Picosecond Radical Kinetics. Fast Ring Openings of Constrained, Aryl-Substituted Cyclopropylcarbinyl Radicals†

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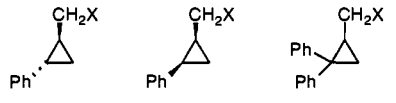
Abstract: The kinetics of ring openings of the *exo*- and *endo*-(2,3-benzobicyclo[3.1.0]hex-2-en-6-yl)methyl radicals (**4a** and **5a**), the *trans*-(spiro[cyclopropane-1,1′-indan]-2-yl)methyl radical (**6a**), and the (spiro[cyclopropane-1,9′-fluorene]-2-yl)methyl radical (**7a**) have been studied by competition kinetics employing benzeneselenol trapping. Arrhenius functions for ring openings were determined for reactions conducted between −80 and 50 °C. Each radical rearranges rapidly, with rate constants at 25 °C of 3×10^{11} (**4a**), 2×10^{11} (**5a**), 6×10^{11} (**6a**), and 6×10^{12} s^{-1} (**7a**). Precursors to these radicals represent hypersensitive mechanistic probes with unambiguous rate constants for rearrangement. The results confirm the utility of a previously employed semiquantitative method for estimating rate constants for aryl-substituted cyclopropylcarbinyl rearrangements based on Marcus theory. However, they also show that severe dihedral angles between the aromatic π-systems and the breaking cyclopropyl C–C bonds in the energy-minimized structures cannot be used to predict kinetic effects in the rearrangement reactions. The ramifications of the kinetic results for mechanistic studies of enzyme-catalyzed oxidations of hydrocarbons that employed hypersensitive probes are discussed.

Precursors to radicals that rearrange have been applied widely in mechanistic probe studies, wherein one seeks to implicate a radical intermediate by detecting rearranged products. For such a purpose, the radical rearrangement must be faster than competing reactions of the unrearranged radical, and exceptionally fast rearrangements are desired. When the rate constant for a radical rearrangement is known, the intermediate becomes a "radical clock"[1,2] which can be used to time competing radical processes. Our interest in radical kinetics and in applications of probes and clocks in studies of biochemical processes that might involve radical intermediates led us to the development of an indirect kinetic method capable of picosecond kinetic resolution[3-6] and to the calibration of ring openings of phenyl-substituted cyclopropylcarbinyl radicals **1a–3a**, which have lifetimes at room temperature of only a few picoseconds; these rearrangements are among the fastest calibrated radical reactions.[5,7] Because direct methods to confirm the kinetic values were not apparent, we employed a Marcus theory approach to estimate the expected rate constants for rearrangements and found reasonable agreement between the measured and predicted values.[7]



1 2 3

a: X = •
b: X = H

The hydrocarbon precursors to radicals **1a** and **3a** have been applied in mechanistic probe studies of oxidations by enzymes in attempts to implicate radical intermediates and (for cases where radical intermediates are implicated) to time the radical hydroxylation step in the oxidation process (see Discussion section). The results have ranged from the detection of only rearranged alcohol products (non-heme monooxygenase in cells of *Pseudomonas oleovorans*)[8] to the observation of no rearranged alcohol products (reconstituted methane monooxygenase (MMO) system from *Methylococcus capsulatus* (Bath)).[9] In cases where both rearranged and unrearranged alcohols have been observed, the calculated rate constants for the radical hydroxylation step have been very large, in excess of 1×10^{12} s^{-1}.[9,10] In studies with microsomal cytochrome P-450 enzymes, the oxygen rebound rate constants resulting from oxidations of **1b** and **3b** did not agree with values obtained with other radical clocks, and Atkinson and Ingold speculated that the radical clocks "ran slow" in the enzyme's reactive pocket due to a stereoelectronic effect resulting from constraint of the phenyl rings.[10] More recent results with microsomal P-450 show that both enantiomers of **1b** are oxidized to give comparable amounts of ring-opened and unrearranged alcohol products.[11]

The possibility that the orientation of the aromatic ring in radical **1a** could affect the rate constants of ring opening has been addressed. In principle, constraint of the aryl groups by the enzyme such that optimal alignment of the aromatic π-systems with the breaking cyclopropyl bond was precluded might slow the ring opening by a stereoelectronic effect. We have applied Marcus theory to predict the extent of this orientational effect for cases where the aryl ring would be held rigidly.[9]

In an attempt to characterize an orientational effect of the aromatic π-systems on rate constants for ring opening of aryl-substituted cyclopropylcarbinyl radicals and with the hope of establishing new radical clocks that might provide less ambiguous results in mechanistic probe investigations, we have now studied a series of constrained, aryl-substituted cyclopropylcarbinyl radical systems (**4a–7a**). We report that the ring openings of all of these radicals are very fast. Thus, a new set of hypersensitive radical probes whose rate constants cannot be influenced by steric

† Dedicated to Dr. Keith Ingold on the occasion of his 65th birthday.
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(1) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.
(2) For a recent review of alkyl radical kinetics and listings of several radical clocks, see: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.
(3) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.
(4) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.
(5) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662.
(6) Newcomb, M.; Varick, T. R.; Ha, C.; Manek, M. B.; Yue, X. *J. Am. Chem. Soc.* **1992**, *114*, 8158.
(7) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915.
(8) Fu, H.; Newcomb, M.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 5878.
(9) Liu, K. E.; Johnson, C. C.; Newcomb, M.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 939.
(10) Atkinson, J. K.; Ingold, K. U. *Biochemistry* **1993**, *32*, 9209.
(11) Atkinson, J. K.; Hollenberg, P. F.; Ingold, K. U.; Johnson, C. C.; Le Tadic, M.-H.; Newcomb, M.; Putt, D. A., submitted for publication.

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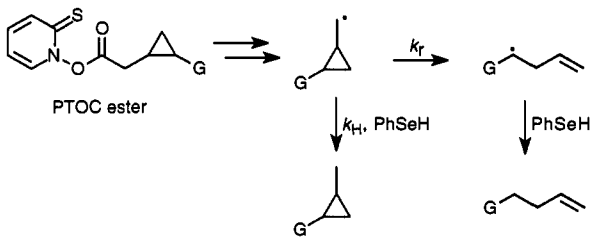
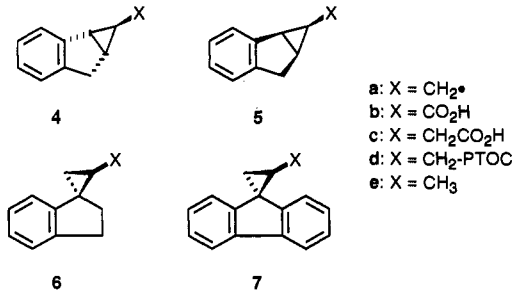
Scheme 1



effects in an enzyme's active site now exists, and the hydrocarbon precursors to these radicals might be useful in studies of enzyme-catalyzed oxidations. In addition, the results suggest that the semiquantitative method employed for predicting the rate constants of aryl-substituted cyclopropylcarbinyl radical ring openings is useful when potential orientational effects of the aromatic π-system are ignored. The kinetic results have important ramifications for the mechanistic probe studies of enzyme-catalyzed oxidations that employed **1b** and **3b**.



