VOLUME 123, NUMBER 16
APRIL 25, 2001

JOURNAL
OF THE
AMERICAN
CHEMICAL
SOCIETY

Product Studies and Laser Flash Photolysis on Alkyl Radicals Containing Two Different β-Leaving Groups Are Consonant with the Formation of an Olefin Cation Radical

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Received December 19, 2000. Revised Manuscript Received February 20, 2001

Abstract: 1-Bromo-2-methoxy-1-phenylpropan-2-yl (**3**) and 2-methoxy-1-phenyl-1-diphenylphosphatopropan-2-yl (**4**) were generated under continual photolysis from the respective PTOC precursors in a mixture of acetonitrile and methanol. The radicals undergo heterolytic fragmentation of the substituent in the β-position to generate the olefin cation radical (**5**). *Z*-2-Methoxy-1-phenylpropene (**15**) is the major product formed in the presence of 1,4-cyclohexadiene, and is believed to result from hydrogen atom transfer to the oxygen of the olefin cation radical, followed by deprotonation. Laser flash photolysis experiments indicate that reaction between **5** and 1,4-cyclohexadiene occurs with a rate constant of $\sim 6 \times 10^5$ M^{-1} s^{-1}. 2,2-Dimethoxy-1-phenylpropane (**18**) is observed as a minor product. Laser flash photolysis experiments place an upper limit on methanol trapping of **5** at $k < 1 \times 10^3$ M^{-1} s^{-1} and do not provide any evidence for the formation of reactive intermediates other than **5**. The use of two PTOC precursors containing different leaving groups to generate a common olefin cation radical enables one to utilize product analysis to probe for the intermediacy of other reactive intermediates. The ratio of **15**:**18** is dependent upon hydrogen atom donor concentration, but is independent of the PTOC precursor. These observations are consistent with the proposal that both products result from trapping of **5** that is formed via heterolysis of **3** and **4**.

Olefin cation radicals are a family of reactive intermediates that are involved in a broad range of chemical reactions. The scope of reactions extends from synthetically useful transformations (e.g. cycloadditions) to DNA damage.[1,2] The utility of olefin cation radicals in organic synthesis stems from their high rates of reaction (bimolecular rate constants can be as large as 10^9 M^{-1} s^{-1}) with nucleophiles, alkenes, and dienes.[3,4] For synthetic purposes, these reactive intermediates are typically generated via one-electron oxidation of alkenes. The range of ion radicals that can be generated by this approach is limited by the oxidation potential of the alkene, as well as by the fact that the precursors themselves are reaction partners for the olefin cation radical. A method for generating olefin cation radicals containing varying reduction potentials from substrates other

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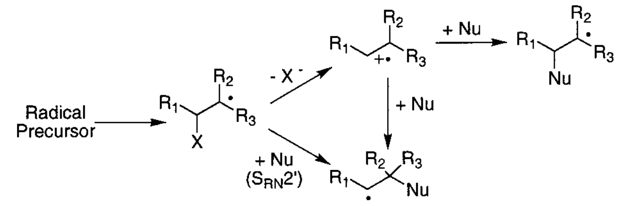
10.1021/ja0042938 CCC: $20.00

Scheme 1

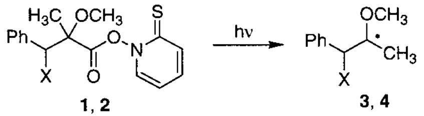


than alkenes would be highly desirable. Nature (in this instance in the form of the effects of ionizing radiation on DNA) has provided the impetus for exploring olefin cation radical generation via heterolysis from the β-position of an alkyl radical (Scheme 1). The feasibility of this reaction has captured the attention of computational chemists and experimentalists. We wish to report herein an investigation, combining product studies and laser flash photolysis (LFP) experiments, of the reactions of two independent precursors to radical cation **5**.

In 1975, γ-irradiation of DNA was proposed to give rise to an olefin cation radical via phosphate monoester elimination following C4′-hydrogen atom abstraction.[5] Pulse radiolysis experiments on model compounds, and more recent studies using chemically modified oligonucleotides, as well as other models, provided compelling evidence for olefin cation radical generation and/or a functionally equivalent nucleophilic substitution reaction ($S_{RN}2'$, Scheme 1).[6-8] The latter process is analogous to an S_N2' reaction, and has been identified in computational experiments as a feasible mechanism for an alkyl radical containing a leaving group in the β-position.[9,10] These studies alerted our groups to the possibility that alkyl radicals, which are readily generated, containing leaving groups in the β-position could serve as synthons for olefin cation radicals. Laser flash photolysis studies have provided a wealth of spectroscopic evidence for the formation of olefin cation radicals via phosphate diester or halide elimination from the β-position of appropriately substituted alkyl radicals.[10-14] The observation of diffusively free cation radicals in these processes is highly dependent upon the polarity of the solvent.[11-14] Evidence for the homolytic substitution mechanism ($S_{RN}2'$) is less ample. Distinguishing mechanisms by product analysis is difficult, because trapping of the olefin cation radical and $S_{RN}2'$ substitution can yield identical products.[11,15] Furthermore, studies that reveal the ratio of products resulting from caged processes relative to freely diffusible species are lacking. We report herein evidence obtained via product analysis and LFP that supports the generation of a diffusively free olefin cation radical as the major reactive intermediate that is responsible for product formation in the case of radical cation **5**. The use of two radical precursors containing different leaving groups in the β-position affirms that a common intermediate, the olefin cation radical, is formed from these species. Furthermore, the use of radicals containing different β-leaving groups enables us to probe for the involvement of reactive intermediates other than a diffusively free cation radical using product studies. Although not all of the products formed can be explained via trapping a diffusively free cation radical by stable molecules, there is no positive evidence for the involvement of other reactive intermediates in product formation.

