Kinetics of Reactions of Cyclopropylcarbinyl Radicals and Alkoxycarbonyl Radicals Containing Stabilizing Substituents: Implications for Their Use as Radical Clocks

Athelstan L. J. Beckwith* and Vincent W. Bowry*

Contribution from the Research School of Chemistry, Institute of Advanced Studies, Australian National University, Canberra ACT 0200, Australia

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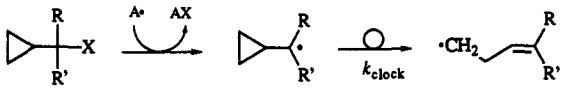
Abstract: The rate constants for rearrangement of α-substituted cyclopropylcarbinyl radicals have been measured by nitroxide radical-trapping (NPT). Those bearing methyl, dimethyl, or cyclopropyl substituents undergo ring opening 2–3 times more slowly than does cyclopropylmethyl radical, but the reaction is essentially irreversible under the conditions used. Phenyl and *tert*-butoxycarbonyl α-substituents retard the rate of ring opening more strongly and enhance the rate of ring closure of the corresponding substituted but-3-enyl radicals. Thus for *c*-$C_3H_5\dot{C}HPh$ at 60 °C, $k_{ring\ open}$ = $5.4 \times 10^5\ s^{-1}$, $k_{ring\ close}$ = $1.5 \times 10^7\ s^{-1}$, and the equilibrium favors the ring closed form (K_{equil} = 0.04). The implications of the possible reversibility of the ring opening of substituted cyclopropylcarbinyl radicals for cyclopropane probe studies of metal hydride reduction and other chemical/biochemical reactions are assessed. Most of the cyclopropylcarbinyl radicals were generated from *tert*-butyl peroxyglyoxalates [$ROC(O)CO_3Bu^t$] via alkoxycarbonyl radicals ($RO\dot{C}O$). This method allowed the determination of the rate constants for decarboxylation of $RO\dot{C}O$ when R is *t*-Bu, $PhCH_2$, *c*-$C_3H_5CMe_2$, *c*-C_3H_5CHMe, $(c\text{-}C_3H_5)_2CH$, or *c*-$C_3H_5CHC_6H_5$.

Introduction

Suitably substituted cyclopropanes have recently been used as mechanistic and kinetic probes for chemical and biochemical transformations thought to involve free radicals.[1] The production of ring-opened products from a cyclopropylcarbinyl substrate is generally accepted as evidence for the formation of a discreet free radical with its center adjacent to the cyclopropane ring, while the ratio of ring-closed to ring-opened products can be used to gauge how rapidly the initially formed radical intermediate undergoes intermolecular reactions ("quenching") in competition with intramolecular ring opening, the so-called "clock reaction" (reaction 1).[2]

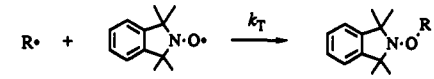


(1)

Attempts to study rapid radical quenching in enzymes have resulted in the calibration[3] and deployment[4,5] of ring-substituted cyclopropylcarbinyl radical clocks with nanosecond and even picosecond[3c] time constants, i.e., $k_{clock} \sim 10^9$–$10^{12}\ s^{-1}$.

However, a cyclopropane probe can only give an unambiguous guide to mechanism if ring opening of the intermediate cyclopropylcarbinyl radical is rapid and if ring closure of the corresponding butenyl radical is slow by comparison with the intermolecular process being studied. This condition has clearly been fulfilled in a number of studies involving simple cyclopropane probes. Since little is known about their kinetics, it is not clear whether cyclopropylcarbinyl radicals with radical-stabilizing groups attached directly to the radical center are also suitable for use as kinetic and mechanistic probes. In particular, there are no firm kinetic data available for the ring opening of α-phenyl-, α-acyl-, or α-cyanocyclopropylmethyl radicals.[6] One reason for this is that it is often not possible to observe the ring-opened forms of such radicals under EPR conditions; another reason is that no reliable data are available for reactions of many types of delocalized radicals with such commonly used atom-transfer radical traps as metal hydrides, arenethiols, and halocarbons.

Nitroxide radical trapping (NRT) seemed an ideal method for filling this gap in the "horlogerie" of radical clocks[2] because nitroxides couple very rapidly with both delocalized and non-delocalized carbon-centered radicals[9–11] (e.g., reaction 2) to afford stable products which are readily quantified by HPLC.



(2)

For NRT calibration of stabilized radicals a suitable precursor for their thermal generation is required. One method successfully used in previous work, viz., hydrogen-atom abstraction from appropriate substrates by the *tert*-butoxyl radicals generated by heating *tert*-butyl hyponitrite,[3a,b] suffers from the disadvantage that reactions of the *tert*-butoxyl radicals with the trap, the solvent, and alternative sites on the substrate sometimes afford complex mixtures of products[3b] quantitative separation of which may not be possible.

The radical precursors mainly used in the present work were alkyl *tert*-butyl peroxyglyoxalates. They are readily prepared

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(1) Suckling, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 537–552.

(2) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323.

(3) (a) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 1927–1928. (b) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687-5698. (c) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915–10921. (d) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151–1176.

(4) Ortiz de Montellano, P. R.; Stearns, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 3415-3420.

(5) (a) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699–5707. (b) Liu, K. E.; Johnson, C. C.; Newcomb, M.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 939–947. (c) Inchley, P.; Lindsay Smith, J. R.; Lower, R. J. *Nouv. J. Chim.* **1989**, *13*, 669–676. (d) Atkinson, J. K.; Ingold, K. U. *Biochemistry* **1993**, *32*, 9209–9214.

(6) A report[7] that α-cyclopropylbenzyl radicals undergo fairly rapid and irreversible ring-opening at 22 °C has been shown to be in error.[8]

(7) Masnovi, J.; Samsel, E. G.; Bullock, R. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1044–1045.

(8) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923–925.

(9) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629–1632.

(10) Beckwith, A. L. J.; Bowry, V. W.; Moad, G. *J. Org. Chem.* **1988**, *53*, 1632-1641.

(11) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992–4996.

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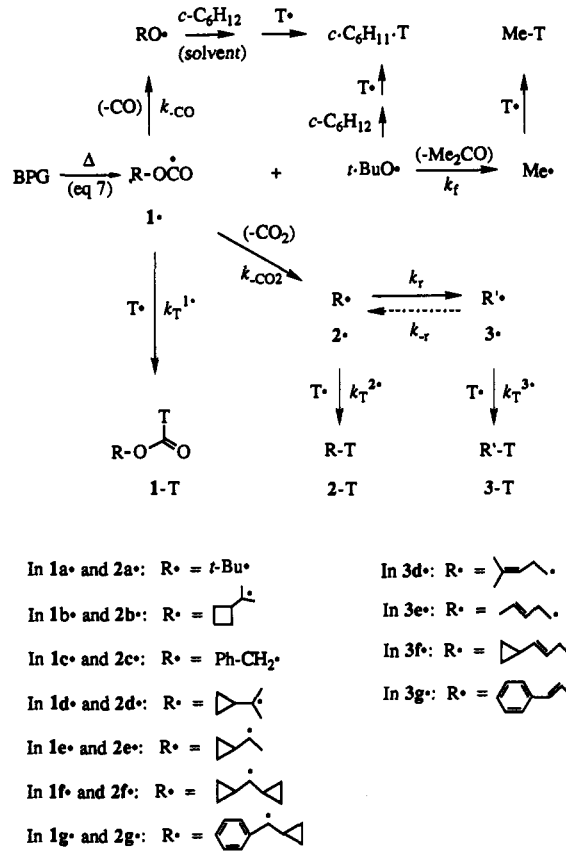
Scheme 1



by treatment of an alcohol with *tert*-butyl peroxyoxalyl chloride (reaction 3) and decompose thermally by sequential homolytic cleavages (reactions 4 and 5).[12]

$$\mathrm{ROH} + \mathrm{ClC(O)CO_3Bu^t} \xrightarrow{\text{base}} \mathrm{ROC(O)CO_3Bu^t} \quad (3)$$

$$\mathrm{ROC(O)CO_3Bu^t} \xrightarrow{\Delta} \mathrm{RO\dot{C}{=}O} + t\text{-}\mathrm{BuO^\bullet} + \mathrm{CO_2} \quad (4)$$

$$\mathrm{RO\dot{C}{=}O} \xrightarrow{k_{-\mathrm{CO_2}}} \mathrm{R^\bullet} + \mathrm{CO_2} \quad (5)$$