The kinetic method employed in these studies was the PTOC-thiol method with benzeneselenol trapping (exemplified in Scheme 1). The radical precursor, a PTOC ester,[12] reacts mainly in radical chain reactions to give an acyloxyl radical that rapidly decarboxylates to give the target radical. In competing reactions, the radical is trapped or rearranges. The rearranged radical also reacts with the trapping agent, and the byproduct radical from the trapping reactions (PhSe• in the case of PhSeH trapping) reacts with the PTOC ester, initiating another cycle in the chain. PhSeH, which can be used in high concentrations, provides the fastest trapping reaction calibrated thus far.[5,6] The product mixture is analyzed by GC, and the rate constant for rearrangement (k_r) is calculated from the product ratio, the known rate constant for trapping (k_H), and the concentration of trapping agent.[13]

Radical Precursors

The PTOC esters react to give acyloxyl radicals that decarboxylate to give the desired radicals. Therefore, the necessary carboxylic acid precursors for these studies were the corresponding cyclopropylacetic acids **4c–7c**. For systems **4**, **5**, and **6**, the appropriate cyclopropanecarboxylic acid was prepared by reaction of ethyl diazoacetate with an alkene (indene and 2-methylideneindan) followed by saponification to give acids **4b–6b**. Homologation of these cyclopropanecarboxylic acids by conversion to the diazo ketone (reaction with oxalyl chloride and then diazomethane) and photochemical Wolff rearrangement in methanol followed by saponification afforded the desired cyclopropylacetic acids **4c–6c**. From these, the PTOC esters **4d–6d** were prepared by conversion of the acids to acid chlorides and subsequent reaction with the sodium salt of *N*-hydroxypyridine-2-thione.

(12) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

(13) For a discussion of indirect kinetic methods applied to radical reactions, see ref 2.

For the isomeric systems **4** and **5**, chromatographic separation of the ethyl esters from the ethyl diazoacetate reaction (*i.e.*, **4** and **5**, X = CO_2Et) was possible. Ultimately, *exo* isomer **4** (X = CO_2Et) in >99% isomeric purity and *endo* isomer **5** (X = CO_2Et) in 98–99% isomeric purity were obtained. PTOC esters **4d** and **5d** were solids that were recrystallized, and neither was contaminated by its epimer as determined by NMR spectroscopic analysis.

In the case of system **6**, the *trans* and *cis* products were obtained in about equal amounts from the initial ethyl diazoacetate reaction, and separation of the isomers proved to be difficult. The *trans* system **6** was enriched at various stages of the synthesis. Eventually, a sample of PTOC ester **6d** of *ca.* 95% isomeric purity was prepared and used for most of the kinetic studies. For kinetic studies at one temperature (−50 °C), the sample of **6d** had partially decomposed upon storage and was *ca.* 85% pure.

Preparation of the appropriate cyclopropylacetic acid for system **7** proved to be difficult, with problems resulting from high reactivity of the system encountered in nearly every step. A number of attempts to homologate carboxylic acid **7b** to the desired cyclopropylacetic acid (**7c**) were unsuccessful. Eventually, we abandoned the homologation scheme in favor of a direct synthesis of **7c**. Several trial reactions led to a specialized protocol for a photochemical reaction of 9-diazofluorene with methyl vinylacetate to give the methyl ester **7** (X = CH_2CO_2Me). Attempts to saponify this ester were thwarted by the reactivity of the system; only products in which the cyclopropane ring was destroyed were obtained. However, carboxylic acid **7c** could be prepared by transesterification of the methyl ester to the trimethylsilyl ester (TMSCl, NaI) followed by hydrolysis with water. PTOC ester **7d** was prepared by a standard procedure (oxalyl chloride, *N*-hydroxypyridine-2-thione sodium salt). Ironically, **7d** proved to be relatively robust; partial decomposition of **7d** occurred upon silica gel chromatography, but the product was isolated in 56% yield and >95% purity as determined by NMR spectroscopy.

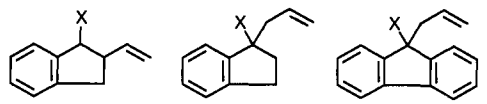
Product Identification and Quantitation

As we discuss below, the radical ring-opening reactions of **4a–7a** are very fast, and even high concentrations of PhSeH give only small amounts of unrearranged product. With product ratios typically exceeding 50:1 (and in some cases exceeding 1000:1), it was critically important that we prepare samples of the ultimate products for GC quantitations and mass spectral identifications. The cyclic hydrocarbon products **4e**, **5e**, and **7e** were obtained by $LiAlH_4$ reduction of the appropriate ethyl carboxylate (**4** and **5**, X = CO_2Et) or carboxylic acid (**7b**) to give the cyclopropylmethanol, mesylation of the alcohol, and reduction of the mesylate with $LiBHEt_3$. An authentic sample of the hydrocarbon product **6e** was prepared according to a reported procedure[14] (Simmons–Smith methylenation of a mixture of isomers of 1-ethylideneindan) that afforded a 5:1 mixture of **6e** and its *cis* isomer, respectively. Because authentic samples of both **6e** and its *cis* isomer were available, we could determine that no *cis* product was produced in detectable amounts from the radical reactions of the PTOC ester **6d** which contained about 5% of the *cis* isomer.

Authentic samples of the products from radical ring opening also were prepared. 2-Vinylindan (**8b**), the product from ring opening of both **4a** and **5a** followed by trapping, was obtained from a radical reaction of PTOC ester **4d** conducted in the presence of PhSH; the product contained no detectable amount of **4e** by GC. 1-Allylindan (**9b**), the ultimate product from opening of radical **6a**, was prepared by reaction of allylmagnesium bromide with the mesylate from 1-indanol. 9-Allylfluorene (**10b**), the ultimate product from ring opening of **7a**, was prepared by reaction of fluorenyllithium with allyl chloride.

For PTOC esters **4d**, **5d**, and **6d**, careful comparisons of the GC mass spectra of the product mixtures from radical reactions

(14) Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454.



8 9 10

a: X = •; b: X = H

run in the presence of PhSeH with the mass spectra of the authentic samples confirmed the identity of the products and showed that no coeluting contaminant was present in any of the product peaks. In addition, there was no evidence of products from ring openings of the radicals in the unexpected direction (*i.e.*, to give the unstabilized alkyl radicals).

In the kinetic studies, the product ratios and total yields of products (determined against an internal standard) in the product mixtures were measured on an FID-equipped GC employing a wide bore capillary column. High ratios of rearranged to unrearranged products were obtained in the kinetic studies. In order to quantify the yields accurately, mixtures of the authentic products in ratios approximating those obtained in the kinetic studies were prepared and analyzed by GC. For **8b** and **4e**, reproducible results were obtained on mixtures with ratios as great as 500:1. However, with mixtures of even greater ratios, the GC results varied appreciably.

