Conformational Control of Regioselectivity: Rearrangements of Cyclopropylcarbinyl and 5-Substituted Pent-3-enyl Radicals[1]

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Alkylthiyl and arylthiyl radicals underwent efficient addition to 1,1-dicyclopropylethylene. The addition was followed by rapid opening of one of the cyclopropyl rings, leading to radicals 3 ($RSCH_2C(c-C_3H_6)CHCH_2\dot{C}H_2$) at temperatures between −90 and −60 °C. Above −60 °C, 3 underwent a second rearrangement, involving a 1,5-hydrogen shift, to give allyl radicals 5 ($RS\dot{C}HC(c-C_3H_6)CHCH_2CH_3$). Both reactions showed a remarkable degree of regiospecificity that was dictated by radical conformation and that led to a single isomer as product. A kinetic study of the rearrangement of 3 to 5 (RS = t-BuS) led to the Arrhenius equation, $\log (k_6/s^{-1}) = (9.5 \pm 0.7) - (6.3 \pm 0.7)/\theta$, where $\theta = 2.303RT$ kcal mol^{-1}. This reaction was used in a product study to measure the rate constant for hydrogen abstraction by a primary alkyl radical from t-BuSH ($k_{14} = 2 \times 10^5$ M^{-1} s^{-1}).

In general, simple olefins do not function as efficient scavengers of sulfur- or tin-centered radicals because these addition reactions are readily reversible (eq 1).[2,3] However, scavenging can be efficient if the β-substituted ethyl radical (1) that results from the addition can undergo a rapid rearrangement.

$$X = R_3Sn, RS$$
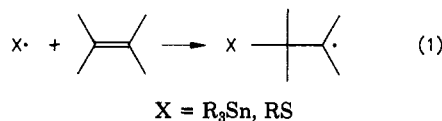
In a series of elegant experiments, Davies and his colleagues[4,5] have shown that various monocyclopropylethylenes serve as excellent traps for both sulfur- and tin-centered radicals (eq 2). The opening of the cyclopropyl ring is far more rapid than the elimination of X, and the regioselectivity of the process shows an interesting dependence on the nature of the ring substituents.[6]
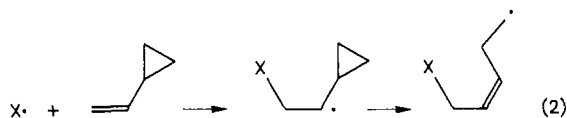
We have taken advantage of the cyclopropylcarbinyl radical rearrangement in kinetic studies of thiyl radical reactions and have used 1,1-dicyclopropylethylene as a thiyl radical scavenger.[7] During the course of this work, we found that the resulting 5-substituted pent-3-enyl radicals underwent a novel 1,5-rearrangement.[8] Both of the rearrangement processes showed a remarkable degree of regioselectivity that was dictated by radical conformation. In this work, we describe kinetic and spectroscopic studies of these reactions and the use of the rearrangement process as a "free-radical clock"[9] for measuring the rate constant for the reaction of a primary alkyl radical with a thiol.

Experimental Section

Materials. With the following exceptions, all of the materials used in this study were reagent grade, commercial samples that were purified by standard methods. Di-*tert*-butyl disulfide was carefully fractionated to remove impurities of tri- and tetrasulfides, which, on photolysis, give rise to the *tert*-butylperthiyl radical. Di-*tert*-butyl peroxide was washed with an aqueous solution of silver nitrate and then water. It was dried over magnesium sulfate

(1) Issued as NRCC publication No. 28741.

(2) Walling, C.; Helmreich, W. *J. Am. Chem. Soc.* **1959**, *81*, 1144.

(3) Jackson, R. A.; Ingold, K. U.; Griller, D.; Nazran, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 208. Davies, A. G.; Roberts, B. P.; Tse, M.-W. *J. Chem. Soc., Perkin Trans. 2* **1978**, 145.

(4) Blum, P. M.; Davies, A. G.; Pereyre, M.; Ratier, M. *J. Chem. Res., Synop.* **1980**, 110. Blum, P. M., et al. *J. Chem. Res., Miniprint* **1980**, 1174.

