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Direct Detection of Ion Pair Formation and Collapse in a Migration Reaction of a β-Phosphate Radical

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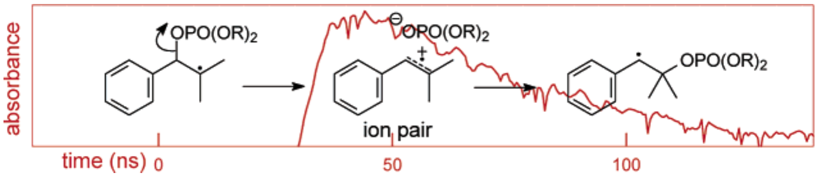
ABSTRACT



In solutions of trifluorotoluene or toluene containing 2,2,2-trifluoroethanol, the β-phosphate radical heterolyzed to give a detectable ion pair, identified as a solvent-separated species. Rate constants for the radical fragmentation reaction forming the ion pair, for ion pair collapse, and for diffusive escape to free ions were measured. The kinetics and entropy of activation for fragmentation indicate that the rearrangement reaction occurs by a heterolysis pathway in all solvents.

Heterolytic fragmentation reactions of radicals containing leaving groups adjacent to the radical center produce alkene radical cations under nonoxidative conditions. Such reactions are known in diverse settings, including strand cleavage of DNA by drugs under anaerobic conditions[1] and organic synthesis.[2,3] The pathway for one-atom migrations of ester groups in β-ester radicals might involve a radical heterolysis reaction that gives a radical cation−anion pair followed by ion recombination. For many such rearrangements, however, activation parameters and stereochemical labeling studies suggested that the reactions were concerted.[2] Concerted pathways for migrations also were found computationally,[4] and, indeed, computational results indicate that concerted or associative pathways are available for any reaction of a radical with a β-leaving group, including eliminations and nucleophilic substitutions.[5]

As synthetic applications of radicals with β-leaving groups have increased in number,[3] the mechanistic details of their reactions have become a more important subject. A concerted migration of a group would avoid side reactions, whereas migration via an intermediate ion pair would compete with reduction and nucleophilic capture of the radical cation. We report here direct spectroscopic detection of formation and collapse of ion pairs formed in a migration reaction of a β-phosphate radical in high-polarity media. The results indicate that a common heterolysis pathway for radical isomerization exists in solvents of high and low polarity.

The β-phosphate radical **1** was produced in laser flash photolysis (LFP) studies from the corresponding PTOC ester precursor (Scheme 1 and Supporting Information).[6,7] Radical **1** is known to rearrange to benzylic radical **2** in low- and medium-polarity solvents without formation of detectable intermediates.[6] When radical **1** was produced in mixtures of toluene or (trifluoromethyl)benzene (trifluorotoluene, TFT) containing 2,2,2-trifluoroethanol (TFE) or 2,2,3,3,4,4,5,5-

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[1] Burger, R. M. *Chem. Rev.* **1998**, *98*, 1153−1169.

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

[3] Crich, D. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2; pp 188−206.

[4] Zipse, H. *J. Am. Chem. Soc.* **1997**, *119*, 2889−2893. Zipse, H. *J. Am. Chem. Soc.* **1997**, *119*, 1087−1093.

[5] Zipse, H. *Acc. Chem. Res.* **1999**, *32*, 571−578.

[6] 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.

[7] Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X. H.; Newcomb, M.; Whitted, P. O. *Tetrahedron* **1999**, *55*, 3317−3726.

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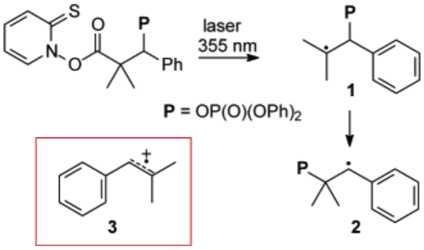
Scheme 1



octafluoropentan-1-ol, we observed rapid formation and biexponential decay of a transient (Figure 1). Radical cation **3** was identified as the transient in both the fast and slow decay processes. The same spectrum was obtained from both decay processes and also from heterolysis of the analogous β-mesylate radical (Figure 2 and Supporting Information), and these spectra matched that reported for **3**, which has λ_{max} at 386 nm.[8]