The analytical procedure was complicated for the fluorenyl system **7**. FID GC analyses of the product mixtures from reactions of PTOC ester **7d** in the presence of PhSeH indicated a small component with the correct retention time for unrearranged hydrocarbon **7e**. However, GC mass spectral analyses of these mixtures showed that the single peak ascribed to **7e** on the basis of GC retention time actually contained at least two components and that **7e** was a minor component in the mixture. The mass spectrum of product **7e** was present but admixed with a mass spectrum of at least one other, unidentified species. Therefore, in order to quantify the yields, we were required to estimate the amounts of product **7e** in the coeluting mixture.

Two protocols for analysis of **7e** were attempted. In one, the GC mass spectra of **7e** and **10b** from each kinetic run were compared directly. The contaminating products coeluting with **7e** appeared to contain no peak at $m/z = 206$, the molecular ion for **7e**. A response factor for the $m/z = 206$ peaks from **7e** and from **10b** was determined from mixtures of authentic compounds, and the ratios of the $m/z = 206$ peaks in the GC mass spectra of each kinetic run were used to determine the ratio of the compounds.

In the second method, the product mixtures were analyzed by GC mass spectrometry, spiked with a known measured amount of cyclic product **7e**, and analyzed once again. From the differences in the peak intensities in the composite mass spectra of the two analyses and the known amount of **7e** added before the second analysis, the amount of **7e** in each original mixture was calculated. The resulting percentage of **7e** was then multiplied by the ratio of peak areas from the FID GC analysis to obtain a corrected ratio of **7e**:**10b**.

The two methods gave comparable values for the ratios of products, but neither was highly precise (see Table 4 below). The former method appeared to give more consistent results, and the values listed in Table 4 below were determined by this method.

Kinetic Studies

Competition kinetic studies were conducted with PTOC esters **4d–7d** in THF with PhSeH trapping, and the product mixtures were determined by GC analysis. Tables 1–3 contain the results from reactions of PTOC esters **4d**, **5d**, and **6d**, respectively. The measured ratios of rearranged to unrearranged hydrocarbons are given. In addition, ratios of rate constants calculated from the product ratios and the concentration of trapping agent also are listed.[13]

Table 1. Results of Competition Kinetic Studies of Radical **4a**

T (°C)[a]	[PhSeH][b]	yield,[c] (%)	**8b**/**4e**[d]	k_r/k_H (M)
54	1.00	66	273	273
	1.57	81	109	171
	2.04	87	70	142
	2.20	77	53	116
23	1.04	88	114	119
	1.57	88	72	113
	2.09	101	47	98
	3.14	83	26	82
3	1.01	77	123	124
	1.51	103	68	103
	2.02	108	54	109
	3.03	90	33	100
−23	1.25	140	94	118
	1.88	104	62	117
−30	0.17	116	1139	194
	0.25	109	416	104
	0.33	118	275	91
	0.41	107	185	76
−45	0.15	102	1393	209
	0.19	102	1028	195
	0.23	43	705	162
−78	0.11	94	291	32
	0.15	79	751	112
	0.19	89	275	52
	0.24	82	200	48

[a] Temperature given ±1 °C. [b] Mean molar concentration. [c] Total yield of hydrocarbons determined by GC against an internal standard. [d] GC ratio of products.

Table 2. Results of Competition Kinetic Studies of Radical **5a**

T (°C)[a]	[PhSeH][b]	yield,[c] (%)	**8b**/**5e**[d]	k_r/k_H (M)
53	2.75	86	43	118
	3.00	87	40	120
	3.25	104	32	104
	3.50	80	33	115
23	2.50	100	42	105
	2.75	105	39	107
	3.00	102	32	96
	3.25	86	31	101
3	2.25	108	43	97
	2.50	118	39	98
	2.75	114	30	82
	3.00	112	28	84
−45	2.25	88	27	61
	2.50	101	26	65
	2.75	106	25	69
	2.94	96	22	65

[a–d] See footnotes to Table 1.

Table 3. Results of Competition Kinetic Studies of Radical **6a**

T (°C)[a]	[PhSeH][b]	yield,[c] (%)	**9b**/**6e**[d]	k_r/k_H (M)
25	2.35	43	58	136
	2.69	45	56	151
	3.27	56	54	177
	3.76	43	47	177
0	1.69	73	193	326
	1.98	70	201	398
	2.54	71	155	393
−50	1.44	86	154	222
	1.63	84	156	254
	1.76	77	155	273
	2.00	75	167	334
−78	1.69	65	191	323
	1.98	62	165	327
	2.17	58	168	365
	2.54	46	168	427

[a–d] See footnotes to Table 1.

The total yields of products from reactions of PTOC esters **4d** and **5d** were high, but the total yields observed in reactions of PTOC ester **6d** were reduced. Low yields of hydrocarbon products from reactions of PTOC esters have been observed previously. These can result either from PhSeH trapping of the acyloxyl

Table 4. Results of Competition Kinetic Studies of Radical **7a**

T (°C)[a]	[PhSeH][b]	yield,[c] (%)	ratio[d]	**10b**/**7e**[e]	k_r/k_H (M)
23	1.95	54	71	1250	2440
	2.20	63	57	2840	6250
1	1.64	95	77	1430	2350
	1.95	66	75	930	1810
−46	1.30	120	183	2600	3380
	1.46	116	148	1880	2740
−80	1.19	80	227	2080	2480
	1.30	114	192	4260	5540

[a–c] See footnotes to Table 1. [d] Ratio of peaks from FID GC analysis; see text. [e] Ratio of products from GC-mass spectral analysis; see text.

radical in competition with the decarboxylation step[7] or from polar transacylation reactions of the PTOC ester (an activated carboxylic acid derivative) with the nucleophilic trapping agent PhSeH.[15] Neither affects the kinetic results other than to reduce the precision by limiting the amount of material analyzed.

From the ratios of rate constants in Tables 1–3, relative Arrhenius functions for $\log(k_r/k_H)$ were calculated.[16] Because we found that product mixtures with a >500:1 ratio could not be measured accurately, we excluded such high ratios from the data in Table 1 in the calculation of the relative Arrhenius function for reactions of radical **4a**. These functions were then added to the Arrhenius function for PhSeH trapping in THF[17] to give Arrhenius functions for the ring-opening reactions in eqs 1–3,

$$\log(k_r \times s) = 13.9(3) - 3.4(3)/2.3RT \quad \text{(radical 4a)} \quad (1)$$

$$\log(k_r \times s) = 13.6(1) - 3.2(1)/2.3RT \quad \text{(radical 5a)} \quad (2)$$

$$\log(k_r \times s) = 13.0(4) - 1.7(5)/2.3RT \quad \text{(radical 6a)} \quad (3)$$

where the errors in the final significant figure at 2σ are given in parentheses. Of course, this procedure involves the commonly made assumption[2] that the rate constants for reaction of PhSeH with the cyclopropylcarbinyl radical and with the substituted cyclopropylcarbinyl radicals studied here are equal. The major portion of the errors in these functions arose from the competition kinetic studies conducted in this work.[16] From the Arrhenius functions in eqs 1–3, the calculated rate constants for ring openings of the radicals at 25 °C are 3×10^{11} (**4a**), 2×10^{11} (**5a**) and 6×10^{11} s^{-1} (**6a**), comparable to the rate constants for ring openings of radicals **1a–3a**.[5,7]

The results of competition kinetic studies of rearrangement of the spirofluorenyl radical 7a are given in Table 4. In this table we list the GC-measured ratios of peaks from the FID GC measurements and the corrected values of product ratios that result from estimations of the amounts of unrearranged product **7e** in the coeluting mixture of components (see above). The data in the final column in Table 4 gave a relative Arrhenius function[16] that was combined with the PhSeH trapping function[17] to give the Arrhenius function for rearrangement of **7a** in eq 4. From

$$\log(k_r \times s) = 14.3(8) - 2.1(9)/2.3RT \quad \text{(radical 7a)} \quad (4)$$

this function, one calculates an incredibly fast ring opening of radical **7a** at 25 °C of 6×10^{12} s^{-1}; this is equal to the calculated rate constant for decay of a transition state at 25 °C.