When peroxyglyoxalates are thermolyzed in the presence of 1,1,3,3-tetramethylisoindolin-2-oxyl (T•) radical trapping of RO$\dot{C}$=O competes with decarboxylation. The reactions involved in most of our experiments are depicted in Scheme 1 in which the radicals **1**• are of the form RO$\dot{C}$=O where R is the α-substituted cyclopropylcarbinyl group corresponding to R• in **2**•. In these cases it was possible to study in the same experiment both the the rearrangement of R• and the decarboxylation of RO$\dot{C}$=O by reaction 5, a step which is critical in the sequence of reactions 3–5 used in one method for homolytic substitutions of alcohols (ROH → RX).[12-14] The reactions employed for the determination and kinetic study of the radical **4**• are depicted in Scheme 2.

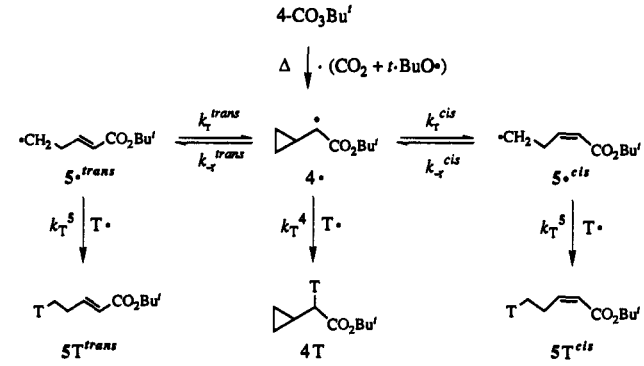
The NRT kinetic data presented herein include rate constants for the ring opening of stabilized cyclopropylcarbinyl radicals and for the ring closure of the corresponding substituted butenyl radicals. They allow the implications of the possibility of reversibility of ring opening for the use of such species as radical

(12) Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1762–1768. Bartlett, P. D.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1769–1773. Bartlett, P. D.; Gontarev, B. A.; Sakurai, H. *J. Am. Chem. Soc.* **1962**, *84*, 3101–3104.

(13) Jensen, F. R.; Moder, T. I. *J. Am. Chem. Soc.* **1975**, *97*, 2281–2283.

(14) Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328-2337.

Scheme 2



clocks and probes to be assessed. In particular, the kinetic data for reactions of the α-cyclopropylbenzyl radical, **2g**•, are used to reexamine cyclopropane probe studies of metal hydride reductions and vinyl migrations involving cyclopropylcarbinyl radical intermediates.

Results

Radical Generation and Product Analysis. Alkyl *tert*-butylperoxyglyoxalates *t*-BuOCOCO$_2$-**1a** through *t*-BuOCOCO$_2$-**1g** were prepared by treating the appropriate alcohol with *tert*-butylperoxyoxalyl chloride in the presence of pyridine (reaction 3).[10,12,13] Di-*tert*-butyl monoperoxycyclopropylmalonate (*t*-BuOCO$_2$-**4**) was prepared by α-carboxylation of *tert*-butyl cyclopropaneacetate, conversion of the acid so formed into its chloride, and treatment of the acid chloride with a mixture of *tert*-butyl hydroperoxide and pyridine. Reaction mixtures containing the radical precursor and a 10-fold excess of T• in cyclohexane were freeze/pump/thaw degassed and heated in ampoules as previously described.[10] After being heated for an estimated five to ten reaction half-lives, the reaction mixtures were analyzed by reversed-phase HPLC with UV detection at 270 nm.[10] Relative yields are listed in Table 1; total yields of nitroxide-trapped products ranged from 50–85% (based on ROH).

Although the cis and trans isomers of **3e**-T, **3f**-T and **3g**-T were not resolved by HPLC, analysis by NMR of samples of **3e**-T and **3f**-T isolated by HPLC from the mixtures formed by reactions conducted at 80 °C indicated that the trans isomer predominated in both cases (trans/cis ≈ 1.6). A similar preparation of **3g**-T gave a product containing more than 95% of the trans form by NMR analysis. In the case of the ring opening of **4**• the cis and trans ring-opened products ^{cis}**5**-T and ^{trans}**5**-T were readily resolved and quantified by reversed phase HPLC.

Kinetic Analysis. The *tert*-butylperoxyglyoxalates gave products consistent with Scheme 1 without any sign of the α-fission, RO$\dot{C}$=O → RO• + CO, previously reported[14] to compete effectively with β-fission when R is aryl or primary alkyl. As expected on the basis of Scheme 1 the cyclohexylhydroxylamine derivative, *c*-C$_6$H$_{11}$-T, derived from the reaction of the cyclohexane solvent with *t*-BuO• made up 50% (within experimental error) of the total yield of nitroxide-trapped product. Had α-fission occurred the reaction of the alkoxy radicals so formed with cyclohexane would have increased the relative yield of *c*-C$_6$H$_{11}$-T. Furthermore, the ratios of products derived from the alkoxycarbonyl radical were consistent with the pseudo first order kinetic equation:

$$[\mathbf{1}\text{-T}]/[\mathbf{2}\text{-T} + \mathbf{3}\text{-T}] = [\mathrm{T^\bullet}]k_{\mathrm{T}}^{\mathbf{1}\bullet}/k_{-\mathrm{CO_2}} \quad (\mathrm{I})$$

Relative decarboxylation rates, $k_{-\mathrm{CO_2}}/k_{\mathrm{T}}^{\mathbf{1}\bullet}$, calculated by substitution of experimental data into eq I are listed in Table 1.