(5) Ratier, M.; Pereyre, M.; Davies, A. G.; Sutcliffe, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1907.

(6) Davies, A. G.; Godet, J.-Y.; Muggleton, B.; Pereyre, M. *J. Chem. Soc., Chem. Commun.* **1976**, 813. Blum, P.; Davies, A. G.; Pereyre, M.; Ratier, M. *J. Chem. Soc., Chem. Commun.* **1976**, 814. Davies, A. G.; Muggleton, B.; Godet, J.-Y.; Pereyre, M.; Pommier, J.-C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1719. Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 287. Davies, A. G.; Al-Hawari, J. A.; Grignon-Dubois, M.; Pereyre, M. *J. Organomet. Chem.* **1983**, *255*, 29.

(7) McPhee, D. J., unpublished results.

(8) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*, de Mayo, P., Ed; Academic: New York, 1980; Vol. 1, Chapter 4, p 251. Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472. Mariano, P. S.; Bay, E. *J. Org. Chem.* **1980**, *45*, 1763.

(9) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

Table I. Hyperfine Splitting Constants and *g* Factors for 3 at -70 °C

X	solvent[a]	g	$a^{H1}(2H)$	$a^{H2}(2H)$	$a^{H3}(1H)$
t-BuS	A	2.0026 (2)	22.1	29.7	0.89
$(CH_3)_2CHS$	A	2.0026 (1)	22.1	30.0	0.89
CH_3S	A	2.0026 (2)	22.0	30.0	0.9
$(CH_3)_3Sn$	B	2.0025 (6)	22.2	30.7	≤0.8
t-BuO	B	2.0021 (3)	22.2	30.0	≤0.8

[a] A = cyclopropane; B = isooctane.

and was finally passed through a column of neutral alumina. This process removes olefinic and hydroperoxide impurities.

Spectroscopy. Electron paramagnetic resonance (EPR) spectra were recorded on a Varian E104 spectrometer equipped with a gaussmeter and frequency counter. The magnetic field strength at the center of the cavity was calibrated by using the spectrum of the tetracene radical cation as a standard.[10] Radicals were generated photolytically by using a 1000-W mercury-xenon arc lamp, and the heating effect of the lamp at the sample was reduced to ca. 1° by filtering the light through a long-path-length, water-filled cell.
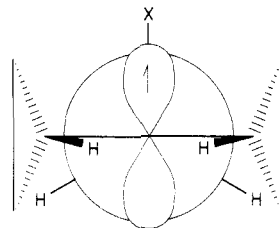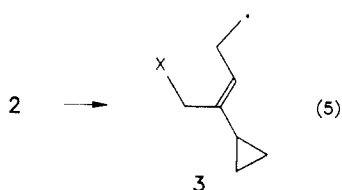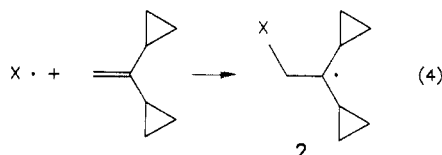
Radical concentrations were measured by double integration of appropriate lines in the EPR spectra and were calibrated by using benzene solutions of the 2,2-diphenyl-1-picrylhydrazyl radical. The signal from a ruby that was located in the spectrometer cavity was used to correct the integrated signals for variations in spectrometer sensitivity.

Samples for spectroscopy were prepared in standard quartz EPR tubes. In a typical preparation, di-*tert*-butyl disulfide (3% v/v) mixed with 1,1-dicyclopropylethylene (10% v/v) was deoxygenated by using three freeze–pump–thaw cycles prior to addition of cyclopropane as solvent.

Product Studies. Product studies were carried out on the radical chain reaction between *tert*-butyl thiol and 1,1-dicyclopropylethylene by using GC/mass spectrometry and GC for the analyses with decane as an internal standard. Mixtures of the thiol, olefin, and decane in isooctane solvent (total volume ca. 0.5 mL) were made up in quartz tubes and were deoxygenated by the freeze–pump–thaw method. The samples were warmed to 25 °C, and the reactions were initiated by photolyzing the samples in a Rayonet reactor (300 nm). The products were identified by using a GC/mass spectrometer (Hewlett-Packard 5995) and were quantified by GC (Hewlett-Packard 5890 A) using 10-m, 0.2-mm-diameter cross-linked methyl silicon columns.