Results

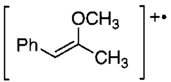
At the time that this project was initiated, laser flash photolysis and product studies had not yet appeared.[10-15] Consequently, not knowing the minimum structural requirements for olefin cation radical formation, a phenyl substituent was incorporated at the β-position to maximize the driving force for β-elimination from the initially formed alkyl radical (eq 1).



1, **2** **3**, **4** (1)

	X
1, **3**	Br
2, **4**	$OP(O)(OPh)_2$

In addition, an alkoxy group at a tertiary radical center was included to model the C4′-position of the furanose ring in DNA where the greatest evidence for β-elimination had been obtained. It should be noted that it was not clear whether the α-methoxy group in the alkyl radical would provide a thermodynamic driving force for β-elimination. Comparing the effects of ether substituents on the oxidation potentials of styrenes and other alkenes, we estimated that the stabilization of the methoxy group on the olefin cation radical (**5**) compared to styrene could be as much as 10.3 kcal/mol.[4b,16] Furthermore, the presence of the methoxy group may facilitate migration of the phosphate group, which could complicate kinetic and product analysis.[17] Efforts to reduce the possibility of migration resulted in examination of a system containing a bromide (**3**) leaving group at the β-position of the original alkyl radical, despite the possibility that β-scission might compete with heterolytic cleavage.[14,18] The β-bromo radical (**3**) could undergo formal rearrangement via heterolysis and subsequent trapping of the olefin cation radical



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[16] The reduction potential of **5** was estimated by considering the oxidation potential of **15**, both of which are unknown. The upper limit for the oxidation potential of **15** is believed to be 1.33 V (versus SCE), and is based upon comparisons to related styrenes whose irreversible oxidation potentials have been measured. The $E_{1/2}^{OX}$(SCE) of β-methyl-4-methoxystyrene = 1.33 V.[4b] The $E_{1/2}^{OX}$(SCE) of α-trimethylsilyloxystyrene = 1.32 V. See: Fukuzumi, S.; Fujita, M.; Otera, J.; Fujita, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10271.

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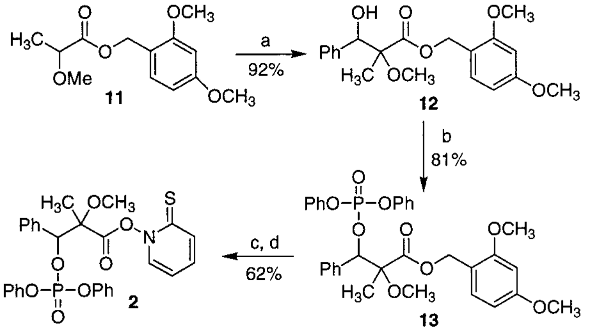
Scheme 3[a]

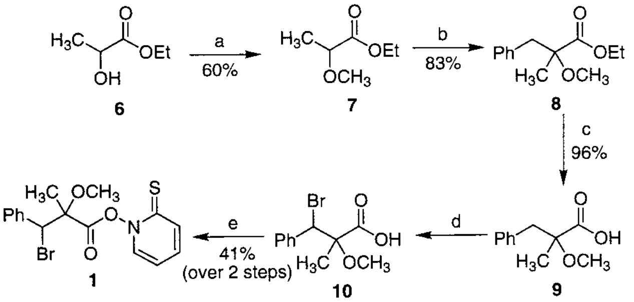


[a] Key: (a) LDA, PhCHO, THF. (b) $(PhO)_2P(O)Cl$, DMAP, CH_2Cl_2. (c) CAN, H_2O:CH_3CN (10:1). (d) PPh_3, 2,2′-dithiopyridine-1,1′-dioxide, CH_2Cl_2.

by the bromide within the solvent cage, but it is highly unlikely that the β-phosphate group would cleave homolytically.[4a,19] Finally, the generation of alkyl radicals with different β-substituents could provide a means for distinguishing between reactive intermediates that are responsible for product formation (*vide infra*).

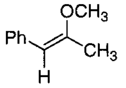
Synthesis of Barton (PTOC, pyridine-2-thione-*N*-oxycarbonyl) Esters and Anticipated Products. PTOCs (**1**, **2**) were chosen as radical precursors, because these molecules undergo homolytic bond scission initiated by long wavelength irradiation to generate carboxyl radicals which decarboxylate on the submicrosecond time scale.[20] The bromo-PTOC (**1**) was synthesized from ethyl lactate (**6**, Scheme 2). The benzylic bromide was introduced by using NBS, and the crude carboxylic acid obtained was transformed into the PTOC (**1**) due to the propensity of **10** to undergo loss of HBr and CO_2 to yield vinyl ethers (**15**, **16**). This facile decarboxylation/elimination dictated the manner in which the phospho-PTOC (**2**) was prepared. To circumvent this problem, following phosphorylation of the aldol product (**12**), the ester was oxidatively cleaved, and the crude acid was carried on to **2** using Mitsunobu conditions (Scheme 3).[13a,21]

Scheme 2[a]



[a] Key: (a) NaH, CH_3I, THF. (b) LDA, BnBr, THF. (c) KOH, EtOH. (d) NBS, CCl_4. (e) PPh_3, 2,2′-dithiopyridine-1,1′-dioxide, CH_2Cl_2.

