

Radical Heterolysis Reactions. Dynamics of Formation, Collapse, and Solvation of Ion Pairs Determined by a Competition Kinetic Method[†]

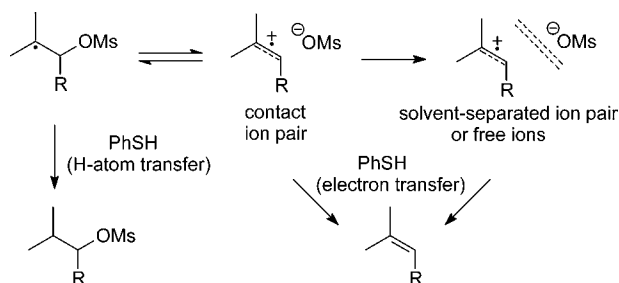
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ABSTRACT



The kinetics of radical heterolysis reactions, including rate constants for radical cation–anion contact ion pair formation, collapse of the contact pair back to the parent radical, and separation of the contact pair to a solvent-separated ion pair or free ions were obtained in several solvents for a β -mesyloxy radical. Rate constants were determined from indirect kinetic studies using thiophenol as both a radical trapping agent via H-atom transfer and an alkene radical cation trapping agent via electron transfer.

Radicals containing β -leaving groups react in substitution and rearrangement reactions that mimic reactions of closed-shell molecules but are much faster.^{1,2} The reactions occur by heterolytic pathways that initially give an alkene radical cation–anion pair, providing a nonoxidative entry to radical cations that has useful synthetic applications.^{3–6} The radical

cation can be produced in an inherently basic or reductive environment, and complete regioselectivity in radical cation generation is possible even when high reactivity donor groups are present in the molecule. Moreover, high stereoselectivity is possible in substitution reactions and has been demonstrated in processes that involve putative achiral radical cations,^{6,7} indicating that reactions of the ion pair can be faster than molecular correlation times.

The utility of radical heterolysis reactions in synthesis will increase with better understanding of the kinetics of various reactions. Rate constants for radical heterolysis reactions

[†] This paper is dedicated to Prof. Bernd Giese in honor of his receipt of the 2006 Tetrahedron Prize.

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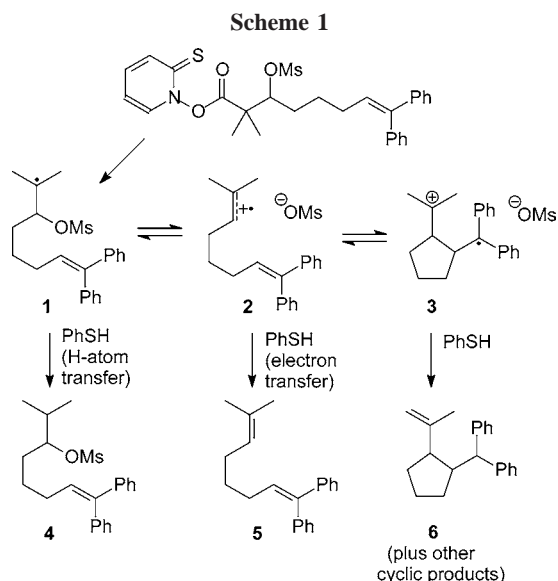
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obviously are important, but the rate constants for reactions of the transient radical cations^{6,8} and their first-formed ion pairs also are necessary for planning purposes. Little kinetic information is known for reactions of ion pairs composed of a radical cation and a closed-shell anion.

We report here rate constants for reactions of a radical containing a β -mesylate group in various solvents including rate constants for the initial heterolysis reactions that give a contact ion pair, for collapse of the contact ion pair back to the neutral radical, and for separation of the contact ion pair to the solvent-separated ion pair. Thiophenol has been employed as a trapping agent for radical heterolysis reactions studied by indirect kinetics methods,^{4,9} and we demonstrate that PhSH can be used not only for timing the initial heterolysis reactions but also for timing reactions of the ion pairs formed in the heterolyses. We are not aware of previous calibrations of such radical cation–anion pair dynamics.

We studied the β -(methanesulfonyloxy)alkyl radical **1** (Scheme 1). The diphenylethenyl group in **1** was incorporated



in part for use in direct kinetic studies of cyclization reactions, which are reported elsewhere.¹⁰ Radical **1** was produced from its PTOC ester radical precursor (Scheme 1).¹⁰ PTOC esters are photosensitive and react in radical chain reactions with thiyl radicals,¹¹ and we initiated reactions by visible light photolysis. Reactions were conducted at ambient temperature with varying concentrations of thiophenol.