Results and Discussion

EPR Spectra. Mixtures of various radical precursors and 1,1-dicyclopropylethylene, in cyclopropane or isooctane as solvent, were photolyzed in the cavity of an EPR spectrometer (eq 3-5). Radicals 2 were not detected even at the lowest accessible temperatures (ca. -90 °C), an observation that is certainly consistent with the known rate constants for the ring-opening of the prototypical radical in this series, cyclopropylcarbinyl.[11]

$$X-X \rightarrow 2X^\bullet \qquad (3)$$

$$(4)$$

$$(5)$$

(10) Segal, D. E.; Kaplan, M.; Fraenkel, G. K. *J. Chem. Phys.* 1965, *43*, 4191.

Figure 1. Conformation of 2 that leads to 3 as a unique product.

Table II. Hyperfine Splitting Constants and *g* Factors for Radicals 5 in Isooctane or Cyclopropane Solvent at 20 °C

| X	g	$a^{H1,3}(2H)$	$a^{H4}(2H)$	$a^{(H)}(1H)^a$	$a^{Hx}(1H)$
t-BuS	2.0038 (1)	11.9	10.4	2.5	
$(CH_3)_2CHS$	2.0035 (8)	12.1	10.3	2.7	1.1
CH_3S	2.0038 (4)	12.1	10.4	2.7	1.7[b]
PhS[c]	2.0033 (6)	12.1	10.1	2.6	

[a] Leading hydrogen of cyclopropyl group. [b] (3H). [c] Radical 3 was not detected at the lowest accessible temperature, -40 °C.

The EPR spectra showed a "triplet of triplets" hyperfine structure with splittings of ca. 22 G (2 H) and ca. 30 G (2 H), which we assigned to 3, Table I. Interestingly, only one isomer was detected even though two were possible (3, 4). We assigned the spectra to 3 on the basis of a

4
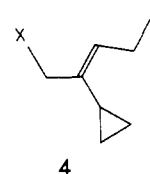
conformational argument, reasoning that the structure shown in Figure 1 would be the most probable conformation of its precursor, 2. Steric interactions are minimized in this conformation, and overlap between the Walsh orbitals[12] of the cyclopropyl rings and the orbital containing the unpaired electron is maximized. Cleavage of any of the cyclopropyl bonds would then lead uniquely to 3.

In the reactions where alkylthiyl or arylthiyl radicals were added to 1,1-dicyclopropylethylene, a new series of radicals, 5, was detected at -60 °C and above. The EPR parameters for these radicals are reported in Table II and indicate that radicals 5 were allylic with exo hydrogens in the 1- and 3-positions.[13] Moreover, as the temperature was increased, spectra due to 5 increased in intensity at the expense of those due to 3 until at 10 °C and above only spectra due to 5 were detected. The observations are entirely consistent with the 1,5 rearrangement described in eq 6. This process must be reasonably exothermic since it involves the transformation of a primary alkyl radical into an allylic radical.

$$3 \longrightarrow \qquad (6)$$

5
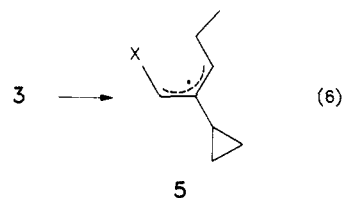
(11) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* 1976, *98*, 7024. Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *J. Am. Chem. Soc.* 1980, *102*, 1734.

(12) March, J. E. *Advanced Organic Chemistry*, 2nd ed.; McGraw Hill: Toronto, 1977; p 142.

(13) Griller, D.; Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* 1984, 1817.
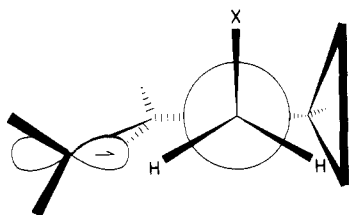
**Figure 2.** Conformation of **3** that leads to **5** as a unique product.