The errors at 2σ in eq 4 are substantial and deserve comment. The major source of error in these measurements came from the estimation of the amount of **7e** in the coeluting product mixture. Specifically, if the mixture eluting at the correct time for hydrocarbon **7e** had contained only **7e**, then the errors at 2σ for both the log A and E_a terms in eq 4 would have been 0.3, about the same level of error we have found in the Arrhenius functions for ring openings of **1a–6a**. The amount of **7e** measured in the mixture of coeluting products was, with one exception, consistently in the 5–10% range. As an alternative to the Arrhenius function in eq 4, we could calculate an apparent Arrhenius function for ring opening of **7a**, assuming that **7e** was the sole component in the coeluting mixture, and then multiply the apparent rate constant by 10–20. This process would lead to a rate constant for ring opening of **7a** at 25 °C of $(5–10) \times 10^{12}$ s^{-1}. In any event, radical **7a** opens very rapidly.

Discussion

As in other studies of very fast radical rearrangements, an alternative method for measuring the rate constants is not readily available. Another fast competition method involves radical trapping by nitroxyl radicals.[18] However, the rate constants for primary alkyl radical trapping by PhSeH actually exceeds those for most nitroxyl–alkyl radical couplings. Given that the thermal instability of the trialkylhydroxylamine products produced in nitroxyl–alkyl radical couplings requires an HPLC analysis and that authentic nitroxyl coupled products are not readily synthesized, it is unlikely that this method would provide other than a minimum limit for the rate constants of the reactions we have studied here. For example, only a limit for the rate constant of ring opening of the (*trans*-2-(ethoxycarbonyl)cyclopropyl)methyl radical was available from a nitroxyl trapping study,[19a] but a PhSeH trapping study[19b] provided the rate constants for ring opening of this radical (which rearranges with a rate constant smaller than those of the radicals studied in this work).

Similarly, a method for direct study of the radical rearrangements is not apparent. The rate constants for decarboxylations of a variety of acyloxyl radical intermediates that give alkyl radicals lie in a narrow range of about 1×10^9 to 1×10^{10} s^{-1} at 25 °C.[20] Thus, an attempted direct study of the kinetics of rearrangements from a precursor such as a PTOC ester would actually measure the rate constant for the slower acyloxyl radical decarboxylation step. Further, with lifetimes on the order of a few picoseconds or less for the radicals studied herein, a conventional picosecond laser kinetic unit would not have adequate temporal resolution. One might hope that eventually a femtosecond kinetic spectrometric technique will be applied to these fast reactions, but this will require the development of new radical precursors that can be cleaved to give the radicals directly (*i.e.*, the precursors cannot be carboxylic acid derivatives), and the results are likely to be complicated by reactions of thermally nonequilibrated radicals produced in a photochemical homolysis.

In the absence of an alternative method for measuring the rate constants directly, one might consider potential systematic errors in our technique. Perhaps the most likely systematic error results from the use of PhSeH at high concentrations. The rate constants for trapping by PhSeH were determined in competition studies employing the ring opening of the cyclopropylcarbinyl (CPC) radical as the basis reaction.[5,6] The CPC ring opening is the most precisely calibrated fast radical reaction, but, unfortunately,

(15) Gawronzka, K.; Gawronski, J.; Walborsky, H. M. *J. Org. Chem.* **1991**, *56*, 2193.

(16) The calculated relative Arrhenius functions are as follows: $\log(k_r/k_H \times M) = 2.9(3) - 1.1(3)/2.3RT$ for **4a**, $\log(k_r/k_H \times M) = 2.6(1) - 0.9(1)/2.3RT$ for **5a**, $\log(k_r/k_H \times M) = 1.9(4) + 0.6(5)/2.3RT$ for **6a**, and $\log(k_r/k_H \times M) = 3.3(8) + 0.2(9)/2.3RT$ for **7a**. Errors at 2σ for the last significant figure are given in parentheses.

(17) The Arrhenius function for PhSeH trapping of cyclopropylcarbinyl radical in THF is $\log(k_H \times Ms) = 11.03(7) - 2.27(9)/2.3RT$, where the errors in the last significant figure (given in parentheses) are at 2σ.[6]

(18) (a) Johnston, L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877. (b) Chateauneuf, J.; Lusztyk, J. Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629. (c) Beckwith, A. L. J.; Bowry, V. W.; Moad, G. *J. Org. Chem.* **1988**, *53*, 1632. (d) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983. (e) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992. See also a discussion of nitroxyl radical trapping in ref 2.

(19) (a) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681. (b) Newcomb, M.; Choi, S.-Y. *Tetrahedron Lett.* **1993**, *34*, 6363.

(20) Falvey, D. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 7419. DeCosta, D. P.; Pincock, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 8948.

it is relatively slow, with $k_r = 1 \times 10^8$ s^{-1} at 25 °C.[21] Therefore, the PhSeH concentrations in the calibration study were substantially smaller than the concentrations employed in this work. The PhSeH trapping rate constants are partially diffusion controlled and are, therefore, a function of solvent viscosity. We do not know the viscosity of the solutions we employed, and it is possible that the PhSeH trapping reactions were somewhat slower than expected. However, we note that a reduction in the diffusional coefficients by a factor of 2 will result in only about a 10% reduction in the partially diffusion controlled PhSeH trapping reactions.[6]

The results in Table 1 suggest a possible systematic error in the PhSeH trapping kinetics. Specifically, the relative rate constants (k_r/k_H) consistently decrease as the concentration of PhSeH increases. However, such behavior is opposite that expected if increasing PhSeH concentrations gave significantly more viscous solutions, and such trends are not seen in the data in Tables 2 and 3. We conclude that the apparent trend in kinetic values in Table 1 is most likely coincidental.