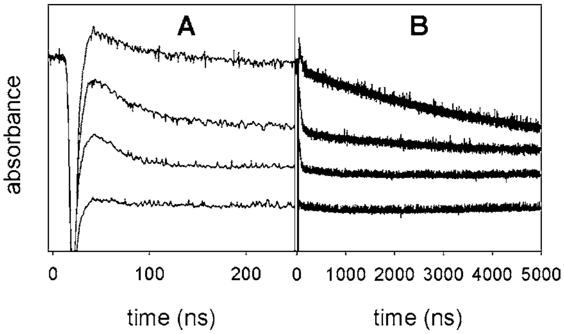


Figure 1. Kinetic traces at $\lambda = 386$ nm shown on two time scales for reactions of radical **1** in TFT solutions containing, from the top, 10, 5, 2.5, and 1% TFE.

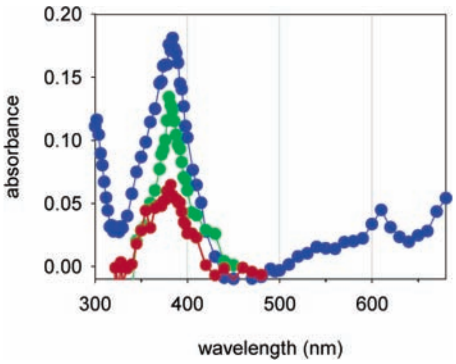


Figure 2. Spectra of radical cation **3**. Blue: spectrum of diffusively free **3** from reaction of the mesylate analogue of radical **1** in 2.5% TFE in TFT. Green: spectrum of diffusively free **3** from radical **1** in 10% TFE in TFT (3×, decay spectrum from 0.3 to 4.5 μs). Red: spectrum of ion-paired **3** from radical **1** in 10% TFE in TFT (3×, decay spectrum from 46 to 200 ns).

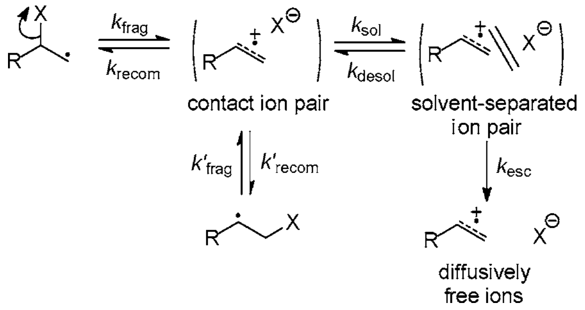
The rapid decay process apparent in Figure 1A was too fast for a bimolecular reaction ($k > 1 \times 10^7$ s^{-1}) and must result from collapse of a short-lived ion pair. The slower decay process had about the same rate constant ($k \approx 2 \times 10^5$ s^{-1}) as that reported for decay of diffusively free radical cation **3**, produced by photoejection from the corresponding styrene in TFE solvent.[8] The measured rate constants for growth (k_{form}) and fast decay (k_{decay}) of **3** are listed in Table 1. When diffusively free radical cation **3** was observed, we used the ratio of free radical cation to total radical cation formed in the ion pair to divide the decay rate constant into a collapse rate constant ($k_{collapse}$) and a diffusive escape rate constant (k_{escape}). Solvent polarity, as measured on the $E_T(30)$ solvatochromatic scale,[9] also is listed in the table. As solvent polarity increased, the rate constants for formation of radical cation **3** and for escape from the ion pair increased, and the rate constant for ion pair collapse decreased.

Table 1. Rate Constants for Reactions of 1[a]

% TFE[b]	$E_T(30)$[c]	k_{form}	k_{decay}	$k_{collapse}$	k_{escape}	τ (μs)[d]
10	56.2	>200	18	7	11	0.09
5	55.6	180	22	16	6	0.17
2.5	55.0	150	35	31	4	0.25
1	53.8	115	50	50	<1	
OFP[e]	53.2	100	70	70	<1	
5%, PhMe[f]	51.3	90	50	50	<1	

[a] Rate constants at 20 ± 2 °C in units of 10^6 s^{-1}. [b] Percentage of TFE by volume in TFT unless noted. [c] Measured $E_T(30)$ value. [d] Lifetime of ion pair defined as $1/k_{escape}$. [e] 2,2,3,3,4,4,5,5-Octafluoropentan-1-ol (0.2 M) in TFT. [f] TFE (5% by volume) in toluene.