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The reactions of interest are shown in Scheme 1. Radical **1** gave radical cation **2**, which cyclized reversibly to distonic radical cation **3**.¹⁰ Thiophenol reacted with **1** by H-atom transfer to give mesylate **4** and with radical cations **2** and **3** to give acyclic product **5** and, in small amounts, cyclic products represented as **6**. Formation of **5** involves an electron transfer from PhSH to radical cation **2**. The mechanism for formation of **6** is not known with certainty but apparently involves a rate-limiting, diffusion-controlled reaction of PhSH with the distonic radical cation **3**, most likely deprotonation of **3** to give a diphenylalkyl radical that subsequently abstracts a hydrogen atom from PhSH to give product **6**.

Product yields were determined by HPLC analysis. In the low reactivity solvents benzene, trifluorotoluene (TFT), and methylene chloride, the total yields of **4** + **5** + **6** were high, approaching quantitative yields. In a reactive solvent such as THF, the total yields were reduced considerably, presumably due to alkylation of the solvent by the radical cations.

Figure 1 shows results obtained in TFT. The ratio of mesylate product **4** to solvolysis products **5** + **6** is plotted

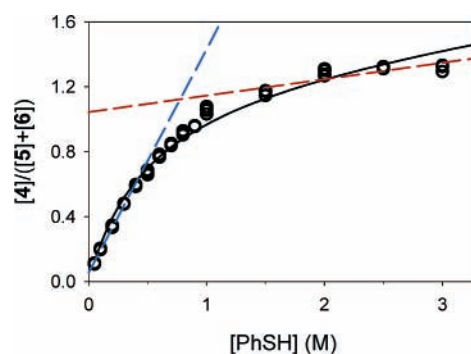
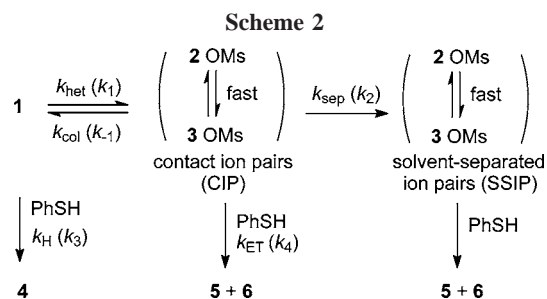


Figure 1. Product ratios from reactions of radical **1** in $PhCF_3$ solutions containing thiophenol. The solid black line is the fit of the data solved by eq 1. The dashed lines are linear least-squares fits for data at ≤ 0.4 M PhSH (blue) and ≥ 1.5 M PhSH (red).

against the concentration of PhSH. The ratio of **5** to **6** was relatively constant at all concentrations of PhSH, indicating that cyclization of **2** to **3** was reversible and that the rate constants for these reactions were large.¹⁰ At low concentrations of PhSH, little mesylate **4** was obtained and extrapolation of the ratio $4/(5 + 6)$ to infinite dilution of PhSH had nearly a zero intercept, as expected for irreversible fragmentation of radical **1**. As the PhSH concentration was increased, however, the plot of the ratio of mesylate **4** to radical cation-derived products **5** and **6** was markedly curved. For the product ratios obtained with PhSH concentrations of 1.5 M and greater, extrapolation of the product ratios to infinite dilution of PhSH gave a large intercept, requiring equilibration between radical **1** and radical cations **2** and **3**.

The results require the kinetic picture shown in Scheme 2. Radical **1** must fragment to give an ion pair, presumed to be a contact ion pair (CIP), that can collapse back to the



radical. At high concentrations of PhSH, radical **1** and the CIP are the only species formed in appreciable amounts, PhSH trapping of radical **1** is important, and PhSH trapping of the CIP is faster than solvation. The extrapolated non-zero intercept for the product ratio from the high PhSH concentration studies (red line in Figure 1) is a clear indication of a fast equilibration between **1** and the CIP. At low concentrations of PhSH, an irreversible process dominates. Thiophenol trapping of the CIP is slow relative to other processes because the concentration of PhSH is small. The CIP solvates to give a solvent-separated ion pair (SSIP) or diffusively free ions, and reactions of the radical cations in SSIP or free ions with PhSH eventually give products **5** and **6**. Thus, the yield of **4** is small at low PhSH concentrations, and the intercept for the product ratio at low concentrations of PhSH (blue line) is nearly zero.

