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Kinetic Analysis of the Rearrangement of a Conformationally Constrained α-Cyclopropylbenzyl Radical

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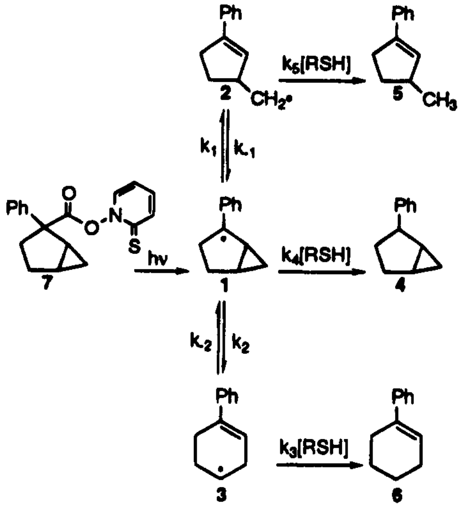
Summary: Modulation of the cyclopropylmethyl (CPM)/homoallyl radical equilibrium by phenyl substitution at the radical center is exploited in determining the kinetic versus thermodynamic preference for bond scission in a bicyclic CPM radical. Exocyclic ring opening is determined to be 28.7 times faster than the respective endocyclic process. This method will be of general use for determining the regioselectivity of radical rearrangements.

Radical rearrangements, including the cyclopropylmethyl system (and its oxiranyl analogue) are not only used as mechanistic probes but are also finding increasing application in organic synthesis.[1,2] Conformationally constrained cyclopropylmethyl radicals often exhibit a high degree of stereoelectronic control in their ring-opening reactions. Under radical-trapping conditions in which ring-opening processes are essentially irreversible, exocyclic cyclopropane bond scission typically predominates over endocyclic bond cleavage, even though the latter transformation is often favored thermodynamically.[1e,3] Strategically positioned radical-stabilizing substituents on the cyclopropane ring are useful for overcoming the stereoelectronically favored exocyclic ring-opening process.[4] Alternatively, it has been shown that the more stable of two possible homoallyl radicals derived from cyclopropane ring opening can be preferentially trapped under conditions where reclosure is competitive with radical quenching.[5] Kinetic analysis of both the ring opening and closing processes is often hindered by the large differences in magnitude of the rate constants that are involved. Herein, we report the first kinetic characterization of a conformationally constrained and readily reversible cyclopropylmethyl radical rearrangement (Scheme 1).

Scheme 1



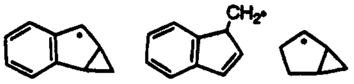
Tin hydride trapping studies of cycloprop[2,3]inden-1-yl (**8**), and the primary radical formed from its ring opening (**9**), illustrate the ability of benzylic stabilization to modulate the equilibria of cyclopropylcarbinyl/allylcarbinyl radical rearrangements.[6,7] Information on the equilibria between ring-opened (**9**) and -closed (**8**) radicals in this system was not extracted from these experiments.[7] However, time-resolved measurements of the parent α-cyclopropyl benzyl radical revealed that the phenyl substituent alters the equilibrium significantly and results in favoring the ring-closed isomer by 1.38 kcal/mol at 315 K.[8] Phenyl-substituted bicyclo[3.1.0]hexyl radical **1** was designed to take advantage of benzylic stabilization, in order to illustrate the thermodynamic preference for endocyclic ring scission. Equations 1−3 which describe

$$\frac{[4]}{[5]} = \frac{k_4[1][RSH]}{k_5[2][RSH]} = \frac{k_{-1}k_4}{k_1k_5} + \frac{k_4}{k_1}[RSH] \qquad (1)$$

$$\frac{[4]}{[6]} = \frac{k_4[1][RSH]}{k_3[3][RSH]} = \frac{k_{-2}k_4}{k_2k_3} + \frac{k_4}{k_2}[RSH] \qquad (2)$$

$$\frac{[5]}{[6]} = \frac{k_5[2][RSH]}{k_3[3][RSH]} = \left(\frac{k_1}{k_2}\right)\left[\frac{(k_{-2}/k_3) + [RSH]}{(k_{-1}/k_5) + [RSH]}\right] \qquad (3)$$

the dependency of product ratios as a function of trap concentration, are based upon the assumption of steady-state behavior for **2** and **3** (Scheme 1). The relative magnitudes of rate constants that describe the reactivity of the radical species depicted in Scheme 1 are obtained from the relationships expressed in eqs 1−3.



