Laser Flash Photolysis Measurements of the Kinetics of Ring Opening of the 2,2-Diphenylcyclobutylcarbinyl Radical

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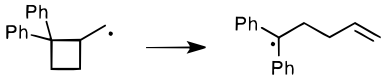
Ring opening of the cyclopropylcarbinyl radical (**1a**) to the homoallyl radical (**2a**) is one of the more familiar radical rearrangements. The addition of aryl groups at C2 in the cyclopropyl ring, such as in **1b**, results in radicals that ring open exceedingly fast, with lifetimes at ambient temperatures of only a few picoseconds.[1,2] Such ultrafast radical rearrangements have been incorporated into mechanistic probes that can compete effectively against any follow-up reaction of a transient radical intermediate. Phenyl-substituted cyclopropylcarbinyl radicals also are useful for mechanistic and kinetic studies that employ laser flash photolysis (LFP) methods because the benzylic and diphenylalkyl radical products have chromophores in a relatively clean region of the UV spectrum, at about 320 and 335 nm, respectively.[3−5]

1a: R = H
1b: R = Ph

2a: R = H
2b: R = Ph

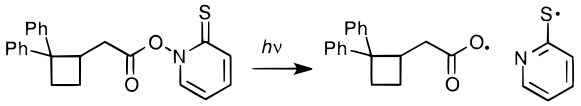
The very fast fragmentations of radical **1b** and other aryl-substituted cyclopropylcarbinyl radicals are appropriate for many studies, but they are too fast for one type of mechanistic investigation. Specifically, if a radical such as **1b** were formed in a radical−radical or radical−ion pair, ring opening would occur faster than diffusion-limited processes that lead to diffusively free species. We desired a relatively fast, UV-detectable radical probe element that could "report" only on diffusively free intermediates to complement the aryl-substituted cyclopropylcarbinyl probes. We describe here the calibration of such a reaction, ring opening of the 2,2-diphenylcyclobutylcarbinyl radical (**3**) to radical **4**.



3 **4**

Results and Discussion

For LFP kinetic studies, alkyl radicals are conveniently produced by decarboxylation of the corresponding acyloxyl radicals, which is "instant" on the nanosecond time scale.[6,7] Barton's PTOC esters[8,9] are especially good sources of acyloxyl radicals because they have a long wavelength chromophore centered at about 360 nm and are cleaved with high efficiency by 355 nm light from a Nd:YAG laser.[10,11] PTOC ester **5** was prepared from (2,2-diphenylcyclobutyl)acetic acid by the mild 2,2′-dipyridyl disulfide bis-*N*-oxide method.[12] Because of the potential utility of radicals such as **3** as reporter groups for LFP kinetic studies, we explored various synthetic pathways for synthesis of the carboxylic acid on a multigram scale. Details of convenient preparative sequences are provided in the Supporting Information.



5 **6** **7**

Photolysis of THF solutions containing PTOC ester **5** with 355 nm light from a Nd:YAG laser initially gave acyloxyl radical **6** and the pyridine-2-thiyl radical (**7**), which has λ_{max} at 490 nm.[13] Decarboxylation of **6** gave radical **3** "instantly", and the signal from radical **4** evolved with time. Figure 1 shows a time-resolved spectrum obtained at −20 °C. The traces in the main figure were "baseline adjusted" by subtraction of the initially observed spectrum from subsequent spectra, and the only apparent change on the short time scale employed is the growth of the signal at $\lambda_{max} = 335$ nm, which is the expected region for absorbance from radical **4**.[14] The inset shows the initial spectrum obtained 30 ns after firing the laser; the strong bleaching centered at about 360 nm is due to destruction of precursor **5**, and the absorbance at 490 nm is due to radical **7** that was formed instantly.

The kinetics of formation of radical **4** were measured in the temperature range −50 to 0 °C. Typical temperature fluctuations during the course of a run were 0.1 °C at 0 °C and 0.6 °C at −50 °C. The random error introduced by temperature fluctuations apparently was the largest source of error. Complete kinetic results are provided in the Supporting Information and are shown graphically in Figure 2.