A steady-state approximation for the concentration of the CIP in Scheme 2 gives the kinetic expression in eq 1,

$$\frac{[\mathbf{4}]/([\mathbf{5}] + [\mathbf{6}])}{[\mathbf{PhSH}]} = \frac{k_3[\mathbf{PhSH}] \times (k_{-1} + k_2 + k_4[\mathbf{PhSH}])}{k_1k_2 + k_1k_4[\mathbf{PhSH}]} \quad (1)$$

where the numbered rate constants are those in Scheme 2 and [PhSH] is the thiophenol concentration. Equation 1 requires that radical cation products **2** and **3** rapidly equilibrate, which was demonstrated experimentally by the finding that the ratio of acycle **5** to cycle **6** in a given solvent was only slightly changed with PhSH concentration. Iterative least-squares solution of the data via eq 1 gave the solid line in Figure 1. In total, we studied reactions in four solvents and two mixtures with up to 3 M PhSH. In all cases, the data was fit to eq 1 (Figure 2). Varying the initial parameters for the regression analyses by a factor of 4 resulted in failures for the fits to converge, and multiple sets of rate constants that described the data were not found; this indicates that the range of solutions was narrow.

The kinetic analysis gives relative rate constants. Absolute rate constants for k_{het} , k_{col} , and k_{sep} require that the values for the PhSH trapping reactions are known. For reactions of radical **1** with PhSH to give mesylate **4**, we used the value of $k_{\text{H}} = 1.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.¹² For electron-transfer trapping

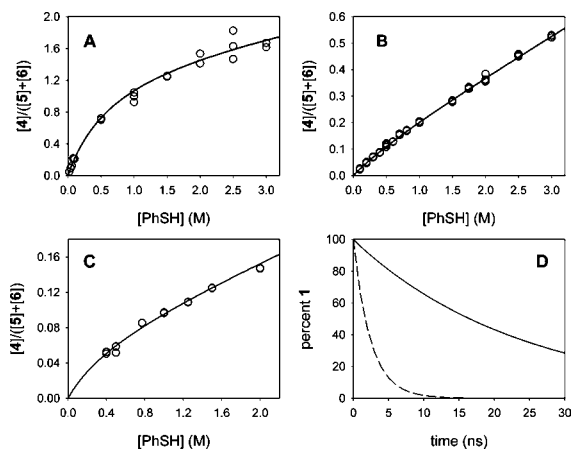


Figure 2. (A–C) Product ratios from reactions of radical **1** in benzene (A), CH_2Cl_2 (B), and CH_3CN (C) where the lines are fits according to eq 1. (D) Percentage of radical **1** as a function of time in benzene (solid line) and in CH_2Cl_2 (dashed line).

of radical cations **2** and **3** by PhSH, we assumed that the reactions were diffusion-controlled on the basis of the large difference in the oxidation potentials of 2-methyl-2-butene ($E_{1/2} = 2.08 \text{ V vs SCE}$)¹³ and PhSH ($E_{\text{ox}} = 1.08 \text{ V vs NHE}$).¹⁴ A diffusional rate constant for PhSH of $k_{\text{ET}} = 2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ was calculated from the von Smulochowski equation¹⁵ and the Stokes–Einstein equation.¹⁶ That value agrees with the rate constant for reaction of PhSH with the chlorobutane radical cation.¹⁷

Solutions of the data with the rate constants for PhSH reactions described above gave the results listed in Table 1. The second and third columns in the table give the dielectric constant (ϵ)¹⁸ and $E_{\text{T}}(30)$ solvent polarity values¹⁹ for each solvent. The equilibrium or pseudo-equilibrium between the CIP and radical **1** affects the observed rate of decay of the radical, and column 8 of Table 1 contains the half-life for decay of the radical at ambient temperature if formation of the SSIP or free ions is irreversible. The effect is demonstrated in Figure 2D for reaction of radical **1** in benzene and in CH_2Cl_2 , where the rate constants for heterolysis are essentially the same but those for CIP collapse differ by 1 order of magnitude. Column 9 lists the average amount of mesylate product **4** that was obtained when radical **1** reacted in the presence of 1 M PhSH in the various solvents, a practical ramification of the various kinetic values.