8 **9** **10**

Radical **1** was generated from the respective [(2-thioxopyridinyl-*N*-oxy]carbonyl (PTOC) substrate (**7**). The PTOC esters have been used extensively in recent years

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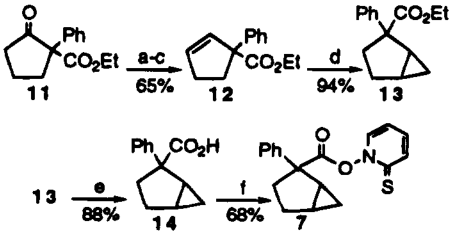
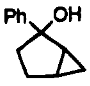
Scheme 2[a]



[a] Key: (a) NaBH$_4$, EtOH, 0 °C; (b) CH$_3$SO$_2$Cl, pyridine, 0 °C; (c) DBU, DMAP (cat.) toluene, reflux; (d) Et$_2$Zn, CH$_2$I$_2$, hexanes, −78 °C to 25 °C; (e) 0.2 N KOH, dioxane/H$_2$O, 90 °C; (f) 2-mercaptopyridine *N*-oxide, DCC, DMAP, CH$_2$Cl$_2$, 25 °C.

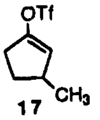
for kinetic studies of radical reactions.[1b,9,10] Ester **7** was prepared from the requisite carboxylic acid **14**, which was synthesized starting from known β-keto ester **11** (Scheme 2).[11] Cyclopropanation of **12** was achieved using diethylzinc and diiodomethane. Although the stereochemistry of the reaction was not rigorously established, we suspect that the carbethoxy group directs the cyclopropyl ring to be *cis* with respect to itself via coordination with the zinc.

Each of the expected products was independently synthesized as well. Ring-closed product **4** was formed via BF$_3$, mediated borane reduction of **15**. The benzyl alcohol was obtained via PhLi addition to the respective bicyclic ketone (**16**).[12a] We believe that the stereochemistry of **4** is such that the phenyl ring is *cis* with respect to the cyclopropane ring, as a result of backside displacement of the activated alcohol by BH$_3$.[12b] The hydroxyl group is believed to be *cis* with respect to the cyclopropane, since nucleophilic attack on the carbonyl of **16** should occur on the face opposite to that containing the cyclopropane. The stereochemistry obtained in independently synthesized **4** should be identical to that which one would expect from quenching **1** with a thiol.[13] Methylcyclopentene (**5**) is unstable for prolonged periods at −20 °C and was freshly prepared for stability studies and analytical standardization from the known vinyl triflate (**17**) via cuprate addition.[14]



15

16



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Quantitative analysis of **4** and **5** was complicated by the fact that they were inseparable on a variety of fused silica capillary columns. Fortunately, **4** and **5** exhibit distinctive mass spectral cracking patterns under EI conditions. Bicyclo[3.1.0]hexane **4** yields a strong styrene fragment (m/z = 104) compared to **5**, which has a much stronger molecular ion (m/z = 158). This enabled quantitation of **4** and **5** under conditions in which they coeluted using selected ion monitoring GC/MS. The intensity of the above-mentioned ions were calibrated for **4** and **5** individually, relative to the C$_6$H$_{13}$ fragment of *n*-hexadecane. For convenience, 1-phenylcyclohexene (**6**) was quantitated by this method as well. Photolyses of degassed benzene solutions of **7** (25 mM) in a temperature-controlled bath using a 275-W tungsten sun lamp were complete within 15 min. Products **4**−**6** were formed between 55% and 85% combined yield. Prolonged irradiation (3 h) of the radical-trapping products under identical conditions resulted in slight (~10%) decomposition of these materials.

The qualitative dependence of product formation on the concentration of hydrogen atom donor (Figures 1 and 2) is consistent with the behavior outlined in Scheme 1. As predicted by eqs 1 and 2, the product ratios of **4**:**5** and **4**:**6** varied linearly with respect to *tert*-butyl thiol concentration (Figure 1).[15] Furthermore, the small variation of the ratio of **4**:**5** with respect to hydrogen atom donor concentration suggests that **1** and **2** are rapidly interconverting under the trapping conditions. The nonlinear dependence of the ratio of **5**:**6** on thiol concentration also indicates that at least one of the ring-opening pathways followed by **1** is reversible (Figure 2). This observation is consistent with the relationship described by eq 3. The small value of the y-intercept obtained from the plot of **4**:**6** versus hydrogen atom donor concentration suggests that $k_{-2} \ll k_3$. Determination of the magnitude of k_{-2} is discussed in more detail below and is supported by extracting k_{-2}/k_3 from the dependency of the ratio of **5**:**6** on thiol concentration (Figure 2, eq 3) using the values of k_1/k_2 and k_{-1}/k_5 determined from the data presented in Figure 1.