The vinyl ether was prepared as a 1:1 mixture of geometrical isomers (**15**, **16**) by treating **10** with Hünig's base. The *Z*- (**15**) and *E*- (**16**) isomers were separable by column chromatography and their identities were established with ^{1}H NMR, by comparing the chemical shifts to the data in the literature and by using spectral tables.[22] The vinyl proton in the *E*-isomer is expected to resonate downfield from the *Z* isomer. Osmylation of a *Z*/*E* mixture of β-methylstyrene followed by etherification provided the vicinal ether (**17**) as a mixture of diastereomers.[23] The dimethyl ketal (**18**) was prepared from phenylacetone.[24] 2-Methoxy-3-phenylpropene (**19**) was prepared via titanocene mediated methylenation of the respective methyl ester.[22b] The products derived from hydrogen atom trapping of the alkyl radicals (**20**, **21**) produced from the respective PTOC esters (**1**, **2**) were prepared from **22**, which was obtained by sequential alkylation and reduction of 2-methoxyacetophenone. Finally, 2-methoxy-1-phenylpropane (**23**) was prepared from the corresponding alcohol by alkylation.



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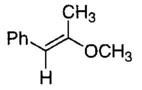

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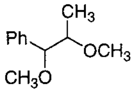

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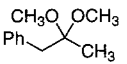

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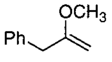

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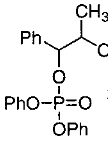

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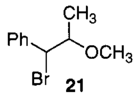

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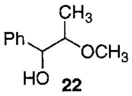

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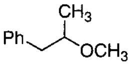

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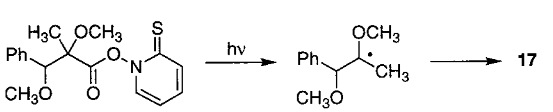
UV−Irradiation of Bromo-PTOC (1) and Phospho-PTOC (2). Samples containing **1** or **2** were freeze−pump−thaw degassed and irradiated in a Rayonet Photoreactor containing λ_{max} = 350 nm lamps for 20 min. The solvent mixture was kept constant (MeOH:CH_3CN, 4:1 (by volume), $E_T(30) = 56.21$ kcal/mol, [MeOH] = 19.75 M) as the type and concentration of other additives were varied.[25] Although varying the concentration of the nucleophile (MeOH) would be a useful mechanistic probe, complications resulting from the strong dependence of formation of diffusively free olefin cation radicals on solvent polarity precluded this.[10−14] The PTOC esters were stable at room temperature in the dark for the period of sample preparation and photolysis, but did undergo some decomposition (up to 30%) upon prolonged exposure (24 h) to these conditions. The dimethoxy-PTOC (**24**) was the exclusive decomposition product observed from **1** and **2**. Photochemically induced decomposition of independently synthesized **24** under the conditions employed for **1** and **2** yielded the vicinal ether (**17**) as a mixture of diastereomers as the sole product attributable to the formation of **25** (eq 2).



24 **25** (2)

Irradiation of **1** and **2** in the presence of independently synthesized potential products revealed that only the vicinal ether (**17**) was stable to the reaction conditions. Phenylacetone was the major product in the absence of amine added as an acid scavenger. All subsequent irradiations were carried out in the

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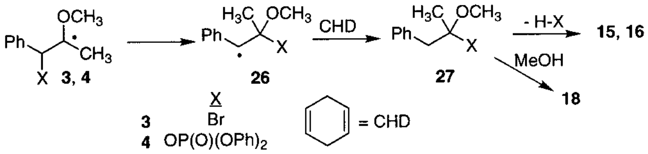
Table 1. Product Distribution in the Presence of 1,4-Cyclohexadiene (CHD) and 3,3,6,6-Tetradeuterio-1,4-cyclohexadiene (d_4-CHD) as a Function of Solvent[a]

			% yield		
PTOC	trap	solvent	**15**	**18**	**23**
1	CHD	MeOH	22.4 ± 1.2	3.7 ± 0.3	3.2 ± 0.2
1	d_4-CHD	MeOH	10.0 ± 1.6	3.7 ± 0.5	2.5 ± 0.2
1	d_4-CHD	d_4-MeOH	11.3 ± 1.5	2.1 ± 0.2	2.9 ± 0.3
2	CHD	MeOH	38.3 ± 2.2	4.4 ± 0.7	–[c]
2	CHD	MeOH	21.6 ± 1.6	4.4 ± 0.7	–[c]
2	d_4-CHD	d_4-MeOH	22.2 ± 1.9	2.3 ± 0.5	–[c]

[a] [PTOC] = 5 mM, [TBP] = 10 mM, [CHD] = [d_4-CHD] = 0.5 M. [b] [MeOH] = 19.75 M, [d_4-MeOH] = 19.73 M, CH_3CN (20 vol %) is a cosolvent. [c] Not observed.