Scheme 2



The kinetic results and yields (see below) indicate the complex ion pair model for radical heterolysis reactions shown in Scheme 2. The heterolysis reaction gives a contact ion pair (CIP) that can collapse to the original radical or its isomer or can solvate to a solvent-separated ion (SSIP), and the SSIP can return to the CIP or further solvate to give diffusively free ions. The varying yields of transient radical

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[8] Johnston, L. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1993**, *115*, 6564−6571.

[9] Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319−2358.

cation **3** with solvent polarity, apparent in Figure 1, require that a very short-lived and undetected species, i.e., the CIP with $\tau < 1$ ns, exist but collapse to rearrangement product in competition with formation of the SSIP. The detectable transient ion pair with τ in the range of 100−250 ns is the SSIP. Short lifetimes for the CIP, reflecting sub-nanosecond solvation phenomena, and longer lifetimes for the SSIP are expected.[10]

The SSIP lifetimes found in this work are exceptionally long for a polar solvent, but they are similar to those found in low-polarity solvents.[10] We speculate that the solvent mixtures “de-mixed” around the incipient ion pair to give a high-polarity local solvent and a lower polarity bulk solvent. This conclusion is supported by the observation of a highly nonlinear plot of $E_T(30)$ versus solvent composition (Supporting Information), which is a signature of solvent demixing in the immediate vicinity of the zwitterionic salt used to measure $E_T(30)$. Thus, high local solvent polarity resulted in fast fragmentations of **1**, whereas the diffusive escape rate constants for the SSIP reflect the lower polarity of the bulk medium.

The ion pair model in Scheme 2 is consistent with the observed yields of ion pairs. The maximum percentage yields of radical cation **3** expected on the basis of measured rate constants were obtained from kinetic simulations, and these values are listed in the “predicted” column in Table 2. The “found” column in Table 2 lists the observed percentage yields of **3** in the ion pairs. The difference between these two values is the percentage of **3** in the CIP that collapsed to rearranged product **2** without solvating to the SSIP. From these values, one can calculate the partitioning of the CIP between collapse and solvation, and these calculated partitioning ratios are given in Table 2. The CIP recombination reaction was faster than solvation in all cases and became increasingly efficient as the solvent polarity decreased. A limit for the CIP recombination reaction in the three lower polarity solvents in Table 2 is $k'_{recom} > 1 \times 10^9$ s^{-1}; this lower limit results from the requirement that CIP collapse is 10−20 times faster than solvation to the SSIP, which in turn must be at least as fast as the measured rate of ion pair formation listed in Table 1.

Table 2. Predicted and Observed Yields of Radical Cation 3[a]

% TFE[b]	$E_T(30)$	predicted	found	partitioning[c]
10	56.2	>80	40	<1:1.3
5	55.6	75	16.5	1:4
2.5	55.0	68	13	1:4
1	53.8	59	2.5	1:20
OFP[d]	53.2	44	2	1:20
5%, PhMe[e]	51.3	48	4.5	1:10

[a] Maximum percentage yield of **3** predicted from rate constants and observed experimentally. [b] Percentage of TFE by volume in TFT unless noted. [c] Partitioning ratio for the CIP between formation of the SSIP and collapse to **2**. [d] 2,2,3,3,4,4,5,5-Octafluoropentan-1-ol (0.2 M) in TFT. [e] TFE (5% by volume) in toluene.