The log A terms in eqs 1, 2, and 4 are somewhat larger than expected; the maximum value for a unimolecular rearrangement is 13.1.[22] However, these log A values are similar to those previously found for ring openings of radicals **1a** and **2a** and the (*trans*-2-(ethoxycarbonyl)cyclopropyl)methyl radical.[7,19b] All six of these radical rearrangements with log A of about 14 were calibrated against PhSeH trapping, and it is possible that a systematic error in the Arrhenius function for PhSeH trapping reaction leads to the high values of log A for the radical ring openings. In this regard, one must note that, because the PhSeH trapping reactions are partially diffusion controlled, the log A and E_a terms for the trapping reaction are operational values and cannot be analyzed in terms of entropic and enthalpic components. However, the Arrhenius functions for ring openings of radicals **3a** and **6a** and the cubylcarbinyl radical[23] also were determined by competition against PhSeH trapping, and the log A values in these functions are consistent with the expected values. We have previously noted that an alternative explanation for the large log A values would be that there are two pathways for formation of the ring-opened radicals, a stepwise pathway involving the cyclopropylcarbinyl radicals (with a log A of *ca.* 13) and a direct pathway involving ring opening *concerted* with decarboxylation (with a log A of *ca.* 16).[7] Were this the case, our kinetic values for ring openings with log $A = 14$ would be larger than the actual rate constants by a factor of about 2. The rearrangement reactions studied here clearly are very fast, but it also is clear that an alternative, direct method for evaluating the rate constants for ring opening of these strained radicals should be sought.

One of the justifications for the current study was a test of the semiquantitative method based on the Marcus equation (eq 5) that was previously employed in predictions of the rate constants for rearrangements of aryl-substituted cyclopropylcarbinyl radicals.[7] In brief, we used the known rate constant and equilibrium constant for the parent CPC rearrangement to calculate an intrinsic barrier ($\Delta G^{\ddagger}_{int}$) for a thermoneutral CPC ring opening. The exothermicity (ΔG^0) of the ring-opening reaction was then estimated from differences in the bond dissociation energies of aryl-substituted and unsubstituted methyl groups plus the known equilibrium constant for ring opening of the parent radical. The value of $\Delta G^{\ddagger}$ in eq 5 was calculated from the $\Delta G^{\ddagger}_{int}$ value and the estimated ΔG^0 for each radical.[7] In order to estimate the

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{int} + {}^1/_2\Delta G^0 + ((\Delta G^0)^2/16\Delta G^{\ddagger}_{int}) \quad (5)$$

potential stereoelectronic effect of constraining the phenyl rings in radical **1a** (as might occur in an enzyme's active site), we corrected the ΔG^0 term by multiplying the expected radical stabilization energy due to conjugation with the aromatic system by $\cos^2\theta$, where θ is the dihedral angle between the aromatic π-system and the breaking C–C bond in the cyclopropane.[9]

In radicals **4a**, **5a**, and **6a**, one has dihedral angles between the aromatic π-systems and the breaking C–C bonds that are structurally enforced, and we can test the premise[9] that substantial kinetic effects in the ring openings of these radicals can result from a stereoelectronic effect due to restricted overlap of the π-system with the breaking bond via the Marcus theory approach previously employed.[7] As before,[7,9] we assume that reactions occur from the minimum energy structures of the radicals and estimate ΔG^0. We estimate the extent of aromatic stabilization (a maximum of −10 kcal/mol[7]) as $\cos^2\theta \times -10$ kcal/mol (where θ is as defined above) and add to this value −3 kcal/mol for the radical stabilization effect of a secondary center relative to a primary center (which should be independent of θ) and −5.2 kcal/mol, which is the ΔG^0 value from the experimental equilibrium constant for cyclopropylcarbinyl radical ring opening.[7] Any *differences* in the amount of strain energy released in the radical ring openings should also be important, but these appear to be relatively minor[24] and have been ignored. MM2 structure minimizations of the radicals gave values for the dihedral angles between the cyclopropyl bond that breaks and the aromatic π-system of 28° (**4a**), 27° (**5a**), and 71° (**6a**). Similar angles were obtained for the corresponding hydrocarbons minimized[25] at the STO-3G level: 27° (**4e**), 26° (**5e**), and 63° (**6e**). The calculated rate constants for ring openings of the radicals at 25 °C would be 4×10^{10} (**4a** and **5a**) and $(1–2) \times 10^9$ s^{-1} (**6a**). The reduced amount of strain released in the **4a** system relative to the others[24] would have led to an even smaller rate constant for **4a** if it had been included in the ΔG^0 estimate.

The predicted kinetic values are far from those determined experimentally, even if we accept the possibility that the kinetic measurements might be in error by a small factor, and we must conclude that our method is not appropriate. The failure probably results from the simplified model for the reacting radicals. Although constrained, our systems are not completely rigid, and it is quite possible that the bond-breaking reactions are linked to molecular motions that increase the overlaps of the aromatic π-systems with the breaking bonds over those present in the energetic minima. Nevertheless, one should appreciate the fact that the $\Delta G^{\ddagger}$ values for the reactions we studied are only about 3 kcal/mol, similar in magnitude to simple C–C bond rotations. Complete dynamic analyses of the reactions should be instructive.

The Marcus theory approach[7] does provide reasonable kinetic estimates when only the ΔG^0 for the overall reaction is considered. On the basis of the stabilities of the product radicals only (as estimated from the bond dissociation energies of the corresponding hydrocarbons),[26] one obtains the results in Table 5. One may

(21) (a) Reference 4. (b) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (c) Beckwith, A. L. J.; Bowry, V. W.; Moad, G. *J. Org. Chem.* **1988**, *53*, 1632. (d) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681. (e) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981. For a discussion of calibration of the cyclopropylcarbinyl radical ring opening, see ref 2.

(22) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976; Chapter 3. See also the discussion in ref 21b.

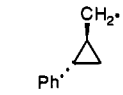
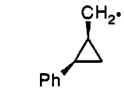
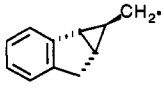
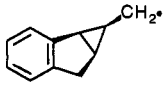
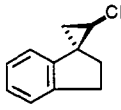
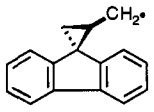
(23) Choi, S. Y.; Eaton, P. E.; Newcomb, M.; Yip, Y. C. *J. Am. Chem. Soc.* **1992**, *114*, 6326.

(24) Strain energies were estimated computationally (Gaussian 92 program, 486-Windows-G92RevD.2, PC version).[25] The structures of hydrocarbons **1b**, **4e**, **5e**, and **6e** and their respective ring-opened isomers 4-phenyl-1-butene, **8b**, and **9b** were minimized at the STO-3G level, and total energies were calculated for these structures at the 3-21G level. Released strain energies in kcal/mol, taken as the differences in the calculated energies for each isomerization, were −11.2 (**1b**), −9.7 (**4e**), −10.9 (**5e**), and −11.1 (**6e**). Because we are near the limit of $\Delta G^{\ddagger}$ approaching zero, a change in ΔG^0 of 2 kcal/mol results in a kinetic effect of a factor of 2.5.

(25) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92*, Revision D.2; Gaussian, Inc.: Pittsburgh, PA, 1992. We thank Prof. H. B. Schlegel for providing us with this program.

(26) From bond dissociation energies,[27] the increased stabilizations of the benzylic, diphenylalkyl, and fluorenyl radicals were taken as 13, 17, and 23 kcal/mol, respectively.

