justus Liebigs Ann. Chem.* **1974**, 523. (b) A similar photocyclization has been observed by: Sheehan, J. C.; Wilson, R. M.; Oxford, A. W. *J. Am. Chem. Soc.* **1971**, *93*, 7222.

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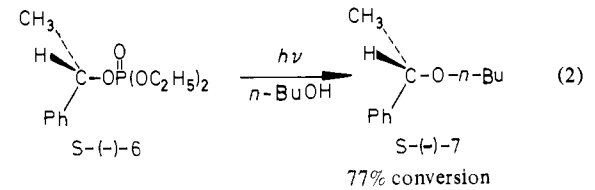


S-(-)-6 S-(-)-7 (2)

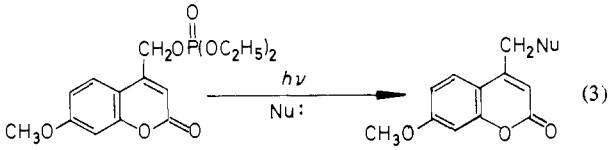
77% conversion

before:	$[\alpha]^{25}_D$ −39.7	
after:	$[\alpha]^{25}_D$ −28.5	$[\alpha]^{25}$ −4.5
	28% net racemization	5.5% net retention

is formed with a slight preference for net retention of configuration. It appears that the weakly basic phosphate anion "delivers" the nucleophile to the front face of the carbocation by a general-base catalyzed deprotonation of the solvent.[9]

Although the sequence of events proceeding to ion-pair formation is not well-defined, an argument in favor of an early development of charge separation, perhaps as early as the initial bond-breaking step, would appear reasonable. For example, examination of the relative rates and efficiencies for nucleophilic photosubstitution of a series of substituted benzylic esters indicates electron demand at the reaction center, in accord with photoionization to an electron-deficient intermediate, presumably the carbocation, both at the bond-breaking stage (based on meta- and para-substituent effects on ϕ_{dis} and k_r) and at the product forming stage (based on ϕ_{app} or k_r vs. σ).[10]

An especially intriguing application of this photochemistry was demonstrated with the coumaryl diethyl phosphate **8** which upon irradiation with 360-nm light reacted with a wide variety of nucleophilic functionalities. As illustrated in eq 3, several organic



8 (3)

Nu:
= CH_3OH (9), piperidine, cysteine, tyrosine, α-chymotrypsin, HMT

substrates were covalently "tagged" with the highly fluorescent coumaryl moiety. In addition to small molecule labeling, **8** has also been employed as a fluorescent tag fot the enzymes α-chymotrypsin and histamine *N*-methyltransferase (HMT).[13] Applications of this method for analytical, affinity labeling, and spectroscopic studies are currently being pursued.

Acknowledgment. The support of the Center for Bioanalytical Research administered by the University of Kansas and an NIH Biomedical Research Grant are gratefully acknowledged.

(9) (a) See Shiner (Shiner, V. J., Jr. "Deuterium Isotope Effects in Solvolytic Substitution at Saturated Carbon"; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand Reinhold: New York, 1970; p 95) and Ritchie (Ritchie, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 3275) for discussions of general-base-catalyzed reactions of nucleophiles with carbocations. (b) Alternatively, the retention of configuration in the substitution product could have resulted by a small fraction of concerted syn attack in competition with carbocation formation, see: Cristol, S. J.; Seapy, D. G.; Aeling, E. O. *J. Am. Chem. Soc.* **1983**, *105*, 7337.

(10) Substituent effects on the photosolvolysis of benzyl diethyl phosphates have been measured by quantum efficiency determinations and by the fluorescence efficiencies and lifetimes (Givens, R. S.; Stoner, M. R. unpublished results). The appearance efficiencies in *tert*-butyl alcohol decreased as the substituent was changed from *p*-MeO to *p*-CF_3; i.e., the efficiencies for *p*-MeO, *p*-Me, *m*-Me, H, *m*-MeO, *m*-CF_3, and *p*-CF_3 are 0.23, 0.17, 0.13, 0.16, 0.18, 0.012, and 0.063, respectively. These efficiencies were converted into relative rate constants by use of the experimental singlet lifetimes obtained[4] by the Berlman method.[11]

(11) Berlman, I. B. "Handbook of Fluorescence Spectra of Aromatic Molecules", 2nd ed.; Academic Press: New York, 1971.

(12) Light output was measured according to the method of Hatchard and Parker (Hatchard, C. G.; Parker, C. A. *Proc. R. Soc. London, Ser. A* **1956**, *235*, 518).

(13) Matuszewska, B.; Borchardt, R. T. *J. Neurochem.* **1983**, *41*, 113. The HMT was kindly supplied by Dr. B. Matuszewska and Professor R. Borchardt, Department of Pharmaceutical Chemistry, the University of Kansas. We also thank Dr. Matuszewska for her advice and assistance in analyzing the labeled enzyme.

Timed Release of Chemicals from Polypyrrole Films

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Research on the controlled release of drugs has made it possible to slowly release many chemicals at a constant rate and to spacially target the release. We have thought it would be worthwhile to learn how to control the release so that it could be turned on and off or adjusted as desired, and in several recent papers we have described neurotransmitter release from a polymer-coated electrode.[1] The neurotransmitter was covalently bound to the polymer backbone so it remained on the polymeric electrode surface until it was released by a pulse of cathodic current.

It was hypothesized that larger quantities of material could be promptly released using a conductive polymer than from the nonconducting polymers previously employed, and described here is the first example of application of conductive polymers to this problem.[2] Many of these polymers can be switched from a conductive ("doped") form containing ions to a neutral insulator state. If during the transformation from the charged to the neutral form the dopant ions were promptly flushed out, then a method for releasing ions could be developed.

The conductive polymer chosen was polypyrrole (PP). A number of electrochemical studies of PP have demonstrated that it can be readily deposited by electrochemical oxidation of pyrrole[3-5] and that the polymer can be cycled electrochemically between the charged and neutral states. Recently the utility of PP as a chloride ion gate membrane was described indicating the potential for success in our endeavor.[6] As dopants we chose ferrocyanide (FCN) or glutamate (Glu). Glu release is of interest to neuroscience and the FCN electroactivity provided a convenient way of studying the conductive films and detecting the excluded material after the reduction of the PP films.

For glutamate delivery, PP holding Glu counterions was needed. Since pyrrole did not polymerize when oxidized by using sodium glutamate as an electrolyte, PP was anodically deposited on a glassy carbon electrode from an aqueous solution containing sodium perchlorate. This coated electrode, which had the voltammetric properties expected from the literature, was then transferred to an aqueous solution containing only sodium glutamate (0.1 M, pH 6.95). A potential/time square wave was applied between the limits of 0.0 and −1.0 (SCE). at −1.0 V the film was reduced; at 0.0 V it was reoxidized. In principle this would force out ClO_4^- and replace it with Glu, and, indeed, the cyclic voltammogram of GC/PP electrodes was changed by this procedure. The fact that the cyclic voltammogram of GC/PP electrode changed when the film was "loaded" with Glu, and was restored to its original shape in a perchlorate solution, encouraged us to carry out a

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(2) Results using other conductive polymers for delivery of glutamate and aspirin have been obtained in this laboratory by R. L. Blankespoor.

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