Scheme 4



Scheme 5

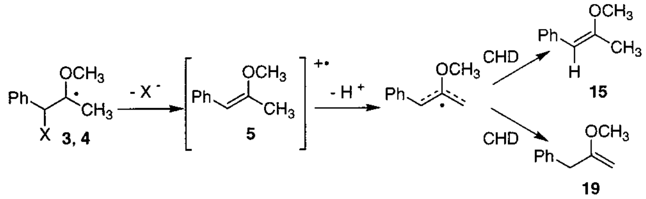


Table 2. The Eeffect of Solvent Deuteration on Deuterium Incorporation in Products[a]

		% ^{2}H		
PTOC	solvent[b]	**15**	**18**	**23**
1	MeOH	3.0 ± 0.6	47.9 ± 0.8	71.0 ± 0.7
1	d_4-MeOH	2.2 ± 0.5	63.1 ± 1.5	82.1 ± 6.5
2	MeOH	2.4 ± 0.4	60.2 ± 0.4	–[c]
2	d_4-MeOH	2.0 ± 0.2	76.9 ± 3.1	–[c]

[a] [PTOC] = 5 mM, [TBP] = 10 mM, [d_4-CHD] = 0.5 M. [b] [MeOH] = 19.75 M, [d_4-MeOH] = 19.73 M, CH_3CN (20 vol %) is a cosolvent. [c] Not observed.

presence of an acid scavenger that would not react with products and intermediates resulting from photolysis. The requirements of poor nucleophilicity and high oxidation potential to avoid reaction with the olefin cation radical (**5**) led us to choose hindered 2,6-di-*tert*-butylpyridine (TBP) as an acid scavenger.[16,26] Similarly, 1,4-cyclohexadiene (CHD) was chosen as a potential hydrogen atom donor, because of concerns that thiols would participate in electron transfer and/or nucleophilic reactions with the olefin cation radical.[27] Despite these precautions, we found that the benzyl vinyl ether (**19**) underwent significant decomposition (~90%) during photolysis of the radical precursors (**1**, **2**).

Irradiation of **1** or **2** (5 mM) in the presence of TBP (10 mM) and 1,4-cyclohexadiene (0.5 M) produced *Z*-2-methoxy-1-phenylpropene (**15**) as the major product (Table 1). Vinyl ether **16** was not observed, and preferential formation of **15** is consistent with molecular mechanics calculations that predict $\Delta\Delta H_f$ of 2.17 kcal/mol favoring the observed isomer.[28] Smaller amounts of dimethyl ketal (**18**) were also observed from both PTOCs, but neither precursor yielded any vicinal ether (**17**). The yields of **15** and **18** obtained from irradiation of the bromo-PTOC (**1**) were consistently lower than those obtained from **2**. Control experiments in which samples of **1** were individually spiked with **15** or **18** prior to photolysis revealed that no more than 2% of **15** decomposed under the reaction conditions.[29] These experiments also indicated that phenyl acetone was the decomposition product of **15**, but not the ketal (**18**). No evidence for decomposition of **18** was obtained from these experiments.[29] Photolysis of the bromo-PTOC also produced 2-methoxy-1-phenylpropane (**23**) in ~3% yield. Control experiments with independently synthesized **21** suggest that **23** is produced from the benzylic bromide under the photolysis conditions. The product analogous to **21** expected from **2** (**20**) could not be detected by GC, and was analyzed for by ^{1}H NMR. Neither **20** nor **23** was observed upon irradiation of **2**.[30] Consistent with the instability noted above, low, variable yields of terminal vinyl ether (**19**) were also observed. It is difficult to quantitate how much **19** is produced during the photolysis. On the basis of mass balances, this vinyl ether could be formed in as great as 71% and 56% yield from **1** and the phosphorylated PTOC (**2**), respectively. However, we consider this unlikely, since **19** is believed to be derived from the allylic radical (Scheme 5), and this intermediate was not formed in high enough yield to be detected by LFP (vide infra).

Photolysis of **1** or **2** (5 mM) in the presence of TBP (10 mM) and d_4-1,4-cyclohexadiene (d_4-CHD, 0.5 M) showed an apparent kinetic isotope effect of ~2 for the formation of **15**, while no effect on the formation of **18** was observed (Table 1). Measurement of the percent ^{2}H incorporation in **15**, **18**, **19**, and **23** showed incomplete isotopic incorporation when d_4-CHD was employed (Table 2).[31] This led us to investigate the possibility of hydrogen/deuterium transfer from methanol to one or more of the intermediates formed upon photolysis of **1** and **2**. The isotopic content in these same products increased when the PTOC esters were photolyzed in d_4-MeOH (19.75 M), but were unaffected by substituting deuterated acetonitrile for its protio analogue. The effect of CHD concentration on the product yield was also determined (Table 3). The proportional relationship of product yields to CHD concentration indicates that CHD is involved in formation of all of the observed products.

Laser flash photolysis (LFP) studies were conducted with PTOC esters **1** and **2**. As with other PTOC esters[32–34] including β-phosphatoxyalkyl radical precursors,[10,12b,13] photolyses with 355 nm laser light cleaved the precursors readily. Photolyses of either **1** or **2** in THF gave the time-resolved spectrum shown

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[26] Trialkylamines were expected to have lower $E_{1/2}^{Ox}$ than **15**. For example, $E_{1/2}^{Ox}$(SCE) of Et_3N = 0.78 V. See: (a) Liu, W.-Z.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 4778. (b) Nelson, S. F.; Hintz, P J. *J. Am. Chem. Soc.* **1972**, *94*, 7114. Pyridines are much less readily oxidized. The $E_{1/2}^{Ox}$(SCE) of pyridine = 2.12 V. See: *CRC Handbook Series in Organic Electrochemistry*; Meites, L., Zuman, P., Eds.; CRC Press: Cleveland, OH, 1974; Vol. 1.

[27] The upper limit for $E_{1/2}^{Ox}$(SCE) of thiols = 1.11 V. See: Asmus, K.-D.; Bonifacic, M. in *S-Centered Radicals*; Alfassi, Z. B., Ed.; John Wiley & Sons: New York, 1999. The $E_{1/2}^{Ox}$(SCE) of 1,4-cyclohexadiene = 1.74 V. See: Shono, T.; Ikeda, A.; Hayashi, J.; Hakozaki, S. *J. Am. Chem. Soc.* **1975**, *97*, 4261.