The formation of **5** with the bulky groups at the 1- and 3-positions in the endo positions is dictated by steric interections in the radical conformation that leads to the 1,5-hydrogen shift, Figure 2. As the hydrogen is transferred from the 5- to the 1-position, steric interaction between the RS and the cyclopropyl groups must cause the incipient allyl radical to collapse into **5**.

During the course of the two rearrangements that transform **2** to **5**, several isomers could have been formed, yet conformational constraints on the radicals involved in each of the steps ensured that only one specific isomer emerged as the final radical product. In essence, the reactions displayed a remarkably high degree of regiospecificity that was dictated by rather subtle conformational requirements.

Spectra due to **5** were only readily detected when alkylthiyl or arylthiyl radicals were added to 1,1-dicyclopropylethylene although, in other instances (X = *t*-BuO, Me$_3$Sn), weak lines were detected that might have been due to very low concentrations of these radicals. We presume that it is the bond-weakening effect of the thiyl group on its neighboring methylene that makes the hydrogen transfer particularly efficient in those cases.

Rate Constants for the Rearrangement of 3. Signal-to-noise levels in the EPR spectra were sufficient for spectral assignment but precluded accurate kinetic measurements for all of the rearrangement processes. As a consequence, we selected the best system (**3**, X = *t*-BuS) from the point of view of spectral intensity and measured rate constants for its rearrangement (eq 6) by using two approximations that were designed to overcome the signal-to-noise limitations.

In a situation where a radical, **5**, and its precursor, **3**, can be detected simultaneously by EPR spectroscopy, the rate constant for the rearrangement process can be defined with respect to the rate constants for the radical–radical reactions (eq 7–9).[14]

$$5 + 5 \rightarrow \text{nonradical products} \qquad (7)$$

$$5 + 3 \rightarrow \text{nonradical products} \qquad (8)$$
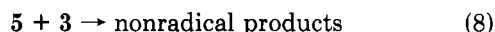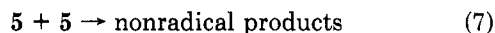
$$1/[5] = (2k_7/k_6)([5]/[3]) + k_8/k_6 \qquad (9)$$

In light of the poor signal-to-noise levels, it was not possible to vary the radical concentrations so as to separate slope and intercept in eq 9. We therefore applied the standard approximation, $2k_7 = k_8$, so as to simplify the treatment.[14] Under this condition, eq 10 applies.

$$1/[5] = (2k_7/k_6)([5]/[3] + 1) \qquad (10)$$

Radical concentrations were measured over the range of temperatures (−78 to 1 °C) and led to the values of $2k_7/k_6$ that are reported in Table III. We made no attempt to measure values for $2k_7$. Fischer and his colleagues[15,16] have shown that these measurements can only
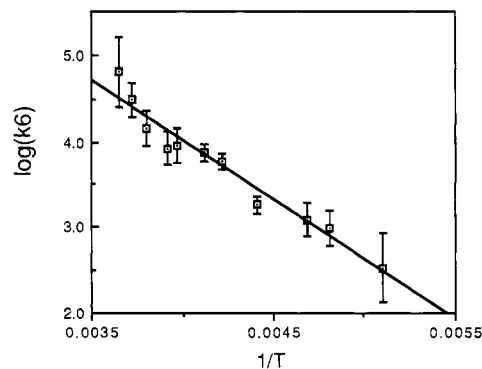

Figure 3. Arrhenius plot of log (k_6/s^{-1}) versus $1/T$ (K^{-1}) for the rearrangement of **3** to **5**.

Table III. Rate Constants for the Rearrangement of 3 to 5 (X = *t*-BuS)

T, K	$k_6/2k_7 \times 10^8$, M	$2k_7 \times 10^{-9}$, M^{-1} s^{-1}	$k_6 \times 10^{-3}$, s^{-1}
196	4.58	7.39	0.338
208	13.3	7.36	0.979
213	15.3	7.97	1.22
227	20.9	8.75	1.82
237	59.4	9.88	5.87
243	62.4	10.4	6.50
252	82.4	11.0	9.07
255	73.3	11.5	8.40
263	118	12.2	14.3
269	235	13.1	30.7
274	476	13.6	64.5

be made reliably under highly controlled conditions that ensure complete homogeneity of the radical concentrations and when signal-to-noise levels in the EPR spectra are particularly high. This was not the case for our spectra.