We have previously shown[10] that the NRT rate constant, $k_{\mathrm{T}}^{\mathbf{1a}\bullet}$, for the *tert*-butoxycarbonyl radical is given by

Table 1. NRT Relative Product Yields[a] and Kinetic Data for Reactions of **1c•**–**1g•**

radical	temp (±0.5 °C)	[T•][b] (mM)	[2-T + 3-T]/[1-T]	k_{-CO_2}/k_T (M)	[3-T]/[2-T]	k_r/k_T (M)	k_{-r}/k_T (M)
1c•	42	19	2.0	0.038			
	42	47	0.78	0.037			
	59	17.2	3.7	0.063			
	79	16.1	6.9	0.11			
	79	43	2.4	0.10			
	79	85	1.32	0.11			
1d•	25(±1)	10.0	0.90	0.0090	6.20	0.062	
	46	9.1	2.1	0.019	19.9	0.18	
	59	24	1.70	0.041	11.4	0.27	
	59	45	0.81	0.036	5.1	0.23	
	80	21	2.82	0.059	21	0.44	
	80	44	1.50	0.066	11.8	0.52	
	80	72	0.81	0.058	6.5	0.47	
1e•	60	17.8	0.76	0.0135	3.9	0.069	
	80	8.4	0.62	0.0052	16.1	0.13	
	80	17.2	0.28	0.0048	7.2	0.12	
	80	72	0.08	0.0058			
1f•	60	18.0	0.81	0.015	10.1	0.18	
	80	8.4	3.0	0.025	–(>30)		
	80	17.3	1.8	0.031	18.8	0.33	
	80	73	0.50	0.036	5.1	0.37	
1g•	42	4.8			0.168		
	42	18.0			0.078	0.0018[d]	0.0059[d]
	42	91	12[c]	0.8[c]	0.019		
	60	4.5			0.32		
	60	17.3			0.169	0.0052[d]	0.013[d]
	60	88	18[c]	1.5[c]	0.052		
	80	4.4			0.62		
	80	17.5			0.41	0.015[d]	0.019[d]
	80	85	29[c]	2.5[c]	0.142		

[a] Approximately 50% of the total nitroxide-trapped product was c-C_6H_{11}-T derived from reaction of the solvent with t-BuO•. [b] Mean concentration. [c] Approximate values, because of poor HPLC separation of **1g**-T from other aromatic products. [d] Reversible, see text.

$$\log(k_T^{1a\bullet}/M^{-1}\,s^{-1}) = 9.5 - 0.3/\theta \qquad (II)$$

from which $k_T^{1a\bullet} = 2 \times 10^9\ M^{-1}\ s^{-1}$ at 80 °C with cyclohexane as solvent. Table 2 lists absolute decarboxylation rate constants (k_{-CO_2}) derived from the relative data on the assumption that k_T for the various ROĊ=O radicals has the same value as $k_T^{1\bullet}$ derived from eq II.[15]

The NRT product yields from the α,α-dimethyl-, α-methyl-, and α-cyclopropylcyclopropylcarbinyl radicals (**2d•**, **2e•**, and **2f•**) were found to conform to the pseudo-first-order kinetic equation for an *irreversible* ring opening, viz.

$$[2\text{-T}]/[3\text{-T}] = [T^\bullet]k_T^{2\bullet}/k_T \qquad (III)$$

The absolute ring opening rate constants, k_r, for **2d•**, **2e•**, and **2f•** in Table 4 were calculated using appropriate values of k_T from laser flash photolysis[9] and radical clock calibrations.[10] For this purpose **2e•** and **2f•** are assumed to have the same trapping rate constant as that for other secondary radicals, i.e., k_T(secondary) = $0.8k_T$(primary) where k_T(primary) is given by $\log k_T$(primary)/$M^{-1}\,s^{-1} = 9.7 - 0.9/\theta$ and θ represents $2.3RT$ kcal/mol. Similarly **2d•** is assumed to have the same value of k_T as the *tert*-butyl radical, i.e. $k_T^{2d\bullet} = k_T^{t\text{-}Bu\bullet} = 0.6k_T$(primary).[9,10]

Product data for the ring openings of **2g•** (Table 1) and **4•** (Table 3) were not compatible with eq III, especially for low [T•]. Analysis of the NRT product mixtures from the peroxyglyoxalate ester t-BuOCOCO$_2$-**1g** showed that the ratio [**2g**-T]/[**3g**-T] converged to a constant value as [T•] was decreased, rather than tending to zero as required by eq III. This behavior is consistent with the steady-state kinetic equation for a reversible rearrangement of **2g•**:

$$[2g\text{-T}]/[3g\text{-T}] = (k_T^{2g\bullet}/k_r)\{(k_{-r}/k_T^{3g\bullet}) + [T^\bullet]\} \qquad (IV)$$

Eq IV indicates that plots of [**2g**-T]/[**3g**-T] *vs* [T•] should be linear with a gradient of $k_T^{2g\bullet}/k_r$ and with gradient/intercept = $k_T^{3g\bullet}/k_{-r}$. The data in Table 1 give values of (gradient)/(intercept/M^{-1}) of (2.51)/(340), (1.64)/(131), and (1.09)/(50) at 42, 60, and 80 °C, respectively ($\langle r \rangle > 0.989$) from which the values of $k_r/k_T^{2g\bullet}$ and $k_{-r}/k_T^{3g\bullet}$ given in Table 1 were derived.

Recent laser flash photolysis measurements[8,11] for the benzylic radical **2g•** indicate that $k_T^{2g\bullet} = 8 \times 10^7\ M^{-1}\ s^{-1}$ at 18 °C, while NRT of primary alkyl radicals for which $k_T = 1.0 \times 10^9\ M^{-1}\ s^{-1}$ at this temperature (see above) should be a good model for NRT of **3g•**. Consequently, we have used $k_T^{2g\bullet} = 0.08k_T^{3g\bullet}$ and $E_{act} = 0.9$ kcal/mol to derive the absolute kinetic data for the ring opening **2g•** → **3g•**, for the ring closure **3g•** → **2g•** (Table 4), and for the equilibrium **2g•** ⇌ **3g•** (eq V).

$$\log K = 1.9 - 5.1/\theta \qquad (K^{60°} = 0.04) \qquad (V)$$

These results are in reasonable agreement with a recent EPR study of vinyl migration in deuterium labeled 4-phenyl-3-butenyl radical in the presence of tri-*n*-butylstannane,[8] which gave $k_r \approx 1 \times 10^6\ s^{-1}$ and $k_{-r} = 1.2 \times 10^7\ s^{-1}$ at 42 °C. Thus both sets of experiments confirm that equilibrium is rapidly established between **2g•** and **3g•** and strongly favors the ring-closed form.

The data for the ring opening of **4•**, which is also reversible under the conditions used were treated similarly to give the relative rate constants listed in Table 3. In this case analytical data for the cis and trans ring-opened products ^{cis}**5**-T and ^{trans}**5**-T were available. The absolute rate constant for ring opening of **4•** is somewhat difficult to determine because there are no reliable data available for the value of k_T for a carboxy- or cyano-substituted carbon-centered radical. The radical stabilization

Table 2. Kinetic Data[a] for Decarboxylations of ROĊ=O

radical	$k_{-CO_2}^{80°C}$ ($10^6\ s^{-1}$)	log $A(s^{-1})$	E_{act} (kcal/mol)
t-BuOĊO (**1a•**)[b]	3.6	13.8	11.7
c-$C_4H_7CMe_2O$-ĊO (**1b•**)[c]	14	13.2	9.8
PhO-ĊO (**1c•**)	220	11.9	5.7
c-$C_3H_5CMe_2O$ĊO (**1d•**)	120	12.9	7.8
c-C_3H_5CHMeO-ĊO (**1e•**)	10.6		
$(c\text{-}C_3H_5)_2$CHOĊO (**1f•**)	62	13.2	8.8
c-C_3H_5CHPhOĊO (**1g•**)	5000[d]	12.9[d]	5.2[d]

[a] From Table 1 by use of eq II. [b] Reference 21 (kinetic standard). [c] Reference 20. [d] Approximate values, because of poor HPLC separation of **1g**-T from other aromatic products.