For the pure solvents we studied, the half-life for decay of radical **1** decreased as the solvent polarity increased, as

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Table 1. Rate Constants for Radical Heterolysis and Ion Pair Reactions Determined from the Kinetic Model in Scheme 2^a

solvent	ϵ^b	$E_T(30)^c$	k_{het}	k_{coll}	K_{het}^d	k_{sep}	$t_{1/2}^e$ (ns)	% 4 ^f
benzene	2.3	34.3	0.7 ± 0.4	220 ± 170	0.003	14 ± 4	16	49
PhCF ₃ (TFT)	9.0	38.5	1.0 ± 0.2	260 ± 70	0.004	10 ± 1	18	51
CH ₂ Cl ₂	8.9	40.7	0.6 ± 0.2	12 ± 4	0.06	17 ± 5	1.7	17
CH ₃ CN	35.9	45.6	2.1 ± 0.3	30 ± 10	0.07	10 ± 5	1.3	9
TFT/0.5% TFE ^g		52.8	0.9 ± 0.1	50 ± 10	0.02	7 ± 2	6	26
TFT/1% TFE ^g		53.8	2.7 ± 0.3	60 ± 10	0.04	7 ± 2	2.4	10

^a Second-order rate constants in units of 10^9 s^{-1} . ^b Dielectric constant at 25 °C.¹⁸ ^c $E_T(30)$ values from ref 19 for pure solvents and measured for mixtures of TFE in TFT. ^d Heterolysis equilibrium constant. ^e Half-life for decay of radical **1** at ambient temperature. ^f Percentage of mesylate **4** obtained from reactions of **1** in the presences of 1 M PhSH. ^g TFE = 2,2,2-trifluoroethanol.

judged by $E_T(30)$ values. The effect was due mainly to changes in the rate constants for CIP collapse instead of those for heterolysis of radical **1**. In more polar solvents, barriers for ionic collapse increase because the polar solvent is structured around the ions, and CIP lifetimes should increase.²⁰

When 2,2,2-trifluoroethanol (TFE) was added in small amounts to TFT, the solvent polarity as evaluated by $E_T(30)$ solvent polarity measurements changed dramatically. This nonlinear effect on $E_T(30)$ values for TFE in aromatic solvents was noted previously⁵ and was rationalized as resulting from “solvent demixing” that gave unusually high concentrations of the polar additive surrounding the betaine salt used for the $E_T(30)$ measurements. The TFE additive has a retarding effect on the rate constant for CIP collapse, and the concentration of the CIP in PhCF₃ solvent was increased by about 1 order of magnitude when TFE was present at the level of 1%. It is interesting to note that polarity as judged by the $E_T(30)$ values is a poor predictor of the ion pair collapse rates in the mixtures.

Limited kinetic information about β -mesylate radical heterolysis reactions is available, and those values are not in good agreement with one another. Heterolysis of a mesylate radical similar to radical **1** in structure was estimated to occur with a rate constant of $k > 5 \times 10^9 \text{ s}^{-1}$ in CH₃CN solution,⁴ but estimated rate constants for heterolysis in aqueous solutions of the radical formed from propyl mesylate ($k = 2 \times 10^5 \text{ s}^{-1}$) and those from butyl and isobutyl mesylate ($k > 10^6 \text{ s}^{-1}$) were much smaller.²¹ The rate constants obtained for radical **1** in this work are likely

to be more accurate than the other values because product ratios were measured directly for reactions in the presence of a wide range of concentrations of PhSH, but we note that the accuracy of those values is a function of the accuracy of estimated rate constants for PhSH trapping reactions.

The half-lives for decay of radical **1** in various solvents are derived from composite rate constants. An intuitive notion that increasing solvent polarity should result in faster radical “heterolysis” is supported by our kinetic studies, but the surprising results are that the heterolysis steps *per se* have comparable rate constants, whereas the CIP collapse rate constants vary considerably with solvent. One practical aspect of the work is that a highly unfavorable equilibrium for radical dissociation in low polarity solvents results from ion recombination rates that are faster than molecular correlation times, which might be a key feature for stereoselective radical substitution reactions;^{6,7} increasing solvent polarity marginally from that of benzene to that of CH₂Cl₂ might have a profound effect on stereoselectivity. The method reported here should be useful in studies of heterolysis reactions of other β -(ester)alkyl radicals, and creation of a kinetic scale for various radical types can be envisioned.

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Supporting Information Available: Tables of product yields in various solvents. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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