[28] Calculations were carried out using Spartan (version 5.0.3) at the AM1 level of theory on an SGI Indigo.

[29] See the Supporting Information.

[30] The yield of **20** must be less than 5% based upon the detection limit of the NMR experiment.

[31] The rate constant for reaction of 1,4-cyclohexadiene with alkyl radicals is $<10^5$ M^{-1} s^{-1}. (Hawari, J. A.; Engel, P. S.; Griller, D. *Int. J. Chem. Kinet.* **1985**, *17*, 1215.)

[32] Ha, C.; Horner, J. H.; Newcomb, M.; Varick, T. R.; Arnold, B. R.; Lusztyk, J. *J. Org. Chem.* **1993**, *58*, 1194.

[33] Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684.

[34] Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S. U. *J. Am. Chem. Soc.* **1995**, *117*, 3674.

Table 3. Product Distribution As a Function of 1,4-cyclohexadiene (CHD) Concentration[a]

		% yield			
PTOC	[CHD] (M)	**15**	**18**	**23**	**15:18**
1	0.5	22.4 ± 1.2	3.7 ± 0.3	3.2 ± 0.2	6.1 ± 0.6
1	0.25	18.2 ± 0.5	1.4 ± 0.3	3.0 ± 0.1	13.0 ± 2.8
1	0.125	14.1 ± 0.7	0.8 ± 0.1	2.6 ± 0.1	17.6 ± 2.4
2	0.5	38.3 ± 2.2	4.4 ± 0.7	–[b]	8.7 ± 1.5
2	0.25	33.6 ± 1.1	2.4 ± 0.1	–[b]	14.0 ± 0.7
2	0.125	26.4 ± 1.0	1.2 ± 0.2	–[b]	22.0 ± 3.8

[a] [PTOC] = 5 mM, [TBP] = 10 mM. [b] Not observed.

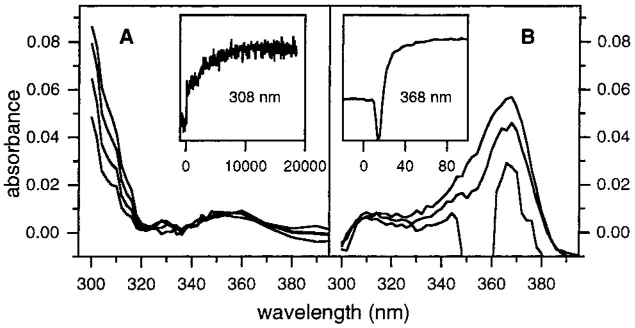

Figure 1. (A) Time-resolved spectrum from photolysis of **2** in THF. The traces are at 0.2, 0.3, 0.5, and 1.1 μs after irradiation with the signal at 50 ns subtracted to give a baseline. (B) Time-resolved spectrum from photolysis of **1** in acetonitrile. The traces are at 20, 30, and 100 ns after photolysis; the negative signal in the trace at 20 ns results because the PM tube has not recovered from the scattered laser light of the photolysis. The insets show typical kinetic traces with time in ns.

in Figure 1a, whereas photolysis of either in acetonitrile gave the spectrum shown in Figure 1b. Photolysis of PTOC ester **1** in acetonitrile containing up to 1 M MeOH gave the same spectrum as observed in neat acetonitrile. The spectrum in Figure 1b is quite similar to those of simple styrene radical cations[4b] and the *p*-methoxy-β,β-dimethylstryene radical cation,[12b] and we ascribe it to radical cation **5**. The spectrum in Figure 1a does not appear to be that of a benzylic radical that should have λ_{max} at about 325 nm,[35] but it is similar to that of the 2-methyl-1-phenylallyl radical;[13b] we tentatively ascribe this spectrum to the 2-methoxy-1-phenylallyl radical. The change in products from radicals **3** and **4** with solvent polarity mirrors the behavior seen with the 1,1-dimethyl-2-(*p*-methoxyphenyl)-2-(diethylphosphatoxy)ethyl radical that gave the benzylic radical migration product in low-polarity solvents and the radical cation in high-polarity solvents.[12b] Our interpretation of the behavior of radicals **3** and **4** is that heterolysis of each gave a radical cation–anion pair that reacted by proton transfer to give the allylic radical in low-polarity THF but dissociated to give diffusively free radical cation **5** in the higher polarity solvents, acetonitrile and MeOH–acetonitrile (4:1). Because all of the trapping studies conducted in this work were performed in the highly polar solvent mixture MeOH–acetonitrile (4:1), we conclude that radical cation **5** was formed from radicals **3** and **4** under the conditions of the product studies.

The amount of radical cation **5** formed from radicals **3** and **4** could be evaluated in the following manner. The intensity of the signal from **5** relative to that of the byproduct of the photolysis reaction, the pyridine-2-thiyl radical, was the same from both **3** and **4** suggesting a high-yield conversion to **5** from both precursor radicals. When **5** was produced from **3** in the presence of tris(*p*-bromophenyl)amine ((p-$BrC_6H_4)_3N$) in acetonitrile, the amine was oxidized to the corresponding aminium cation radical. Using the molar extinction coefficient of the aminium cation radical determined by triplet chloranil oxidation in the same solvent, we estimated the concentration of aminium cation radical produced at the end of the oxidation relative to the concentration of the pyridine-2-thiyl radical byproduct initially produced in the photolysis. In experiments with both PTOC esters **1** and **2**, the relative yield of aminium cation radical was in the range 65–85%. This range represents a minimum yield of **5** from radicals **3** and **4** because we do not know if electron transfer to **5** from (p-$BrC_6H_4)_3N$ is the only reaction pathway. In fact, when the same quantitation studies were attempted with Ph_3N, which is more easily oxidized than (p-$BrC_6H_4)_3N$, the yield of aminium cation radical was in the 40–50% range. The latter results suggest that radical cation **5** reacted in part with Ph_3N by electrophilic addition, presumably to a phenyl group. Irrespective of the details of the reaction pathways with the amine, the yield of aminium cation radical produced from (p-$BrC_6H_4)_3N$ indicates that heterolyses of **3** and **4** were the major, if not only, primary reactions occurring in acetonitrile.