Table 5. Rate Constants for Radical Ring Openings

radical	k ($\times 10^{11}$ s^{-1}) pred[a]	exptl[b]	ref
	1	3	7
	1	4	7
	1	3	this work
	1	2	this work
	1	6	this work
	4	5	7
	30	60	this work

[a] Rate constant at 25 °C predicted by Marcus theory using resonance stabilization energies of the product radicals of 13 (benzylic), 17 (diphenylmethyl), and 23 kcal/mol (fluorenyl).[26] [b] Rate constant at 25 °C determined experimentally.

note that the Marcus theory approach provides reasonable kinetic estimates not only for the phenyl-substituted and indanyl systems but also for the diphenyl-substituted radical **3a** and for the fluorenyl system **7a**, which also has a poor overlap between the π-system and the breaking C–C bond in the relaxed structure. Given the approximate nature of any free energy analysis, the experimental errors in the BDE values,[27] the questionable assumption that BDE values accurately reflect radical stabilities, and the fact that the only kinetic point used in the calculations (that for the CPC ring opening) is more than 3 orders of magnitude smaller than any of the extrapolated values in Table 5, the fit between experimental and predicted values is actually quite good. The important points are that the kinetic values correlate with the final resonance stabilization energies and that the minimized orientations of the reactants have, at most, only a subtle effect on the rates.

The conclusion that any structural constraints present in radicals **4a**, **5a**, and **6a** have essentially no effect on the kinetics of radical ring openings has important ramifications for the mechanistic studies of enzyme oxidations that employed hydrocarbons **1b** and **3b**. The consensus view of the mechanism for hydrocarbon hydroxylation by cytochrome P-450 enzymes is shown in Figure 1.[28] Hydrogen atom abstraction by a high-valent iron–oxo intermediate gives a radical and an iron–hydroxy species. Homolytic substitution (the "oxygen rebound" step)[29]

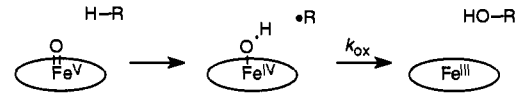


Figure 1. Hydrogen abstraction, oxygen rebound mechanism for cytochrome P-450 enzyme catalyzed hydrocarbon hydroxylations. A high-valent iron–oxo species abstracts hydrogen to give an alkyl radical and an iron–hydroxy species. A homolytic substitution reaction, the oxygen rebound step, follows.

then follows. Because high-valent iron–oxo intermediates are also implicated in oxidations by the hydroxylase enzyme of methane monooxygenase (MMO) systems (a non-heme, diiron protein), it is possible that MMO oxidations proceed by a similar pathway.[30]

In a study of oxidations of a series of mechanistic probes by reconstituted MMO from *M. capsulatus* (Bath), Liu *et al.* found no rearranged products from oxidations of **1b**, **3b**, and other probes.[9] Because radicals **1a** and **3a** react so rapidly, one concludes that if a single pathway was involved then radical intermediates were not formed. However, Liu *et al.* cautioned that the rate constants for rearrangements of radicals **1a** and **3a** might have been affected by constraints in the enzyme's active site.[9] In our opinion, the present results suggest that the caveat[9] was not necessary. Specifically, if structural constraints in radicals **4a**, **5a** and **6a** are not severe enough to reduce the rate constants for ring openings of these radicals in comparison to that for radical **1a**, then it is unlikely that nonbonding steric effects on **1a** would severely retard the rate constant for opening of this radical.

More importantly, in the case of P-450-catalyzed oxidations of a series of radical clock precursors including **1b** and **3b**, Atkinson and Ingold found widely disparate apparent k_{ox} values (see Figure 1).[31] They concluded that the kinetics of opening of both **1a** and **3a** were strongly influenced by steric constraints in the enzyme's active site.[10] Recent results[11] require that both enantiomers of **1a** must be constrained to a similar extent despite the fact that the chiral enzyme will undoubtedly interact differently with each enantiomer. Again, we believe that the present results suggest that such an explanation is unlikely, and we conclude that the incongruence in the results[31] from oxidations of various radical clock precursors by P-450 must have an alternative explanation. The most likely explanations would appear to be either that the entire PTOC-thiol kinetic method with PhSeH trapping is grossly in error (by more than an order of magnitude) or that the accepted mechanism for P-450 oxidation involving formation of a radical intermediate is incorrect or incomplete. The accuracy of the kinetic method with PhSeH trapping has been supported directly by comparison to PhSH trapping and nitroxyl radical couplings[32] and in limiting cases by studies involving other PhSH trapping reactions[6,23] and nitroxyl radical trappings.[19] Some compression in the rate constants of unimolecular reactions at the top end of the kinetic scale due to minor reductions in PhSeH trapping rate constant values from decreased diffusional coefficients (see above) cannot be excluded. However, for the kinetic method with PhSeH trapping to be in error by more than an order of magnitude, all fast radical kinetic methods must also be in error by a comparable amount. Corrections in the kinetics of all of the radical clocks used by Atkinson and Ingold might result in downward adjustments, but the *ratios* of rate constants for any of the clocks would be unchanged. We suggest that further studies of P-450 enzyme-

(27) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. Bordwell, F. G.; Harrelson, J. A.; Satish, A. V. *J. Org. Chem.* **1989**, *54*, 3101. Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1992**, *114*, 10173.

(28) For discussions of the consensus radical pathway in cytochrome P-450-catalyzed hydroxylations of hydrocarbons, see the following: Ortiz de Montellano, P. R. In *Cytochrome P-450 Structure, Mechanism, and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum: New York, 1986; Chapter 7. Woggon, W.-D.; Fretz, H. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI: Greenwich, CT, 1992; Vol. 2; pp 111–147.

(29) Groves J. T.; McClusky, G. A.; White, R. E.; Coon, M. J. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154.

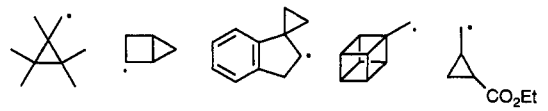
(30) For a discussion of MMO mechanisms, see ref 9.

(31) The calculated k_{ox} values from the results with the various probes[10,11] differ by nearly 3 orders of magnitude, giving *differences* in activation free energies of up to 4 kcal/mol. Such a result is highly unlikely, because the fastest calculated k_{ox} values ($(3–7) \times 10^{12}$ s^{-1}) would have *total* activation free energies of only 0.0–0.5 kcal/mol.

(32) The PhSeH kinetic values are calibrated against cyclopropylcarbinyl ring opening in the same temperature range for which CPC ring opening was calibrated by PhSH trapping, nitroxyl radical trapping, and kinetic ESR spectroscopy.[21] In addition, determinations of the kinetics of 6-cyano-5-hexenyl radical cyclization using both PhSH and PhSeH trapping gave comparable results.[6]

catalyzed oxidations are most likely to provide insight into the origins of the highly variable radical clock results.