The ratio of k_1:k_2 is determined from the average values of k_4/k_1 and k_4/k_2, which are obtained from the slopes of the plots of [**4**]:[**5**] and [**4**]:[**6**] versus *tert*-butyl thiol concentration. The ratio of rate constants for ring opening is independent of the magnitude of k_4 and is equal to 28.7. This is very similar to the analogous ratio of rate constants that can be extracted from the products formed from the ring opening of **10** in neat Bu$_3$SnH. Depending upon the magnitude approximated for k_4, the rate constant for exocyclic ring opening from **1** (k_1) is estimated to be between 0.4−3.1 (±0.1)) × 10^7 s^{-1} and k_2 = (0.16−1.1 (± 0.2)) × 10^6 s^{-1}.[16] Information regarding the rate constants for ring closure of **2** and **3** are also obtainable from the dependency of product ratios on trap concentration (Figure 1). Dividing the value of the y-intercept by the slope of the line obtained from plotting [**4**]:[**5**] versus trap concentration indicates that $k_{-1} = 3k_5$ (eq 1). Similar analysis of the line obtained by plotting [**4**]:[**6**] versus trap concentration indicates that the rate constant for ring closure of **3** is essentially too slow to compete with hydrogen atom trapping (eq 2). Assuming that $k_3 \sim k_5 \sim 8.0 \times 10^6$ M^{-1} s^{-1}, we estimate that $k_{-1} \sim 2.4 \times 10^7$ s^{-1} and $k_{-2} < 2.4 \times 10^4$ s^{-1}.[17,18] Absolute rate constant data for *t*-BuSH

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[13] Capillary GC/MS analysis does not provide any evidence for another diastereomer of **4**.

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[15] Each data point in Figure 1 is an average of at least two injections. Product ratios as a function of thiol concentration were measured three times. Average values obtained from linear regression analysis of these data are as follows: $k_4/k_1 = 3.83\ (\pm 0.2) \times 10^{-3}$; $(k_4k_{-1})/(k_1k_5) = 1.15\ (\pm 0.06) \times 10^{-2}$; $k_4/k_2 = 0.11\ (\pm 0.01)$; $(k_4k_{-2})/(k_2k_3) = 3.25\ (\pm 5.3) \times 10^{-4}$.

[16] The absolute rate constant for hydrogen atom abstraction from *tert*-butyl thiol by a benzyl radical has not been reported. The range of k_4 is estimated by extrapolating from the reported value for k_H from Bu$_3$SnH and PhSH by benzyl radical. The relative reactivity of *tert*-butyl thiol versus these donors with respect to other similar alkyl radicals is used as a calibration. By using this method, k_4 is estimated to lie between 1.8 × 10^4 M^{-1} s^{-1} (based upon PhSH) and 1.2 × 10^5 M^{-1} s^{-1} (based upon Bu$_3$SnH). For a tabulation of absolute rate constants for hydrogen atom abstraction by alkyl radicals, see ref 1b and references cited therein.

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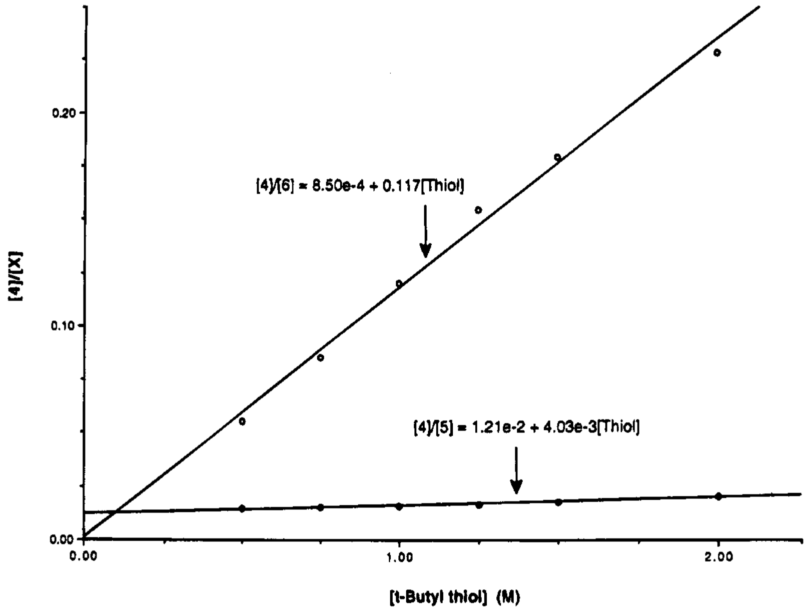

Figure 1. Plots of [**4**]/[**5**] (●) and [**4**]/[**6**] (○) versus [*tert*-butyl thiol].