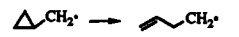
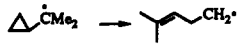
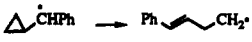
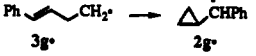
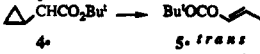
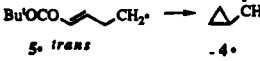
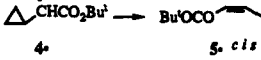
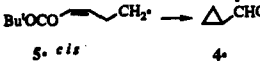
Table 3. Relative Hydroxylamine Yields from Radical **4•** [a]

temp (°C)	[T•][b] (mM)	[4-T]/[^{trans}**5**-T]	$k_r^{trans}/k_T^{4\bullet}$	$k_{-r}/k_T^{trans\text{-}5\bullet}$	[4-T]/[^{cis}**5**-T]	$k_r^{cis}/k_T^{4\bullet}$	$k_{-r}/k_T^{cis\text{-}5\bullet}$
59	4.5	0.28			4.33		
59	18.0	0.69	0.033	0.0050	6.47	0.0064	0.023
59	73	2.35			15.1		
83	4.2	0.181			2.85		
83	16.8	0.33			3.62		
83	42	0.68	0.078	0.0096	4.83	0.018	0.047
83	76	1.10			6.93		
100	4.0	0.137			1.99		
100	15.4	0.21	0.17	0.020	2.24	0.041	0.078
100	70	0.53			3.58		
121	3.8	0.088			1.27		
121	41	0.200	0.32	0.025	1.64	0.099	0.12
121	66	0.28			1.90		

[a] Approximately 50% of the total nitroxide-trapped product was c-C_6H_{11}-T derived from reaction of the solvent with t-BuO•. [b] Mean concentration.

(15) Equation II should be accurate for most ROĊ=O radicals, regardless of the particular R group, because NRT is not very sensitive to steric effects in nondelocalized radicals,[9-11] and because the nearest substituent on R is three bonds removed from the radical center, i.e., ROĊ=O cannot be neopentylic.

Table 4. Rearrangements of α-Substituted Cyclopropylcarbinyl Radicals

reaction	$k_r^{80°C}$ (10^7 s^{-1})[a]	log (A/s^{-1})	E_{act} (kcal/mol)
	61	13.15[b]	7.05[b]
 **2d•** **3d•**	36 37	13.7 13.15[c]	8.3 7.4[c]
 **2e•** **3e•**	22 32	13.1 13.15[c]	7.7 7.5[c]
 **2f•** **3f•**	19	13.6[d]	8.6
 **2g•** **3g•**	0.16	14.0	12.6
 **3g•** **2g•**	2.8	12.1	7.5
 **4•** **5. *trans***	1.2	13.7	10.7
 **5. *trans*** **4•**	1.6	12.1	7.9
 **4•** **5. *cis***	0.21	14.0	12.4
 **5. *cis*** **4•**	6.5	12.7	7.9

[a] Calculated from Arrhenius parameters. [b] Values from refs 11 and 27. [c] Values from ref 11. [d] Since this radical contains two cyclopropyl groups, a statistical factor of −0.3 has been applied to log A.

afforded by a CO_2Bu^t group is probably in the range $E_{stab.} \sim 7$–9 kcal/mol.[16] If we assume a correlation between k_T and the reaction enthalpy, $k_T^{4•}$ should lie somewhere between the known value of k_T (1.2×10^8 M^{-1} s^{-1} at 60 °C) for the benzylic radical **2g•** ($E_{stab.} \sim 11$ kcal/mol)[17] and that for a typical secondary alkyl radical ($k_T = 10 \times 10^8$ M^{-1} s^{-1} at 60 °C).[11] We have chosen $k_T^{4•} = 0.2k_T^{5•}$ ($k_T^{4•} = 2.5 \times 10^8$ M^{-1} s^{-1} at 60 °C). However, it should be emphasized that this rather arbitrary estimate based on a linear free-energy approach does not affect the validity of the data for ring fission selectivity and ring closure.

Discussion

Decarboxylations. Table 2 gives the kinetic parameters derived from the data in Table 1 for the decarboxylation of the radicals **1c•**–**1g•** together with literature data for **1a•** and **1b•**. The data indicate that decarboxylation of ROĊ=O radicals by reaction 5 is assisted by stabilization of the product radical R•, by the relief of steric crowding, and possibly by electron release. They complement earlier studies which showed that the rates of decarboxylation for species with various groups R are in the order aryl < primary < secondary < tertiary ≪ benzylic[12,14] and that the relative rates for primary, secondary, and tertiary alkyl groups R are 1:4:19 at 80 °C in benzene.[14]

The effect of electronic stabilization of the product radical on the rate of β-fission of ROĊ=O is exemplified by the behavior of the benzyloxycarbonyl radical **1c•** which undergoes decarboxylation 60 times faster than the *tert*-butoxycarbonyl radical **1a•** at 60 °C. Combining this result with the previous observation[14] that a tertiary alkoxycarbonyl radical decarboxylates about 19 times more rapidly than does a primary alkoxycarbonyl radical we estimate the decarboxylation of **1c•** to be about 1200 times faster than that of a primary alkoxycarbonyl radical. The Arrhenius data (Table 2) show that the increase in k_{-CO_2} upon substitution of a benzylic R group for an alkyl R group in ROĊ=O arises from the fall in the enthalpy term, i.e., $\Delta\Delta H^{\ddagger} \sim -6$ kcal/mol; this represents about half of the stabilization energy for a benzyl radical (ca. 11 kcal/mol).[17] It is consistent with the decarboxylation being a roughly thermoneutral reaction.[18]

The kinetic data for **1b•**, **1d•**, and **1a•** in Table 2 show that a cyclobutyl or cyclopropyl group adjacent to the radical center of R• also promote the decarboxylation of ROĊ=O. Ingold and co-workers[20] have previously attributed accelerated decarboxylation of **1b•** relative to **1a•** to participation of the cyclobutane ring bonds in the transition state thus lowering the activation energy but entailing a loss of internal rotational freedom. It may be relevant that the preexponential terms for decarboxylation of **1b•**, like those for decarboxylations of **1c•**, **1d•**, **1f•**, and **1g•**, are all lower than that for **1a•**. Possibly steric effects are also significant since decarboxylation reduces back strain in the R group. However, the fact that the cyclopropyl substituent in **1d•** gives a larger kinetic acceleration than the bulkier cyclobutyl group in **1b•** suggests that interaction of the pseudo-π orbitals of the cyclopropane with the developing radical center in the transition state may compound or override the steric effect of incorporating a strained ring into R•. The decarboxylation of **1g•** which gives the secondary cyclopropylcarbinyl radical bearing both a phenyl and a cyclopropyl substituent is considerably faster than that of the other radicals studied. Unfortunately, analytical difficulties precluded the accurate determination of the rate constant and its temperature dependence.

The practical implications of our findings for reactions involving alkoxycarbonyl radicals are clear: reactions leading to substituted tertiary and/or delocalized R• radicals will tend to afford high yields of decarboxylated products, but the relatively large temperature variation of k_{-CO_2} allows the yield-reducing effect of bimolecular reactions of the ROĊ=O radicals containing a primary or secondary alkyl group R to be minimized by raising the reaction temperature.[14] Earlier work[13] on the chlorodehydroxylation of alcohols via *tert*-butylperoxyglyoxalate formation and thermolysis in CCl_4 solvent confirms the expected trend in that the order of yields of alkyl RCl at 95 °C is tertiary > secondary > primary.