The radical rearrangements studied in this work increase the "horology" [1] of fast radical clocks that can be applied in studies where potential competing reactions are especially rapid. In addition to the radicals listed in Table 5, fast radical unimolecular clocks include the rearrangements of poly(methyl)-substituted cyclopropylcarbinyl radicals[33] (such as **11**, $k_r = 4 \times 10^9$ s^{-1} at 25 °C), the bicyclo[2.1.0]pent-2-yl radical[33,34] (**12**, $k_r = 1.5 \times 10^9$ s^{-1} at 25 °C), spirocyclic radicals[14] such as **13** ($k_r = 2 \times 10^9$ s^{-1} at 75 °C), the cubylcarbinyl radical[23] (**14**, $k_r = 3 \times 10^{10}$ s^{-1} at 25 °C), and the (*trans*-2-(ethoxycarbonyl)cyclopropyl)methyl radical[19] (**15**, $k_r = 8 \times 10^{10}$ s^{-1} at 25 °C). The spirofluorenyl system **7a** appears to represent a kinetic pinnacle in that it rearranges with a rate constant essentially equivalent to that for decomposition of a transition state. Nevertheless, successful trapping of small amounts of transient radicals, even in the case of **7a**, shows that these species exist as discrete intermediates.



11 12 13 14 15

Experimental Section

General. Reagents were purchased from Aldrich Chemical Co. unless noted otherwise. The sodium salt of *N*-hydroxypyridine-2-thione was obtained from an aqueous solution of the salt (Olin Chemical Co.) as previously described.[35] NMR spectra of $CDCl_3$ solutions (unless noted) were obtained at 300 (^{1}H) or 75 MHz (^{13}C); chemical shifts are reported in δ units relative to internal TMS (^{1}H, $\delta = 0.0$) or the center line of $CDCl_3$ (^{13}C, $\delta = 77.0$). High-resolution mass spectral analyses were performed by the Central Instrument Facility at Wayne State University (Detroit, MI). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The cyclopropaneacetic acids **4c–6c** and hydrocarbon products **4e–7e** and **8b–10b** were prepared according to conventional methods; preparations of and spectral data for these compounds are given in the supplementary material.

***exo*-[[((2,3-Benzobicyclo[3.1.0]hex-2-en-6-yl)methyl)carbonyl]oxy]-2(1*H*)-pyridinethione (4d).** To acid **4c** (0.63 g, 3.4 mmol) in dry benzene (25 mL) at room temperature was added a catalytic amount of DMF (2 drops) and oxalyl chloride (0.59 mL, 6.75 mmol) under N_2. The solution was stirred for 12 h, and solvent and excess oxalyl chloride were distilled at reduced pressure using a base trap. The residual acid chloride was dissolved in dry benzene (20 mL) under N_2. All subsequent procedures were conducted in vessels shielded from laboratory light. The solution was cooled to 5 °C and added via cannula to a cooled (5 °C) suspension of the sodium salt of 2-mercaptopyridine *N*-oxide (0.58 g, 3.88 mmol) and DMAP (0.04 g, 0.34 mmol) in dry benzene (20 mL). The stirred reaction mixture was allowed to warm to room temperature over 4 h. The benzene mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and quickly filtered through a sintered glass funnel. Solvent was distilled at reduced pressure, and the residual orange oil was crystallized from benzene–hexanes to yield 0.71 g (74%) of **4d** as a bright yellow solid with mp 107.0–110.5 °C dec. ^{1}H NMR: δ 0.85–0.87 (m, 1 H), 1.86–1.90 (m, 1 H), 2.43 (d, 1 H, J = 6.0 Hz), 2.70 (dd, 1 H, J = 16.7, 7.5 Hz), 2.83 (dd, 1 H, J = 16.7, 7.2 Hz), 3.05 (d, 1 H, J = 17.1 Hz), 3.22 (dd, 1 H, J = 17.1, 6.6 Hz), 6.63 (dt, 1 H, J = 6.9 Hz, 1.5 Hz), 7.08–7.15 (m, 3 H), 7.17–7.23 (m, 1 H), 7.31–7.36 (m, 1 H), 7.58 (dd, 1 H, J = 6.9, 1.2 Hz), 7.69 (dd, 1 H, J = 4.5, 1.5 Hz).

***endo*-[[((2,3-Benzobicyclo[3.1.0]hex-2-en-6-yl)methyl)carbonyl]oxy]-2(1*H*)-pyridinethione (5d)** was prepared from acid **5c** (1.0 g, 5.3 mmol) which was contaminated with small amounts of acids **4c** (<2%) and **5b** (<10%) by a procedure similar to that given above for **4d**. The oily yellow residue obtained from the preparation was crystallized from benzene–hexanes to give a first crop of **5d** as a bright yellow solid (329 mg, 24%) with mp of 100–105 °C dec. The ^{1}H NMR spectrum showed no signals from **4d**, and the sample was judged to be >95% pure by NMR spectroscopy. ^{1}H NMR: δ 1.71 (quin, 1 H, J = 7.5 Hz), 2.06 (q, 1 H, J = 7.5 Hz), 2.21 (dd, 1 H, J = 17.6, 7.2 Hz), 2.33 (dd, 1 H, J = 17.6, 7.5 Hz), 2.70–2.75 (m, 1 H), 2.91 (d, 1 H, J = 18.0 Hz), 3.23 (dd, 1 H, J = 17.7, 7.2 Hz), 6.60 (dt, 1 H, J = 6.8, 1.8 Hz), 7.10–7.21 (m, 4 H), 7.27–7.30 (m, 1 H), 7.41–7.44 (m, 1 H), 7.64–7.67 (m, 1 H).

[[[*trans*-(Spiro[cyclopropane-1,1′-indan]-2-yl)methyl]carbonyl]oxy]-2(1*H*)-pyridinethione (6d) was prepared from crude acid **6c** (from saponification of the corresponding methyl ester) by a procedure similar to that given above for the preparation of **4d**. Efforts to crystallize the crude PTOC ester were unsuccessful. Crude PTOC ester **6d** was purified by rapid elution through a silica gel column (hexanes–ethyl acetate, 1:1). The PTOC ester was obtained as an orange oil in about 20% yield. The sample of **6d** used for most of the kinetic studies contained *ca.* 5% of the corresponding *cis* isomer as determined by NMR spectroscopy. The ^{1}H NMR spectrum of **6d** was deduced from the spectrum of the 95:5 isomeric mixture. ^{1}H NMR: δ 0.88 (t, 1 H, J = 6.0 Hz), 1.22–1.25 (m, 1 H), 1.59–1.70 (m, 1 H), 2.00–2.15 (m, 1 H), 2.20–2.40 (m, 1 H), 2.80 (dd, 1 H, J = 16.0, 7.2 Hz), 2.95 (dd, 1 H, J = 16.0, 7.2 Hz), 3.00–3.15 (m, 2 H), 6.60–6.69 (m, 1 H), 6.70–6.75 (m, 1 H), 7.10–7.30 (m, 4 H), 7.60 (d, 1 H, J = 7.2 Hz), 7.70 (d, 1 H, J = 7.2 Hz).