We estimated $2k_7$ by taking Fischer's data for the self-reaction of benzyl radicals, in toluene as solvent,[16] which were obtained over the range of temperatures used in this work. The data were then corrected by using the von Smoluchowski[15,16] and Stokes–Einstein equations[17] so as to allow for differences in the solvent viscosities[18,19] and radical sizes.[17] The latter correction was significant since, for the benzyl radical system that we used as a standard, both radicals and solvent molecules were of essentially the same size whereas, in our case, **5** (X = *t*-BuS) was much larger than the cyclopropane solvent molecules. The data for $2k_7$ are reported in Table III together with values of k_6.

An Arrhenius plot of the rate constants, k_6, for the rearrangement reaction is shown in Figure 3. The bars reflect the errors associated with measurements of the radical concentrations. These were much greater at the upper and lower extremes of temperature where the concentration of one of the radicals involved in the rearrangement was very much higher than the other. The data were fitted by a least-squares method that weighted the individual points so as to reflect these uncertainties, and the best fit to the data is shown in eq 11. The magnitude

$$\log (k_6/\text{s}^{-1}) = (9.5 \pm 0.7) - (6.3 \pm 0.7)/\theta \qquad (11)$$

where $\theta = 2.303RT$ kcal mol^{-1}

of the Arrhenius A factor reflects the loss in entropy associated with the formation of the transition state for the

(14) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 193.
(15) Schuh, H. H.; Fischer, H. *Helv. Chim. Acta* **1978**, *61*, 2130.
(16) Lehni, M.; Schuh, H.; Fischer, H. *Int. J. Chem. Kinet.* **1979**, *11*, 705.

(17) Levine, I. N. In *Physical Chemistry*; McGraw-Hill: New York, 1978; p 449.
(18) Andrusson, L. In *Landolt–Bornstein Numerical Data and Functional Relationships in Science and Technology*; Schafer, K., Ed.; Springer-Verlag: New York, 1969; Group II, Vol. 5, Subvol. a, p 160.
(19) Yaws, C. L.; Turnbough, A. C. *Chem. Eng. (N.Y.)* **1975**, *82*, 119.

rearrangement process and is close to that measured for the 5-hexenyl cyclization (log (A/s^{-1}) = 10.5)[20] where similar constraints apply. Extrapolation of the data to 25 °C gives $k_6 = 8 \times 10^4$ s^{-1}.

Rate Constant for Hydrogen Abstraction from *t*-BuSH. In a final series of experiments, we used the rearrangement of **3** to **5** as a "free-radical clock"[9] to measure the rate constant for hydrogen abstraction by a primary alkyl radical, **3**, from *tert*-butyl thiol. The kinetic scheme was based on a simple competition in which **3** underwent rearrangement to **5** or abstracted a hydrogen from the thiol (eq 12–14). The *tert*-butylthiyl radicals that are formed
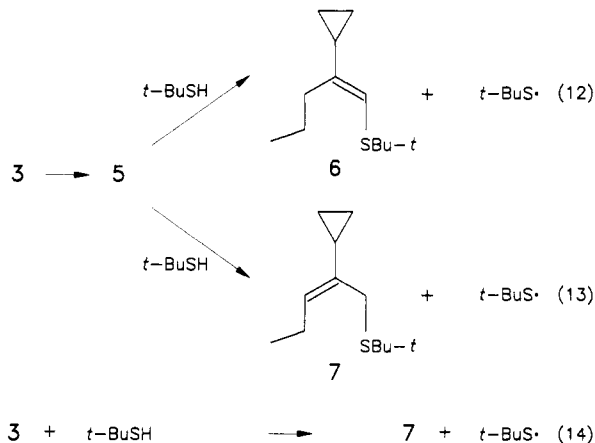
in these processes propagate the chain via reactions 4 and 5. There was a slight complexity in that product **7** is formed in both processes, but the problem was easily overcome by working at extremes of thiol concentration (vide infra).