The kinetics of the primary reactions of radicals **3** and **4** were studied in THF and in acetonitrile. Reactions of both in THF were slow enough to follow by LFP with nanosecond resolution methods. At 20 °C, radical **3** reacted with a rate constant of 2.8×10^5 s^{-1}, and radical **4** reacted with a rate constant of 3.4×10^6 s^{-1}. In acetonitrile, both radicals gave radical cation **5** rapidly; the reaction of **4** at 20 °C was too fast to measure with our unit, but an approximate rate constant ($k = 8 \times 10^7$ s^{-1}) was found for radical **3**.

The results of the LFP studies with **3** and **4** are similar to those found with related radicals containing β-leaving groups.[10,12b,13] Specifically, increases in solvent polarity were found to result in accelerations in the rates of reactions and, in some cases, changes from products resulting from concerted reaction pathways or ion pair collapse pathways to diffusively free radical cations. In the earlier work where the products were sensitive to solvent polarity, we concluded that the reactions occurred by initial heterolysis followed by collapse or dissociation of the ion pair, with the latter becoming increasingly efficient as the polarity of the solvent increased.[10,12b] The mechanistic details for **3** and **4** are discussed below, but one can conclude from the LFP kinetic studies that no bimolecular reactions of these radicals are fast enough to compete with the unimolecular processes; in MeOH–acetonitrile (4:1), the lifetime of radical **3** is less than 1 ns, and radical **4** has a shorter lifetime.

LFP studies of reactions of radical cation **5** were conducted by following the decay of the signal at 368 nm in the presence of potential reactants. From studies with varying concentrations of 1,4-cyclohexadiene (CHD) in acetonitrile at 20 °C, a plot of k_{obs} versus concentration of CHD had a slope of $k = 6 \times 10^5$ M^{-1} s^{-1}. We consider this to be an approximate rate constant for reaction of CHD with **5** because biexponential decays were observed at all concentrations of CHD studied. When radical **5** was produced in acetonitrile at ambient temperature in the presence of varying concentrations of MeOH (up to 1 M), we observed no increase in signal decay; the limit for the rate constant for reaction of **5** with MeOH is $k < 1 \times 10^3$ M^{-1} s^{-1}.

Discussion

Initially, a variety of mechanisms involving several reactive intermediates was envisioned to explain the formation of the products described above. Possible mechanisms for the forma-

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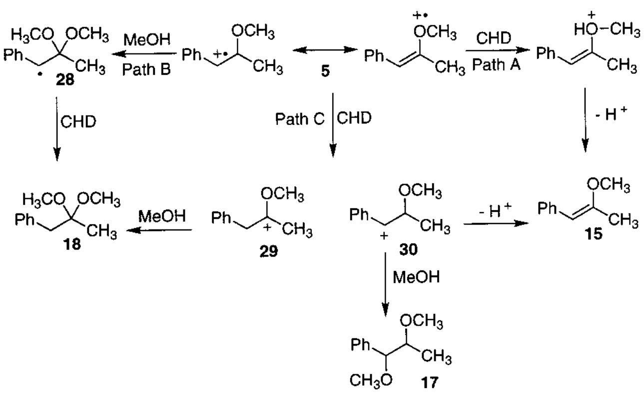
(35) Chatgilialoglu, C. In *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. 2, pp 3–11.

Scheme 6



tion of the major product, vinyl ether **15**, are discussed below: (1) β-scission from **3** and/or **4**; (2) hydrogen atom donation to **3** and/or **4**, followed by elimination of H−X; (3) migration of "X" in the initially formed radical (**3**, **4**), followed by sequential hydrogen atom transfer and β-elimination of H−X (Scheme 4); (4) formation and subsequent hydrogen atom donation to the allyl radical formed via proton abstraction from **5** within the solvent cage by the respective anion (phosphate diester, bromide) (Scheme 5); and (5) sequential hydrogen atom abstraction followed by deprotonation of the resulting cation. Hydrogen atom abstraction could occur at either carbon or oxygen (Scheme 6).

On the basis of the high energy of phosphate radicals, mechanism 1 was deemed unlikely for **4**.[19] Although this mechanism could not be excluded a priori as a contributor to the formation of **15** from the β-bromo radical (**3**), the dependence of the yield of **15** from **1** (and **2**) on the concentration and isotopic content of CHD is inconsistent with this unimolecular pathway. Moreover, LFP experiments indicated that the phosphate and bromo radicals produced equivalent yields of olefin cation radical (**5**), suggesting the β-scission was not occurring in either **3** or **4**.