Variable-temperature studies were performed in a solution of 5% TFE in toluene. In this solvent mixture, the ion pair collapsed to product radical **2**, and no diffusively free radical cation **3** was formed. The rate constants for formation of **3** were described by $\log k_{form} = (11.0 \pm 0.3) - (4.2 \pm 0.4)/\theta$ (errors are 2σ, $\theta = 2.3RT$ kcal/mol), and the rate constants for ion pair collapse were described by $\log k_{decay} = (13.6 \pm 0.5) - (8.0 \pm 0.5)/\theta$. Note that, in this case, the “collapse” reaction involves two processes, desolvation of a solvent-separated ion pair and true collapse of the contact ion pair to rearranged product **2**, and the desolvation step must be the slower reaction because CIP collapse has $k'_{recom} > 1 \times 10^9$ s^{-1} (see above). Thus, the relatively high activation energy measured for the collapse reaction is the energy required to desolvate the ions, and the large entropy term in this process reflects liberation of tightly bound solvent molecules.

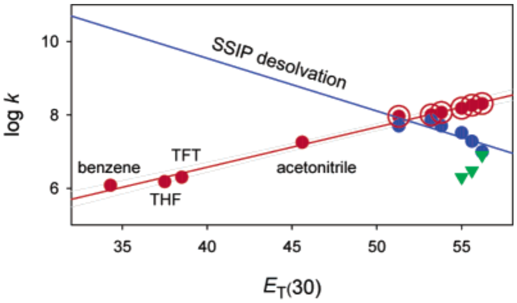

Figure 3. Rate constants for reactions of radical **1** at 20 °C from ref 6 and the present work (red circles labeled with the solvent) and from Table 1 (red double circles), rate constants for SSIP desolvation (blue), and rate constants for ion pair escape (green). The regression line for the rate constants for reactions of **1** shows the 99% confidence interval in gray.

The kinetic results in this work combined with those for rearrangement of radical **1** to radical **2** in low- and medium-polarity solvents[6] indicate that reactions of **1** proceed by initial heterolytic fragmentation in all solvents. Figure 3 contains plots of rate constants as a function of solvent polarity as determined by $E_T(30)$ values.[9] The combination of fragmentation rate constants in high-polarity media and rearrangement rate constants in low- and medium-polarity solvents displays an excellent correlation with $E_T(30)$, indicating a common mechanism in all solvents. Similar conclusions were reached for other β-phosphate radical reactions, where rearrangement products and/or radical cations were observed as a function of solvent polarity.[11] A common mechanism is also suggested by the entropic factor found for reaction of **1**. Specifically, the log $A = 11$ value

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[10] Zhou, J. W.; Findley, B. R.; Teslja, A.; Braun, C. L.; Sutin, N. *J. Phys. Chem. A* **2000**, *104*, 11512−11521. Devadoss, C.; Fessenden, R. W. *J. Phys. Chem.* **1990**, *94*, 4540−4549. Vauthey, E.; Parker, A. W.; Nohova, B.; Phillips, D. *J. Am. Chem. Soc.* **1994**, *116*, 9182−9186.

[11] (a) Whitted, P. O.; Horner, J. H.; Newcomb, M.; Huang, X. H.; Crich, D. *Org. Lett.* **1999**, *1*, 153−156. (b) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X. H.; Yao, Q. W.; Zipse, H. *J. Am. Chem. Soc.* **1999**, *121*, 10685−10694.

for ion pair formation in 5% TFE in toluene is the same as the log A values found for rearrangement of **1** to **2** in low-polarity (THF) and medium-polarity (CH_3CN) solvents.[6]

The rate constants for collapse of the ion pair, although limited in number, also appear to correlate with $E_T(30)$ values (Figure 3). The measured values are the rate constants for the slow step in conversion of the SSIP to product radical **2**, which, as noted above, is desolvation of the SSIP to give the CIP. For acetonitrile, the extrapolated SSIP desolvation rate constant would be $k_{desol} \approx 1 \times 10^9$ s^{-1}, which is 2−5 times faster than diffusive escape rate constants for ion pairs in this solvent.[12] Thus, one would predict that, even if the SSIP were formed in CH_3CN, free ions would not be observed in this solvent. Consistent with this prediction, radical **1** rearranged to radical **2** in acetonitrile without formation of a detectable amount of radical cation **3**.[6]