Similarly, deoxygenation of alcohols by treatment of their phenylselenocarbonates[14] with tributylstannane is limited by competition between decarboxylation of ROĊ=O radicals and hydrogen-atom transfer from the stannane. The reported product yields for a tertiary R-group (ROCHO/RH = 81%/15% when [Bu_3SnH] is 20 mM)[14] give $k_H^{1•}/k_{-CO_2} \approx 9.3$ thus indicating that Bu_3SnH is very reactive towards alkoxycarbonyl radicals. It follows[21,22] that $k_H^{1•}$ is ca. 3×10^7 M^{-1} s^{-1} at 80 °C, i.e., ROĊ=O radicals react with Bu_3SnH at 80 °C about 5 times more rapidly that do alkyl radicals.[23,24] However, the unwanted reduction of alkoxycarbonyl radicals can be minimized by using a lower

(16) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062–3072; Luedtke, A.; Meng, K.; Timberlake, J. W. *Tetrahedron Lett.* **1987**, 4255–4258.

(17) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, NY, 1976.

(18) Using Benson's method and data,[17] and data from ref 19, we estimate $\Delta H° \approx -2$ kcal/mol for a primary alkyl R group.

(19) *CRC Handbook of Chemistry and Physics*; Chemical Rubber Company: Boca Raton, FL, 1992.

(20) Ingold, K. U., Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 970–974.

(21) Rüegge, R.; Fischer, H. *Int. J. Chem. Kinet.* **1986**, *18*, 145–158.

(22) This assumes that the tertiary steroidal radical previously studied[14] decarboxylates at the same rate as **1a•**. Time-resolved infrared spectroscopy indicates that alkylcarbonyl radicals are considerably less reactive, e.g., $k_{Bu_3SnD}^{EtĊC} = 3 \times 10^5$ M^{-1} s^{-1}.[23]

(23) Neville, A.; Ingold, K. U. private communication.

(24) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.

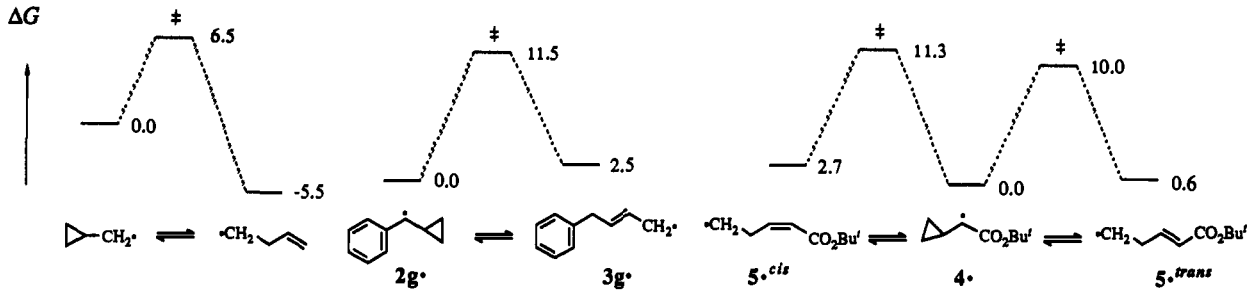


Figure 1. Relative free energy levels (25 °C) calculated from kinetic data (not shown to scale).

stannane concentration and/or a higher temperature,[14] because the energy barrier for decarboxylation is some 6–9 kcal/mol higher than it is for hydrogen-atom transfer from Bu_3SnH.

Ring Opening of α-Substituted Cyclopropylcarbinyl Radicals. Kinetic data for the ring opening of α-substituted cyclopropylmethyl radicals are summarized in Table 4. In accord with previous observations[3b] they show that α-alkyl substituted cyclopropylcarbinyl radicals undergo ring opening more slowly than does the unsubstituted cyclopropylmethyl radical. For example the replacement of an α-proton in cyclopropylmethyl radical by a methyl group reduces the rate of ring opening by about 50%. However, the ring opening remains so much faster than the reverse process that radicals **2c–2f**• can be used as radical clocks for measuring the kinetics of competing, rapid bimolecular reactions.[3b,5a]

As expected the presence of the radical stabilizing groups Ph and CO_2Bu^t in **2d**• and **4**• strongly retard their rates of ring opening. Previous studies of cyclopropylcarbinyl radicals with α-CO_2Me, α-NO_2, or α-O^- (ketyl) groups have also revealed dramatic decreases in the ring-opening rates.[1,25] The Arrhenius data for **2g**• and **4**• show that the loss of electron delocalization in the transition structures causes a substantial increase in the activation energies as compared with those for the alkyl substituted species **2d**•, **2e**•, and **2f**•. The Ph and CO_2Bu^t substituents also promote the reverse reaction. At 25 °C the ring-closure of **3g**• ($k_r^{25°} = 4.0 \times 10^6\ s^{-1}$) is about 50 times faster than that of the unsubstituted but-3-enyl radical ($k_r^{25°} = 8.5 \times 10^4\ s^{-1}$).[26] The preexponential terms for ring opening of all of the radicals **2d–2g**• and **4**• are all somewhat higher than that expected (log $A \approx 13.15$).[3d,11,27] This may reflect the limited temperature range over which the measurements were made or it may indicate that at least part of the rotational constraint of the substituents is relieved in the transition state. Ring closure of **5**• at 25 °C is about 90 times faster than that of the but-3-enyl radical. For comparison the presence of a cyano substituent at C-6 in the 5-hexenyl system increases the rate of 1,5-cyclization by about 280 times,[28a] while the methoxycarbonyl and cyano substituents increase the rate of intermolecular radical addition by about 3200 and 6000 times, respectively.[28b] The smaller effect of alkoxycarbonyl substitution in **5**• probably reflects the fact that a 1,3-closure is ~27 kcal/mol (the cyclopropane ring strain) less exothermic than an intermolecular or a 1,5-intramolecular radical addition and is therefore more dependent on product radical stability than on the frontier reactivity of the double bond.

Figure 1 shows the effect of radical delocalization on the ground and transition-state free energies for rearrangements between cyclopropylcarbinyl radicals and their homoallylic counterparts, as calculated from the kinetic data.[26] The radical stabilizing moieties in **2g**• and **4**• make the ring-closed forms thermodynamically favored except at high temperature; the estimated isokinetic temperatures are about 500 °C and 100 °C, respectively. Comparison of the relative ground-state energies of **2g**• and **4**• with that of the cyclopropylmethyl radical indicates that the α-phenyl and α-CO_2R groups stabilize the cyclopropylcarbinyl radical by ~11 and ~7 kcal/mol, respectively; these values are consistent with earlier estimates[16,17] of the relevant ΔE_{stab}.

Steric repulsion between the ring and α-substituent(s) can either promote or hinder ring opening in cyclopropylcarbinyl radicals.[3b] The relief of nonbonding interactions as a ring bond begins to break in a cyclopropylcarbinyl radical may accelerate the ring opening; possibly this is the reason why $k_r^{2d•} > k_r^{2e•}$. However, bulky α-groups can hinder the fission of a particular bond in the cyclopropyl ring because of the requirement that the radical orbital should overlap with the bond being broken. Thus, the kinetic stereoselectivity of ring opening of cyclopropylcarbinyl radicals[3b] (and of cyclobutylcarbinyl radicals[29]) is largely determined by steric repulsion between the α-substituent(s) and the ring in the *cisoid* versus *transoid* transition states.