2-((Methoxycarbonyl)methyl)spiro[cyclopropane-1,9′-fluorene] (7, X = CH_2CO_2Me). The spiro ester was prepared in varying purities from the photolysis of 9-diazofluorene[36] in freshly prepared methyl vinylacetate.[37] In the best runs, *ca.* 2–3 g portions of methyl vinylacetate were placed in quartz test tubes, and *ca.* 50–100 mg of freshly prepared diazofluorene (2.5–6 mmol) was added to each tube. The tubes were then purged with argon for 10 min before being photolyzed with a mercury lamp (400 W, 280–320 nm) for *ca.* 4–6 h. Another portion of 9-diazofluorene of similar amount was then added, the solutions were again purged with argon, and the photolysis was resumed. This procedure was repeated once more, and the resulting intensely orange-colored solutions from all tubes were combined. The majority of the unreacted methyl vinylacetate was recovered by vacuum transfer at room temperature to a liquid N_2 trap. The remaining gummy orange residue was purified by silica gel chromatography (benzene eluent). The product was isolated in varying yields (*ca.* 0.3–1.0 g for *ca.* 12 g of olefin and 1.8 g of 9-diazofluorene). ^{1}H NMR: δ 1.66 (dd, 1 H, J = 5, 8 Hz), 2.04 (dd, 1 H, J = 5, 9 Hz), 2.24 (q, 1 H, J = 8 Hz), 2.65–2.85 (m, 2 H), 3.65 (s, 3 H), 7.06 (d, 1 H, J = 7 Hz), 7.15 (d, 1 H, J = 8 Hz), 7.25–7.45 (m, 4 H), 7.83 (dd, 2 H, J = 8, 15 Hz). ^{13}C NMR: δ 22.9, 26.2, 33.7, 51.7, 118.9, 119.7, 120.2, 121.3, 126.0, 126.2, 126.9, 128.2, 139.2, 141.1, 144.1, 148.2, 172.7. HRMS (ethyl ester): calcd for $C_{19}H_{18}O_2$, 278.1306; found, 278.1304.

2-(Carboxymethyl)spiro[cyclopropane-1,9′-fluorene] (7c). The spiro acid was prepared by transesterification of the corresponding methyl ester to the trimethylsilyl ester and hydrolysis according too a reported procedure.[39] Ester **7** (X = CH_2CO_2Me) (1.2 g, 4.55 mmol) was added to a suspension of anhydrous NaI (3.41 g, 22.73 mmol) in 100 mL of dry acetonitrile. Distilled trimethylsilyl chloride (2.9 mL, 22.73 mmol) was added dropwise via a syringe. The mixture was heated at reflux for 48 h. The reaction was cooled to room temperature and quenched by the addition of 5 mL of chilled water. The mixture was concentrated under reduced pressure, and the residue was dissolved in ether. The organic phase was washed once with water and aqueous 1 N HCl solution and thrice with aqueous 10% NaOH solution (until the basic wash was colorless). The basic washes were then combined and acidified with concentrated HCl. The carboxylic acid was extracted by washing the aqueous extracts several times with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and concentrated to give a beige oil (0.8 g, 70%) that was used in the preparation of **7d** without purification. ^{1}H NMR (for **7c**): δ 1.66 (t, 1 H, J = 5 Hz), 2.05 (dd, 1 H, J = 5, 9 Hz), 2.23 (q, 1 H, J = 7 Hz), 2.65–2.90 (m, 2 H), 7.06 (d, 1 H, J = 7 Hz), 7.14 (d, 1 H, J = 7 Hz), 7.25–7.45 (m, 4 H), 7.83 (dd, 2 H, J = 7, 15 Hz). A signal for the hydroxyl proton was not observed.

[[(Spiro[cyclopropane-1,9′-fluorene]-2-yl)methyl]carbonyl]oxy]-2(1*H*)-pyridinethione (7d). Acid chloride **7** (X = CH_2COCl) was prepared

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(37) Prepared by reaction of the corresponding acid chloride[38] with methanol, bp 100–105 °C.

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from acid **7c** (0.42 g, 1.7 mmol) by the method described above in the preparation of **4d**. Subsequent procedures were conducted in vessels shielded from light. The crude acid chloride in 5 mL of benzene was transferred by cannula into a suspension of 2-mercaptopyridine *N*-oxide sodium salt (0.29 g, 2.0 mmol) and DMAP (20 mg, 0.2 mmol) in 10 mL of benzene. The mixture was stirred overnight before a conventional workup. Drying ($MgSO_4$) and distillation of solvent at reduced pressure gave 0.54 g (89%) of crude **7d** as an oil. Silica gel chromatography (benzene–ethyl acetate, 9:1) yielded 0.34 g (56%) of **7d** as a light yellow oil that was judged to be >95% pure by ^1H NMR analysis. ^1H NMR (C_6D_6): δ 1.34 (t, 1 H, J = 7 Hz), 1.64 (dd, 1 H, J = 5, 9 Hz), 2.08 (qt, 1 H, J = 6 Hz), 2.51 (dd, 1 H, J = 7, 18 Hz), 3.01 (dd, 1 H, J = 8, 17 Hz), 5.23 (t, 1 H, J = 6 Hz), 5.89 (t, 1 H, J = 7 Hz), 6.15 (d, 1 H, J = 8 Hz), 6.61 (d, 1 H, J = 8 Hz), 6.85 (d, 1 H, J = 8 Hz), 7.0–7.2 (m, under C_6HD_5 signal), 7.31 (d, 1 H, J = 6 Hz), 7.57 (d, 1 H, J = 8 Hz), 7.62 (d, 1 H, J = 8 Hz).

Kinetic studies were similar to those previously reported,[7] with the exception that stock solutions of PhSeH in THF were prepared immediately before the mixtures for kinetic studies were prepared. PhSeH was contaminated with PhSeSePh (<10%) and bromobenzene (<2%), as determined by GC analysis, for which the concentration of PhSeH was corrected. Reaction mixtures were prepared in Pyrex tubes that were flame-dried under N_2, septum-sealed, wrapped in aluminum foil, and held in a −78 °C bath and that contained a small stir bar. Mixtures of the appropriate PTOC ester and an internal standard (pentadecane for **4d**, **5d**, and **6d**; heneicosane for **7d**) in THF were added by syringe followed by a solution of PhSeH in THF; typical total volumes were 0.8–1.2 mL. The tubes were flame-sealed under reduced pressure and then placed in a bath at the desired reaction temperature. The bath temperatures were observed to be constant to ±1 °C. After several minutes of equilibration, the aluminum foil shields were removed, and the mixtures were irradiated with a 150 W tungsten filament lamp at a distance of *ca.* 1 m. After 30–60 min, the reaction tubes were cooled to −78 °C and opened, and the mixtures were immediately analyzed by GC on a low-polarity (SE-54 or DB-5), wide-bore capillary column. Yields were determined relative to the internal standard using predetermined response factors. The identities of the products were confirmed by co-injection with authentic samples and by GC mass spectral analysis (DB-5 column). The method employed for determining the yields of cyclic product **7e** from reaction of PTOC ester **7d** is discussed in the text.

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Supplementary Material Available: Methods for preparations and spectral properties of compounds **4c–6c**, **4e–7e**, and **8b–10b** and intermediates in their syntheses (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.