Product studies and LFP also ruled out mechanism 2 as a viable option. Independent synthesis of **20** and **21** enabled us to eliminate mechanism 2 as the source of **15**. The phosphate triester (**20**) was stable to the reaction conditions. The respective benzylic bromide (**21**) was unstable, but yielded **23** and not **15**. Hydrogen atom transfer to **3** or **4** was shown to be untenable on the basis of the absolute rate constants of heterolysis measured for **3** and **4** ($>10^7$ s^{-1}). Bimolecular trapping by CHD could not possibly compete with these unimolecular processes.[35]

Independent synthesis could not be used to dismiss mechanism 3 (Scheme 4), but further consideration is unnecessary due to the determination by LFP that benzyl radicals are not produced in appreciable yields from reactions of the PTOC esters in acetonitrile. Furthermore, if mechanism 3 was responsible for a significant fraction of **15**, anticipated KIEs for the elimination reaction would have yielded **15** with a much higher level of deuterium incorporation from d_4-CHD than was observed (Table 2). Product studies do not allow us to rule out a migration mechanism completely, on account of the presence of small amounts of deuterium in **15** (Table 2). However, the absence of benzyl radicals in the current LFP experiments (and others) suggests that invoking this pathway would be an unnecessary obfuscation.

Higher levels of deuterium content in the vinyl ether would also be observed if significant amounts of **15** were formed via hydrogen atom donation to the allylic radical (mechanism 4, Scheme 5). The observation of small amounts of **19** from both PTOC precursors does not enable us to eliminate involvement of mechanism 4 in product formation, in which deprotonation of the highly acidic olefin cation radical (**5**) is effected by the counterion in the solvent cage.[1b,36] The small amount of deuterium observed in **15** formed in the presence of d_4-CHD is also consistent with this cage process. LFP experiments provided no evidence that the requisite allylic radical was formed from **3** or **4** in acetonitrile. Nonetheless, we believe the transient observed in the less polar solvent THF was due to this radical, and we cannot exclude formation of small amounts of the allylic radical in more polar media.

Laser flash photolysis unambiguously supports trapping **5** by CHD ($k = 6 \times 10^5$ M^{-1} s^{-1}), which ultimately results in vinyl ether (**15**) formation. Hydrogen atom transfer to **5** can occur to carbon or oxygen (mechanism 5, Scheme 6). The small amount of deuterium in **15** when d_4-CHD is employed (Table 1) could be indicative of a minor contribution of hydrogen atom transfer to the α-carbon relative to the phenyl ring (path C). If hydrogen atom abstraction by the α- and/or β-carbon of **5** provided a major route to **15** (path C, Scheme 6), methanol trapping of **29** and/or **30** to yield the ketal (**18**) and/or vicinal ether (**17**), respectively, was expected to be faster than deprotonation.[37] Absence of nucleophilic trapping product **17**, combined with the formation of **18** in low yield, is inconsistent with hydrogen atom abstraction by the carbon(s) of **5** providing a major contribution to product formation.

The mechanism most consistent with these observations is one in which 1,4-cyclohexadiene (CHD) transfers a hydrogen (deuterium) atom to the oxygen of the olefin cation radical (**5**), followed by deprotonation of the resulting protonated vinyl ether (Scheme 6). Analogous hydrogen atom transfers to cation radicals of ethers and sulfides have been observed in the gas phase, and may be germane to reports of hydrogen atom abstraction by fullerene cation radicals.[38−40] Involvement of CHD in the formation of the vinyl ether is indicated by the effect of deuteration (Table 1), as well as the effect of CHD concentration on the yield of **15** (Table 3). Substitution of d_4-CHD results in approximately a 2-fold reduction in the yield of **15**, independent of the PTOC precursor. The overall observed KIE of ∼2 is a manifestation of primary and secondary effects, and is in-line with those reported for hydrogen atom abstraction by other cation radicals.[41] In addition, the observation of comparable KIEs for the formation of **15** derived from **1** and **2** indicates that the two PTOC esters yield **15** via a common intermediate, the olefin cation radical (**5**). These results are fully consistent with laser flash photolysis studies carried out on **1** and **2**. Reactions of cation radicals in the gas phase led us to investigate the possibility that methanol donates a hydrogen atom to **5**.[38] However, LFP provided no evidence for scavenging the transient assigned to **5**, and established an upper limit for trapping by methanol to be $k = 1 \times 10^3$ M^{-1} s^{-1}. These

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(36) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243.

(37) Thibblin, A. *J. Am. Chem. Soc.* **1989**, *111*, 5412.

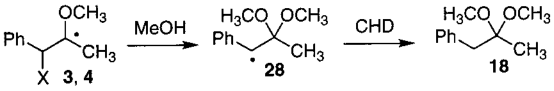
(38) (a) Biermann, H. W.; Morton, T. H. *J. Am. Chem. Soc.* **1983**, *105*, 5025. (b) Morton, T. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 2355. (c) Berruyer-Penaud, F.; Bouchoux, G.; Tortajada, J. *Rapid Commun. Mass Spectrom.* **1992**, *6*, 37.

(39) Chyall, L. J.; Byrd, M. H. C.; Kenttämaa, H. I. *J. Am. Chem. Soc.* **1994**, *116*, 10767.

(40) (a) Siedschlag, C.; Luftmann, H.; Wolff, C.; Mattay, J. *Tetrahedron* **1999**, *55*, 7805. (b) Dunsch, L.; Ziegs, F.; Siedschlag, C.; Mattay, J. *Chem. Eur. J.* **2000**, *6*, 3547.

(41) Primary KIE measurements for McLafferty rearrangements, cation radicals of ethers, and intermediates in the Loeffler−Freytag reaction vary from 1.2 to 1.6. See: (a) Green, M. M. *Tetrahedron* **1980**, *36*, 2687. (b) Morton, T. H. *Tetrahedron* **1982**, *38*, 3195.

Scheme 7



experiments are supported by product studies in which the yield of **15** was unaffected by substituting d_4-MeOH for MeOH (Table 1).