Three reactions were carried out in isooctane solvent with 0.1 M 1,1-dicyclopropylethylene and relatively low concentrations of *t*-BuSH (0.03 to 0.08 M) and to ca. 50% conversion of the thiol. In these runs, there was very little variation in the ratio [7]/[6]. This implies that **3** was predominantly undergoing rearrangement and was barely being trapped by the thiol. Extrapolation of [7]/[6] to zero thiol concentration, i.e., to the point where [7]/[6] = k_{12}/k_{13}, led to a value of 1.9 for the ratio of rate constants.

At much higher concentrations of thiol, the product ratio increased dramatically. For example, at 1 M *t*-BuSH, [7]/[6] was 10.5 at 10% conversion of the thiol. Six reactions were carried out over the range of thiol concentrations 0.03–1 M. The ratios of rate constants, $a = k_{14}/k_6$, were obtained by applying eq 15, which takes account of

$$a^{-1} \ln \{(a[\text{RSH}]_i + 1)/(a[\text{RSH}]_f + 1)\} = (k_{12}/k_{13} + 1)[6]$$
(15)

the fact that the thiol concentration diminished during the course of the reactions. The equation was derived by applying the steady-state approximation to the rate of formation of **5**. In the expression, the subscripted i and f indicate initial and final concentrations. The equations were solved by an iterative method to give the best fit to the data and led to $a = k_{14}/k_6 = 2.9$ M^{-1} at 25 °C. Com-

bining this result with the value for k_6 led to $k_{14} = 2.3 \times 10^5$ M^{-1} s^{-1}.

The value obtained for k_{14} is in poor agreement with literature data. Newcomb and Park[21] measured the rate constant for the reaction between a primary alkyl radical and a thiol to be 1.1×10^7 M^{-1} s^{-1} in tetrahydrofuran as solvent, using a more complex "radical clock" technique. While the polar solvent may have influenced the rate constant, it is more likely that the discrepancy reflects the experimental errors associated with the calibration of the clocks themselves.

Calibration of free-radical clocks by EPR methods alone leads to high experimental errors that are associated with the difficulties of measuring radical concentrations and rate constants for radical-radical reactions. The problems are compounded when, as in this case, the data are extrapolated beyond the range of the experimental measurements. This is because the Arrhenius parameters tend to be defined by the rate constants measured at the ends of the accessible temperature range, i.e., where the signal due to one of the radicals is very small and therefore difficult to integrate. Under these circumstances, the value obtained for k_{14} may well be in error by an order of magnitude and hence would crudely overlap with the result[21] obtained by Newcomb and Park where the same problems arise.

By comparison, the ratio k_{14}/k_6 is well defined since it was quantified in a simple product study. Indeed, a referee has suggested that the calculation be reversed and that a literature value of k_{14}, the rate constant for hydrogen abstraction from a thiol, might be used to better define the rate constants for the clock reaction. This proposal has a great deal of merit. However, finding reliable data for hydrogen abstraction from thiols is difficult.

Burkhart and Merrill[22] obtained values for the reaction between alkyl radicals and their corresponding thiols that were in the range 10^5–10^6 M^{-1} s^{-1}. However, their experiments also led to values for the rates of self-reaction of simple alkyl radicls that were, in some instances, substantially less than the diffusion-controlled limit. This casts doubt on the reliability of the rate constants and suggests that further investigation of the experimental approach is required.

Overall, the difficulties suggest that the best method to determine rate constants for the reaction of primary alkyl radical with a thiol would be to use the 5-hexenyl radical cyclization as a "radical clock" since this has been carefully calibrated by using two independent experimental techniques.[20]

Summary

Alkylthiyl and arylthiyl radical additions to 1,1-diphenylethylene lead to the familiar ring-opening of the cyclopropyl moiety. However, this reaction and subsequent rearrangement of the ring-opened radical were found to proceed with a remarkable degree of regiospecificity that was dictated by radical conformation. The high specificity suggests that these conformational factors could be used to advantage in the design of syntheses.

(20) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

(21) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.
(22) Burkhart, R. D.; Merrill, J. C. *J. Phys. Chem.* **1969**, *73*, 2699 and references cited therein.