Accordingly, ring opening of **4**•, which contains the bulky *tert*-butoxycarbonyl group, is about three times more selective (trans/cis = 5.7 at 80 °C) than is ring opening of **2e**• which contains the methyl group (trans/cis = 1.6 at 80 °C). The "cis effect"[30] may be critical in **2g**• since it appears that eclipsing of an *ortho* aryl hydrogen with the cyclopropane ring in the *cisoid* transition state effectively eliminates the *cis* ring-opening (trans/cis ≥ 20).[8,31]

Implications for Radical Clocking. Reversibility in the ring opening of stabilized cyclopropylcarbinyl radicals such as **2g**• and **4**• might be seen as a good reason *not* to use them as radical clocks. To overcome this perceived problem a fast and essentially irreversible benzylic radical clock has recently been introduced.[31] However, in some situations reversibility is not an insurmountable problem and can even be used to gain extra information about the competitive bimolecular reaction being investigated. For instance, the major product of the Bu_3SnH reduction of **3g**-Br is the ring-opened **3g**-H rather than ring-closed **2g**-H.[8] However, the fact that the product ratio is nearly independent of the stannane concentration ([**3g**-H]/[**2g**-H] ≈ 8.8 at 42 °C) indicates that an equilibrium between the ring-opened and ring-closed radicals is established *before* hydrogen-atom transfer from the stannane. Since the NRT data for **2g**• indicate the equilibrium ratio of radical concentrations, [**3g**•]/[**2g**•], to be about 0.03 at 42 °C we deduce that the alkyl radical **3g**• must be about 200 times more reactive toward the stannane than is the secondary benzylic radical **2g**•; this conclusion is consistent with the 70-fold difference between a primary alkyl radical ($k_H \approx 2 \times 10^6$ at 25 °C)[24] and the benzyl radical ($k_H \approx 3 \times 10^4\ M^{-1}\ s^{-1}$ at 25 °C).[32]

A closely related example is provided by the spiro-10-cyclopropylanthracen-9-yl radical (**9**•) which appears not to undergo ring opening under EPR conditions but which is obviously

(25) Russell, G. A.; Dedolph, D. F. *J. Org. Chem.* **1985**, *50*, 2498–2502. Tanko, J.M.; Drumwright, R. E. *J. Am. Chem. Soc.* **1992**, *114*, 1844–1854. Tanner, D.D.; Chen, J. J.; Luelo, C.; Peters, P. M. *J. Am. Chem. Soc.* **1992**, *114*, 713–717.

(26) Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 1734–1736.

(27) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275–277.

(28) (a) Park, S. U.; Chung, S. K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240–244; (b) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753–764.

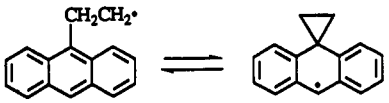
(29) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083–1092.

(30) Curtin, D. Y.; Crew, M. C. *J. Am. Chem. Soc.* **1955**, *77*, 354–357.

(31) Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992**, *57*, 4284–4287.

(32) Franz, J. A.; Suleman, N. K.; Alnajjar, M. S. *J. Org. Chem.* **1986**, *51*, 19–25.

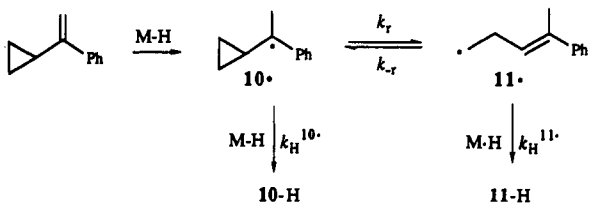
an intermediate in the rapid isomerization of deuterium labeled **8**· in the presence of Bu_3SnH.[33] The absence of **9**-H in products from the Bu_3SnH reduction of **8**-Br can be attributed to the *selective trapping* of **8**·; i.e. k_H for **8**· must be much greater than k_H for the highly stabilized radical **9**· ($E_{stab.} \sim 24$ kcal/mol).[34] Indeed, the formation of dimeric spirocyclopropyl species in the stannane reduction of **8**-Br indicates that the radical present in highest concentration (**9**·) is relatively unreactive toward stannane. However, the results of the stannane experiments show that the isomerization of **8**· is clearly very rapid (>5×10^7 s^{-1} at 70 °C).[33]



8· **9**·

Ring openings of radicals similar to **2g**· have been used as kinetic and mechanistic probes for reduction of alkenes by various transition metal hydrides (Scheme 3 where M–H represents the

Scheme 3



metal hydride).[35] The production of ring-opened products indicates the intermediacy of free radicals in the mechanism, while the product ratios can be used to determine the kinetics of their reduction.

In a recent example involving the reduction of α-cyclopropylstyrene by $HFe(CO)_2(C_5Me_5)$ (M–H) Samsel and Bullock found that plots of [**10**-H]/[**11**-H] against [M–H] are linear but have non-zero intercepts and conform to eq VI.[35]

$$[\mathbf{10}\text{-H}]/[\mathbf{11}\text{-H}] = (k_H^{10\cdot}/k_H^{11\cdot})K^{-1} + (k_H^{10\cdot}/k_r)[\text{M-H}] \quad \text{(VI)}$$

Substitution of their data into this equation gives $k_H^{10\cdot}/k_r = 8$ M^{-1} and $(k_H^{10\cdot}/k_H^{11\cdot})K^{-1} = 0.3$. These values can be combined with the NRT data for **2g**· on the assumption that the latter is a good model for **10**· to give $k_H^{10\cdot} \approx 8 \times 10^6$ M^{-1} s^{-1} and $k_H^{11\cdot} \approx 4 \times 10^8$ M^{-1} s^{-1}; i.e., the *selectivity* ($k_H^{11\cdot}/k_H^{10\cdot}$) is about 80.

In the same study, the ring opening of the tertiary alkyl cyclopropylcarbinyl radical **2d**· was also used as a probe for the mechanism of reduction of 2-cyclopylpropene by $HFe(CO)_2(C_5Me_5)$. The reduction yield data afforded intercept = 0 and gradient = $k_H^{2d\cdot}/k_r = 3.1$ M^{-1} at 68 °C. Substitution from Table 4 affords $k_H^{2d\cdot} \approx 6 \times 10^8$ M^{-1} s^{-1} at 68 °C. Franz and co-workers found $k_H^{hex\text{-}5\text{-}enyl\cdot} = 2.5 \times 10^8$ M^{-1} s^{-1} for $HMo(CO)_3(C_5Me_5)$ at this temperature.[36] Since the k_H for an active metal hydride varies little between nondelocalized alkyl radicals the rough agreement between $k_H^{2d\cdot}$, $k_H^{hex\text{-}5\text{-}enyl\cdot}$, and $k_H^{11\cdot}$ provides independent supporting evidence for the accuracy of both the present analysis and Bullock and Samsel's study of the hydride reduction mechanism.[35]

In summary, the rate constants for the quenching of radicals by such reagents as metal hydrides,[3d] thiols[3d] and CCl_4[37] can vary widely depending on the nature of the radical. Even a highly reactive alkyl-radical trap like phenylthiol which has k_H for alkyl radicals of ca. 1×10^8 M^{-1} s^{-1} at 25 °C[3d] can be orders of magnitude less reactive toward a benzylic radical ($k_H \approx 3 \times 10^5$ M^{-1} s^{-1}).[32] Since the selectivity invariably favors nondelocalized over delocalized radicals, there is a tendency for reactions involving stabilized cyclopropylcarbinyl radicals to afford ring-opened products.[8] The calibration of rearrangements of stabilized cyclopropylcarbinyl radicals (or of those an unusual electronic structure)[38] is, therefore, most conveniently conducted with radical traps that do not markedly discriminate between localized and delocalized species. Laser flash photolysis with direct UV monitoring meets this requirement as does kinetic EPR spectroscopy because the radical-consuming reactions are nonselective radical–radical combinations. Whether the extremely fast trap benzeneselenol also exhibits low selectivity is not yet clear.[39] NRT exhibits some steric and thermodynamic selectivity, but it appears to be less selective than any of the calibrated atom-transfer reactions.[3d] The unhindered ("Bredt's rule protected") nitroxide[11] 9-azabicyclo[3.3.1]nonane *N*-oxyl is the radical trap of choice for examining rearrangements of strongly delocalized or strained ring radicals[11,31] since it offers even higher k_T and, more importantly, lower radical selectivity than the hindered nitroxides such as Tempo.