Several pathways can also be envisioned for ketal (**18**) formation: (1) $S_{RN}2'$ reaction with the respective β-substituted radicals (Scheme 7); (2) methanolysis of the product (**27**) resulting from sequential migration of “X” in the initially formed radical (**3**, **4**) and hydrogen atom transfer (Scheme 4); (3) nucleophilic trapping of the olefin cation radical (**5**), followed by hydrogen atom transfer to the benzylic radical (**28**, path B, Scheme 6); and (4) hydrogen atom transfer to **5** at the benzylic position, followed by nucleophilic trapping of the oxocarbenium ion (**29**, path C, Scheme 6).

Ketal formation via the $S_{RN}2'$ mechanism (mechanism 3, Scheme 7) or via migration of X (mechanism 4, Scheme 4) in the originally formed radicals (**3**, **4**) (mechanism 4) is inconsistent with laser flash photolysis experiments. Both pathways require the formation of benzyl radicals from **3** and **4** in competition with production of radical cation **5**. We conservatively estimate that benzylic radical formation in acetonitrile was <10% that of radical cation **5**, and production of benzylic radicals should be even less competitive in the more polar solvent mixture MeOH−acetonitrile (4:1). Furthermore, formation of **18** via pathways 1 and 2 (above) requires derivation of this product from reactive intermediates other than the olefin cation radical (**5**). Product studies show that the ratio of **15**:**18** is identical within experimental error over a range of CHD concentrations (Table 3). If **18** were formed from an intermediate other than olefin cation radical (**5**) the product studies require that the intermediates produced upon irradiation of **1** and **2** fortuitously be trapped at the same rate constant. A simpler proposal is that product **18** is derived from reaction of CHD and/or MeOH with olefin cation radical **5**.

This interpretation is consistent with the product studies. Formation of **18** from olefin cation radical can also be reconciled with LFP studies if one allows for the possibility that hydrogen atom transfer to the carbon atom of **5** occurs to a minor extent (in competition with transfer to oxygen) and occurs exclusively at the less hindered benzylic position. Atom transfer from either CHD or MeOH is consistent with isotopic analysis of **18** (Table 2). The subsequently formed carbocation would then be trapped by the nucleophile.

Regioselective nucleophilic trapping of **5** by MeOH, followed by hydrogen atom transfer may also contribute to the formation of **18**. As per above, isotopic labeling studies indicate that **28** produced would have to be trapped by CHD and MeOH (Table 2).[42] The fact that LFP experiments were only able to place an upper limit on the reaction of **5** with MeOH does not rule out this possibility, given the high [MeOH] (19.75 M) employed. With use of the upper limit for MeOH trapping ($k < 1\times 10^3$ M^{-1} s^{-1}) and the observed rate constant for CHD (0.5 M) trapping ($k = 6 \times 10^5$ M^{-1} s^{-1}), the expected ratio of **15**:**18** would be ≥15, provided this were the sole pathway for the formation of **18**.

Summary

Product studies suggest that both β-substituted radicals (**3**, **4**) generate freely diffusible olefin cation radical **5** in a solution composed of methanol−acetonitrile (4:1). Laser flash photolysis experiments carried out in neat acetonitrile unequivocally demonstrate the formation of **5** in equal amounts from **3** and **4**. The majority of **15** is believed to be formed by hydrogen atom transfer to the oxygen of **5** by CHD, which reacts with diffusively free cation radical at $k = 6 \times 10^5$ M^{-1} s^{-1}. While such reactions are well precedented in the gas phase, they have at most been rarely observed in solution.[38−41] Low yields of ketal (**18**) are also produced. Laser flash photolysis experiments and product studies indicate that nucleophilic trapping of **5** by methanol ($<1 \times 10^3$ M^{-1} s^{-1}) is slow compared with hydrogen atom transfer by 1,4-cyclohexadiene (CHD). The increased “radical” reactivity and decreased “cation” reactivity seen with **5** are important features of radical cations that can be exploited in synthetic applications, and the high radical reactivity in hydrogen atom abstraction might be important in understanding the details of other radical cation reactions with hydrogen atom donors. LFP provides no evidence for the formation of any reactive intermediates other than olefin cation radical, and imply that both products (**15**, **18**) are formed from reaction with **5**. Product studies support this proposal. By employing cation radical precursors containing different leaving groups, we are able to utilize the measurement of product ratios (**15**:**18**) to probe for the involvement of reactive intermediates other than **5**. The observation that **1** and **2** produce ratios of **15**:**18** that are within experimental error of each other supports the proposal that both products are derived from a common reactive intermediate, the olefin cation radical.

Experimental Section

Detailed experimental procedures are provided in the Supporting Information.

Acknowledgment. We are grateful for research support from the National Institutes of Health (CA60500 to D.C., GM-54996 to M.M.G.) and the National Science Foundation (CHE-9986200 to D.C., CHE-9732843 to M.M.G., CHE-9981746 to M.N.). Mass spectra at CSU were obtained on instruments supported by the NIH shared instrumentation grant GM-49631.

Supporting Information Available: Experimental procedures for the synthesis of PTOC esters and products derived from them as well as procedures for the photolysis of PTOC esters and subsequent analysis, including product stability studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[42] The absolute bimolecular rate constant for reaction between CHD and benzyl radical was estimated to be $<10^2$ M^{-1} s^{-1} (see ref 31.). The respective rate constant for reaction of a benzyl radical with methanol has not been reported, but is expected to be less than that for CHD. We believe that the high concentrations of the reagents ([CHD] = 0.5 M, [CH_3OH] = 19.75 M) help overcome these kinetic barriers.