The CIP partitioning ratios in Table 2 indicate that the rate constants for collapse of the CIP will be much larger than the rate constants for solvation to give the SSIP in low-polarity solvents. If the CIP collapse rate constants exceed rotational correlation times (ca. $10^{11}-10^{12}$ s^{-1}), then stereochemical information would be preserved even when the isolated radical cation is achiral; that is, a stereochemical memory effect is predicted for the CIP in low-polarity medium.[13] Such behavior was found in studies of a system related to radical **1** reported by Crich and co-workers. That group found no stereochemical scrambling in benzene for migration of a phosphate group that converted a homoallylic radical to an allylic radical, whereas some stereochemical scrambling was found when the reaction was conducted in *t*-BuOH, a medium-polarity solvent.[14]

The combined results indicate that isomerization of radical **1** to radical **2** is likely to proceed by heterolysis reactions in all solvents. Ion pairs and/or free ions are observed in high-polarity solvents but not in solvents of medium polarity, where the rate of SSIP desolvation exceeds the rate of escape from the ion pair. In low-polarity solvents, the rate of CIP collapse will exceed that of solvation to the SSIP, and stereochemical memory effects mimicking concerted rearrangement reactions can be observed.

This work provides kinetic information for the very fast ion pair phenomena involved in a radical heterolysis reaction and establishes an ion pair model with some predictive aspects. One should expect reactivity patterns similar to those found for radical **1** in other radicals containing β-leaving groups, with the rate constants for various processes offset according to the stability of the incipient radical cation and anion. Thus, the *p*-methoxyphenyl analogue of radical **1** gave some diffusively free radical cation in medium-polarity solvent, apparently due to smaller CIP collapse and SSIP desolvation rate constants relative to those of **1**, reflecting the increased stability of the radical cation.[11a] In a similar manner, the mesylate analogue of radical **1** gives high yields of diffusively free radical cation **3** relative to those obtained from **1** due to the increased stability of the anionic group.[15] Reduced stability of either the radical cation or the anion is expected to have the opposite effect, with slower overall heterolysis reactions, less efficient production of diffusively free radical cations, and an onset of stereochemical memory effects in medium-polarity solvents. Stereoselective reactions have provided the primary evidence for concerted migrations of β-ester radicals,[2] but they are readily rationalized in the context of heterolysis reactions proceeding through short-lived CIPs.[16]

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Supporting Information Available: Synthetic details and NMR spectra for the radical precursor to the mesylate analogue of **1**, description of LFP studies, and a plot of measured $E_T(30)$ values for TFE mixtures in TFT. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Gould, I. R.; Farid, S. *Acc. Chem. Res.* **1996**, *29*, 522−528. Taxil, E.; Bagnol, L.; Horner, J. H.; Newcomb, M. *Org. Lett.* **2003**, *5*, 827−830. Gould, I. R.; Ege, D.; Moser, J. E.; Farid, S. *J. Am. Chem. Soc.* **1990**, *112*, 4290−4301. Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402−5410.

[13] Crich, D.; Ranganathan, K. *J. Am. Chem. Soc.* **2002**, *124*, 12422−12423.

[14] Crich, D.; Yao, Q. W.; Filzen, G. F. *J. Am. Chem. Soc.* **1995**, *117*, 11455−11470. Crich, D.; Escalante, J.; Jiao, X. Y. *J. Chem. Soc., Perkin Trans. 2* **1997**, 627−630.

[15] Bagnol, L.; Horner, J. H.; Newcomb, M. Unpublished results.

[16] Unusual solvent character of the mixtures of TFE in aromatic solvents found in this work also deserves note. The mixtures act as highly polar solvents for ion-forming reactions but as low-polarity solvents for ion pair escape processes. This behavior permitted direct detection of ion pairs with exceptionally long lifetimes, a property that can be exploited in studies of many ion pair reactions. We note that 5% of the polar solvent TFE in toluene and in TFT appeared to result in a constant offset of the polarity of the parent solvents (see Figure 3), suggesting that mixtures of TFE in solvents less polar than toluene might increase the operating polarity range of these exotic mixtures and provide media in which ion pairs have even longer lifetimes than those found here.