Radical Probes. Since biochemical reactions can involve extremely selective trapping of transient intermediates, determined by spatial factors rather than by chemical reactivity *per se*, it is important to evaluate the possible effects of reversibility in any substrate used to detect the intermediacy of a free radical on the reaction pathway.[40] This is especially true for cyclopropane probes because, unlike the 5-alkenyl ring-closure,[41] the cyclopropylcarbinyl ring opening is not intrinsically a highly exergonic reaction, and it can become reversible upon substitution at the radical center (see Figure 1).

The rate constants and kinetic trends described here can be used to guide the interpretion of such cyclopropane probe experiments; in particular, it is clear that for intermediates similar to **2g**· or **4**·, a lack of ring-opened products would not constitute compelling evidence for a nonradical mechanism or that quenching was faster than ring opening (cf. interpretation in ref 5c). On the other hand, predominant formation of a ring-opened product from such a probe would imply that a spatial or reactivity selectivity effect is at play to overcome the radical's thermodynamic tendency to remain ring-closed.

Experimental Section

Details of the instrumentation and reaction/analysis procedures have been described previously.[10] The only variation was that reaction mixtures containing *tert*-butylperoxyglyoxalates, which decomposed at lower temperatures[12] than most acyl peroxides, were maintained below 10 °C before immersion in thermostatted oil baths. Experimentally useful temperature ranges were 25–80 °C for the *tert*-butylperoxyglyoxalates and 60–125 °C for the acyl peroxides. All NRT experiments were conducted in cyclohexane solvent. The hydroxylamine product ratios were reproducible (analyses in triplicate) and were not significantly affected by increasing the reaction times or by prolonged exposure of product mixtures to the HPLC solvent ($MeOH/H_2O$) used for analysis.

(33) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* **1989**, *111*, 7723–7732.
(34) Based on thermochemical calculations[17,19] and EPR data.[33]
(35) Bullock, R. M.; Samsel, E. G. *J. Am. Chem. Soc.* **1990**, *112*, 6886–6898.
(36) Franz, H. A.; Linehan, J. C.; Alnajjar, M. S., unpublished results cited in footnote 29 of Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268–275.
(37) Hawari, J. A.; Davis, S.; Engel, P. S.; Gilbert, B. C.; Griller, D. *J. Am. Chem. Soc.* **1985**, *107*, 4721–4724.
(38) For a remarkable and unexpected example of selective trapping, see the high selectivity for *endo* reduction of the bicyclo[2.1.0]pent-4-yl radical by PhSH, in Newcomb, M.; Manek, J. M.; Glenn, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 949–958.
(39) Newcomb, M.; Varick, T. R.; Ha, C.; Manek, M. B.; Xu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8158–8163.
(40) For further discussions of clock substrates see refs 5a, 5b, and 5d and Nonhebel, D.C. *Chem. Soc. Rev.* **1993**, 347–329
(41) The unsubstituted 5-hexenyl ring closure is estimated[17] to be ~10 kcal/mol more exothermic than the cyclopropylmethyl radical's ring opening (cf. Figure 1).

Starting Materials. 2-Cyclopropylpropan-2-ol (**2d-OH**)[42] was prepared by treatment of acetylcyclopropane with excess MeMgI in ether at reflux (82% yield). Dicyclopropylmethanol (**2e-OH**),[43] 1-cyclopropylethanol (**2f-OH**),[44] and cyclopropylphenylmethanol (**2g-OH**)[45] were prepared by $LiAlH_4$ reduction of the corresponding ketones (Aldrich). Properties and spectral data agreed with those in the cited publications. Preparation and properties of **1a-CO_3Bu^t**, **1b-CO_3Bu^t**, and **1c-CO_3Bu^t** have previously been described.[10,12,13] **1d-CO_3Bu^t**–**1g-CO_3Bu^t** were formed on 2–4 mmol scale in pentane by the same procedure but were not isolated due to the observed explosive lability of at least one (**1d-CO_3Bu^t**) when free of solvent;[13] instead the pentane was removed by evaporative displacement by cyclohexane (10 mmHg at <10 °C), after which the precursor solution was made up to volume with cyclohexane and standardized by iodometric titration.[46]

Di-*tert*-butyl Cyclopropanemonoperoxymalonate (4-CO_3t-Bu). Cyclopropaneacetic acid, made by Arnd–Eistert homologation of cyclopropanecarbonyl chloride (Aldrich), was converted into its *tert*-butyl ester (65%) via the acid chloride.[10] The ester (4.0 g) in THF (25 mL) was added to LDA (1.0 mol equiv) in THF/hexane at −30 °C. After 5 min a fast stream of dry CO_2 was passed in for 10 min (<−20 °C), and the reaction mixture was diluted with water and extracted with chloroform. Base extraction (aqueous $NaHCO_3$), careful acidification (HCl), isolation with chloroform, and recrystallization from hexane afforded *tert*-butyl hydrogen cyclopropanemalonate (2.8 g, 48%) as colorless plates: mp 70 °C; ^{1}H NMR (100 MHz, CCl_4) δ 0.4 (m, 2H), 0.55 (m, 2H), 1.1 (m, 1H), 1.30 (s, 9H), 2.55 (d, 1H, J = 8 Hz), 10.8 (s, 1H); IR ν_{max} 1730, 1773 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99 H, 8.05. Found: C, 60.23 H, 8.32. The hydrogen malonate ester was converted into its acid chloride with oxalyl chloride and then treated with anhydrous *tert*-butyl hydroperoxide/pyridine[10] to afford the title perester (63%) of 96% iodometric[46] purity: ^{1}H NMR (100 MHz, CCl_4) δ 0.4 (m, 2H), 0.6 (m, 2H), 1.05 (m, 1H), 1.38 (s, 9H), 1.53 (s, 9H), 2.62 (d, 1H, J = 8 Hz); IR ν_{max} 1736, 1773 (C=O) cm^{-1}.

Hydroxylamines. The methods used for the preparation and identification of the hydroxylamines have previously been described as have their characteristic NMR, IR, and UV spectral features.[10,47] All hydroxylamines were colorless viscous oils unless otherwise noted.