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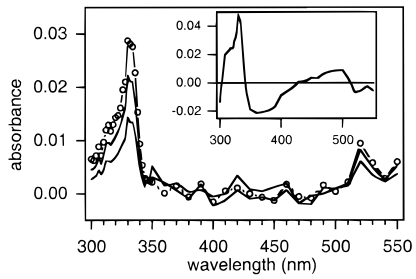


Figure 1. Time-resolved spectra from reaction of radical **3** in THF at −20 °C. The spectra are from 60, 40, and 30 ns with data from 20 ns subtracted to give a baseline. Symbols on the 60 ns trace show the monitoring wavelengths. The inset shows the actual spectrum observed at 20 ns.

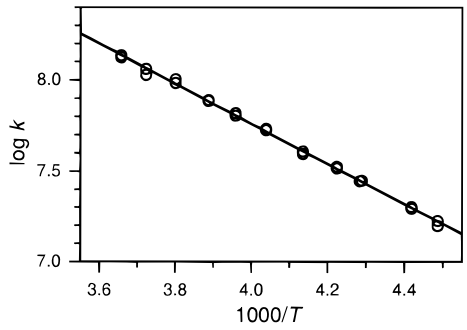


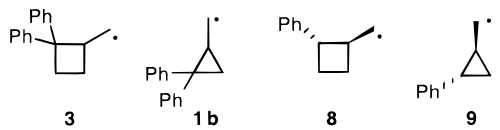
Figure 2. Kinetics of ring opening of radical **3** in THF. The line is eq 1.

The rate constants for ring opening of radical **3** ranged from 1.6×10^7 s^{-1} at −50 °C to 1.4×10^8 s^{-1} at 0 °C. In the configuration of the kinetic spectrometer used for this study, an instantaneous impulse signal gave a measured rate of growth of 5×10^8 s^{-1}. Convolution of this instrument response with the fast rate constants measured at 0 °C is relatively unimportant. Data obtained at temperatures greater than 0 °C were convoluted with the instrument response and are not reported. Only data acquired after the end of the laser pulse was used for the kinetic solutions.

The Arrhenius function for ring opening of **3** is given in eq 1

$$\log(k/\mathrm{s}^{-1}) = (12.17 \pm 0.09) - (5.04 \pm 0.10)/\theta \quad (1)$$

where $\theta = 2.3RT$ in kcal/mol and the listed errors are at 2σ. The precision in the Arrhenius parameters is noteworthy in that it is better than the precision in the determinations of the second-order rate constants for reactions of radicals with hydrogen atom transfer trapping agents that are used to calibrate radical clocks via indirect studies.[15−17] From eq 1, one calculates a rate constant for ring opening of radical **3** of 2.54×10^8 s^{-1} at 20 °C. This reaction is about 3 orders of magnitude less rapid at 20 °C than ring opening of the corresponding cyclopropylcarbinyl system, the (2,2-diphenylcyclopropyl)-methyl radical (**1b**).[1,18,19]



On the basis of the kinetics of ring openings of unsubstituted cyclobutylcarbinyl[20,21] and cyclopropylcarbinyl[19] radicals, one would have expected the difference in kinetics of ring openings of radicals **3** and **1b** to be 4 orders of magnitude. In fact, the difference in rate constants for ring opening of the (*trans*-2-phenylcyclobutyl)methyl[22] radical (**8**) and the (*trans*-2-phenylcyclopropyl)methyl[1,18,19] radical (**9**) is almost exactly 4 orders of magnitude. Thus, the ring opening of **3** is faster than expected; this results from a considerable reduction in the activation energy for cleavage of **3** relative to that found for radical **8** (about 3 kcal/mol), which more than offsets an entropic term for **3** that is slightly less favorable than that of **8**.[22] High-level computations have shown that the kinetics of ring openings of cyclopropylcarbinyl radicals are influenced by subtle steric effects in the transition states,[23,24] and we speculate that ring opening of radical **3** might be accelerated by relief of strain energy from an interaction involving the *cis*-phenyl group.