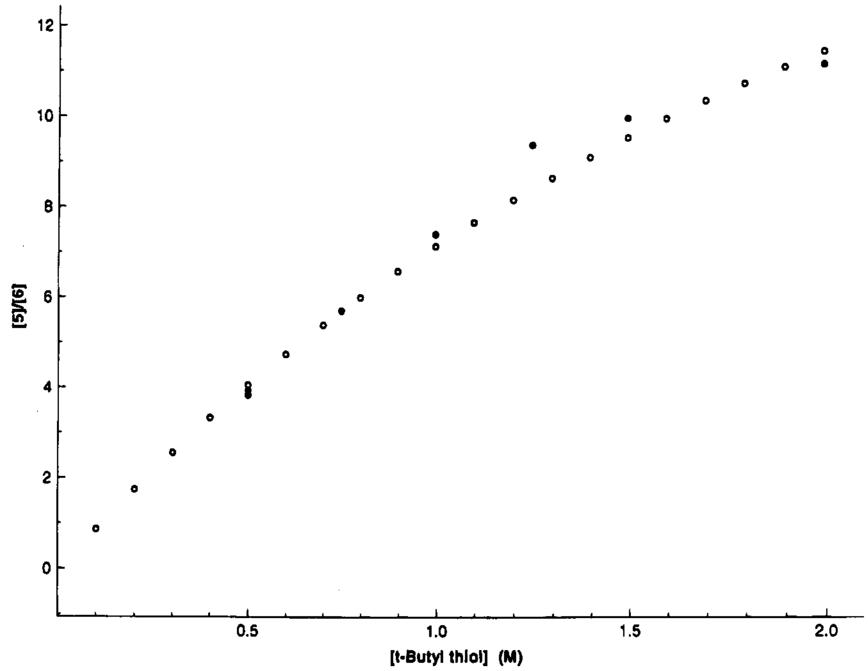

Figure 2. Plot of [**5**]/[**6**] versus [*tert*-butyl thiol]. (●) Experimentally determined. (○) Calculated.[20]

and Bu_3SnH, which react with alkyl radicals at very similar rates, suggest that the ratio of k_5:k_3 ranges between 1 and 2.[1b] Therefore, it is possible that the magnitude of k_{-2} is half as large as the value stated.

The equilibria constants K_{13} (~6.7–45.8) and K_{12} (~0.17–1.3) are estimated directly from the magnitude of rate constants determined for ring-opening and -closing processes.[19] At 298 K this translates into a $\Delta\Delta G$ = 2.1–2.3 kcal/mol for the two equilibria and confirms the prediction that endocyclic ring fission is the thermodynamic pathway for **1**. Assuming that $k_3 \sim k_5$, the difference in ΔG can also be obtained from the ratio of *y*-intercepts of the plots in Figure 1. Modulation of the cyclopropylmethyl radical equilibria by the phenyl substituent is crucial for enabling us to determine the differences in these two systems. Similar stabilization should be a useful tool for determining the effects of structure on the regioselectivity and equilibria of other radical rearrangements.

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[18] The magnitude of k_{-2} noted is believed to represent a maximum for this process. The standard deviation (6.6 × 10^{-3}) of the *y*-intercept (from which k_{-2} is extracted) obtained from a plot of [**4**]:[**6**] versus [thiol] is greater than its average magnitude. Nonlinear regression analysis of [**5**]:[**6**] versus [thiol] is consistent with this (k_{-2}/k_3 = −0.006). Numerical analysis was carried out using the computer program, Horizon II (Star Blue Software, Inc. v 1.1.2).

[19] K_{13} = [**3**]/[**1**] = k_2/k_{-2}; K_{12} = [**2**]/[**1**] = k_1/k_{-1}.

[20] The simulated data in Figure 2 result from evaluating eq 3 using values for k_1/k_2 and k_{-1}/k_5 derived from data presented in Figure 1 and k_{-2}/k_3 determined via nonlinear regression analysis.

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Supplementary Material Available: Experimental procedures for the synthesis of **4**, **5**, and **7**, as well as derivation of kinetic expressions and equations for the quantitative analysis of **4** and **5** by GC/MS (5 pages). This material is contained in 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.