Our objective in studying the ring opening of radical **3** was to obtain a well calibrated, radical reaction that provided a strong chromophore in the product for use in LFP applications and reacted less rapidly than diffusional processes. In a mechanistic study, any rearrangement of radical **3** or other 2-aryl-substituted cyclobutylcarbinyl radicals must occur from diffusionally free species. This property complements that of the corresponding diphenylcyclopropylcarbinyl radicals such as **1b**, which fragment fast enough to compete with coupling reactions within a radical−radical or radical−ion pair. Rearrangement of radical **3** also provides two other potentially useful facets. It can serve as a calibrated radical clock, somewhat faster than the cyclopropylcarbinyl radical, with rate constants determined at least as precisely as those of the cyclopropylcarbinyl radical.[19] In addition, the high precision in the Arrhenius parameters found in this work could prove useful for computational chemists who wish to evaluate their methods for calculations of aryl-substituted radical systems, which are notoriously difficult to handle computationally.

Experimental Section

(2,2-Diphenylcyclobutyl)acetic Acid 2-Thioxo-2*H*-pyridin-1-yl Ester (5). To a solution of (2,2-diphenylcyclobutyl)acetic acid (see Supporting Information) (200 mg, 0.75 mmol) and 2,2′-dipyridyl disulfide bis-*N*-oxide[12] (208 mg, 0.83 mmol) in dry CH_2-

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Cl_2 (5 mL) in a 25 mL flask wrapped with aluminum foil and placed in an ice−salt bath was added *n*-Bu_3P (190 μL, 0.75 mmol) under N_2. The reaction mixture was stirred for 40 min at room temperature and diluted with 10 mL of CH_2Cl_2. The solution was washed with 10% Na_2CO_3, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was isolated by column chromatography on silica gel (1:1, hexanes/ethyl acetate) to yield 200 mg (0.53 mmol, 71%) of **5** as a yellow oil. The sample was judged to be 90% pure on the basis of the NMR spectra. ^{1}H NMR: δ 1.98 (m, 1H), 2.26 (dd, J = 16.8 Hz, J = 6.4 Hz, 1H), 2.33−2.49 (m, 2H), 2.67 (dd, J = 16.4 Hz, J = 5.2 Hz, 1H), 3.05 (m, 1H), 3.78 (m, 1H), 6.58 (dt, J = 6.8 Hz, J = 2.0 Hz, 1H), 7.15−7.33 (m, 11H), 7.40 (dd, J = 6.8 Hz, J = 1.6 Hz, 1H), 7.64 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H). ^{13}C NMR: δ 23.5, 31.9, 35.4, 38.7, 53.8, 112.5, 125.8, 126.3, 126.4, 127.8, 128.3, 128.3, 133.5, 137.3, 137.5, 143.4, 149.8, 167.9, 175.7.

Kinetic studies were accomplished with an Applied Photophysics LK-50 kinetic spectrometer employing a Nd:YAG laser for production of 355 nm light (ca. 40 mJ/pulse)**.** Data were acquired with a 2 GHz digitization rate. Dilute solutions of radical precursor **5** in THF were prepared such that the absorbance at 355 nm was 0.4−0.5 (ca. 3 × 10^{-5} M). The solutions were thermally equilibrated in a jacketed addition funnel with continuous He sparging through a gas dispersion tube. Temperature control was accomplished by circulating solution from a temperature-regulated bath through the outer jacket of the addition funnel. The solutions were allowed to flow through a 1 cm × 1 cm quartz flow cell of conventional design at a rate of ca. 20 mL/min; under the conditions used, a fresh solution of precursor was used for each pulse experiment. The reaction temperatures were measured with a thermocouple inserted in the flowing stream a few millimeters above the irradiation zone. Detailed results are given in Supporting Information. Typical errors in the kinetic solutions were <5%.

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Supporting Information Available: Experimental methods for preparation of (2,2-diphenylcyclobutyl)acetic acid, NMR spectra of new compounds, and kinetic results for ring opening reactions of radical **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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