2-(1-Cyclopropyl-1-methyl)ethyl 1,1,3,3-tetramethylisoindolin-2-yl carbonate (1d-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.50 (m, 4H), 0.9 (m, 1H), 1.38 (s, 6H), 1.40 (s, 6H), 1.43 (s, 6H), 7.09 (m, 2H), 7.21 (m, 2H); IR ν_{max} (CCl_4) 1774, 1749 (C=O) cm^{-1}.

2-(1-Cyclopropyl-1-methyl)ethoxy-1,1,3,3-tetramethylisoindoline (2d-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.46 (m, 4H), 0.96 (m, 1H), 1.22 (s, 6H), 1.42 (s + d, 6H + 6H), 7.02 (m, 2H), 7.16 (m, 2H).

Dicyclopropylmethyl 1,1,3,3-tetramethylisoindolin-2-yl carbonate (1f-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.41 (m, 8H), 0.92 (m, 2H), 1.38 (s, 6H), 1.43 (s, 6H), 3.54 (t, 1H, 5 J = 5 Hz), 7.09 (m, 2H), 7.21 (m, 2H); IR ν_{max} (CCl_4) 1776, 1759 (C=O) cm-1.

2-Dicyclopropylmethoxy-1,1,3,3-tetramethylisoindoline (2f-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.35 (m, 8H), 0.98 (m, 2H), 1.42 (m, 12H), 2.85 (t, 1H, J = 6 Hz), 7.02 (m, 2H), 7.16 (m, 2H).

2-(4-Cyclopropylbut-3-en-1-oxy)-1,1,3,3-tetramethylisoindoline (3f-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.4–1.0 (m, 4H), 1.38 (br s, 12H), 1.56 (m, 1H), 2.45 (q, 2H), 3.89 (t 2H, J = 6.3 Hz), 5.32 (m, 2H), 7.02 (m, 2H), 7.16 (m, 2H).

1-Cyclopropylethyl 1,1,3,3-tetramethylisoindolin-2-yl carbonate (1e-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.4 (m, 4H), 0.99 (m, 1H), 1.25 (d, 3H, J = 6 Hz), 1.48 (br s, 12H), 3.05 (q, 1H, J = 6 Hz), 7.08 (m, 2H), 7.20 (m, 2H); IR ν_{max} (CCl_4) 1772, 1749 (C=O) cm^{-1}.

2-(1-Cyclopropylethoxy)-1,1,3,3-tetramethylisoindoline (2e-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.4 (m, 4H), 0.95 (m, 1H), 1.15 (d, 3H, J = 6 Hz), 1.42 (m, 12H), 3.35 (q, 1H, J = 6 Hz), 7.02 (m, 2H), 7.16 (m, 2H).

2-(Pent-3-en-1-oxy)-1,1,3,3-tetramethylisoindoline (3e-T): The ^{1}H NMR spectrum of the isomer mixture was consistent with a 1.6:1 *trans*:*cis* ratio based on the following assignments which are congruent with those of authentic *cis*- and *trans*-3-penten-1-ol:[48] ^{trans}**3f-T**, δ 1.42 (brs, 12H), 1.68 (dd, 3H, J = 4, 1 Hz), 2.17 (m, 2H), 3.85 (t, 2H, J = 7 Hz), 5.50 (m, 2H), 7.02 (m, 2H), 7.18 (m, 2H); ^{cis}**3f-T**, the same except for δ 1.63 (d, 5H), and 2.30 (q, 2H, J = 6 Hz).

Cyclopropylphenylmethyl 1,1,3,3-tetramethylisoindolin-2-yl carbonate (1g-T): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.3 (m, 2H), 0.5 (m, 2H), 0.98 (m, 1H), 1.48 (brs, 12H), 4.55 (d, 1H, J = 6 Hz), 7.15 (m, 2H), 7.20 (m, 2H), 7.30 (m, 5H); IR ν_{max} (CCl_4) 1770, 1743 (C=O) cm^{-1}; UV λ_{max} (log ε) (MeOH), 228 (3.21), 257 (2.90), 264 (3.04), 270 (3.04) nm.

2-(Cyclopropylphenylmethoxy)-1,1,3,3-tetramethylisoindoline (2g-T): ^{1}H NMR ($CDCl_3$, 200 MHz), δ 0.3 (m, 2H), 0.5 (m, 2H), 0.95 (m, 1H), 1.40 (m, 12H), 4.75 (d, 1H, J = 6 Hz), 7.05 (m, 2H), 7.19 (m, 2H), 7.25 (m, 5H); UV λ_{max} (log ε) (MeOH), 229 (3.19), 255 (2.87), 264 (3.02), 271 (3.02).

2-(4-Phenylbut-3-enoxy)-1,1,3,3-tetramethylisoindoline (3g-T): Only the trans isomer could be discerned by ^{1}H NMR analysis (cf. authentic *trans*-4-phenyl-3-buten-1-ol[48]); δ 1.43 ($\beta\rho\sigma$, 1H, 12H), 2.45 (θ, 2H, J = 6 Hz), 3.91 (t, 2H, J = 7 Hz), 6.10 (dt, 1H, J = 17, 6 Hz), 6.51–7.02 (m-2H), 7.08 (m, 2H), 7.14-7.35 (m, 5H); UV λ_{max} (log ε) (MeOH), 251 (4.25), 264 sh (3.22), 270 (3.23), 273 (3.02).

***tert*-Butyl α-(1,1,3,3-tetramethylisoindolin-2-yl)-cyclopropaneacetate (4-T):** ^{1}H NMR ($CDCl_3$, 200 MHz), δ 0.4 (m, 2H), 0.6 (m, 2H), 0.98 (m, 1H), 1.15–1.50 (m, 21H), 5.05 (d, 1H, J = 6 Hz), 7.05 (m, 2H), 7.19 (m, 2H); IR ν_{max} 1778, 1640 (C=O) cm^{-1}.

***tert*-Butyl *cis*-5-(1,1,3,3-tetramethylisoindolin-2-yl)-pent-2-enoate (^{cis}5-T):** ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.32 (s, 9H), 1.45 (br s, 12H), 2.61 (m, 2H), 3.75 (t, 2H, J = 8.1 Hz), 5.74 (dt, 1H, J = 11.4 ,2.2 Hz), 6.32 (dt, 1H, J = 11.4 ,7.3 Hz), 7.07 (m, 2H), 7.19 (m, 2H); IR ν_{max} 1718 (C=O) cm^{-1}.

***tert*-Butyl *trans*-5-(1,1,3,3-Tetramethylisoindolin-2-yl)-pent-2-enoate (^{trans}5-T):** ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.34 (s, 9H), 1.45 (br s, 12H), 2.40 (m, 2H), 3.80 (t, 2H, J = 8.1 Hz), 5.79 (dt, 1H, J = 14.9, 1.8 Hz), 6.98 (dt, 1H, J = 14.9, 6.8 Hz), 7.07 (m, 2H), 7.19 (m, 2H); IR ν_{max} 1722 (C=O) cm^{-1}.

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(42) Slabey, V. A.; Wise, P. H. *J. Am. Chem. Soc.* **1952**, *74*, 1473–1476.
(43) Hart, H.; Curtis, O. E. *J. Am. Chem. Soc.* **1956**, *78*, 112–116.
(44) Pearson, R. G.; Langer, S. L. *J. Am. Chem. Soc.* **1953**, *75*, 1065–1068.
(45) Close, W. J. *J. Am. Chem. Soc.* **1957**, *79*, 1455–1458.
(46) Mair, R. D.; Graupner, A. J. *Anal. Chem.* **1964**, *36*, 194–199.
(47) Busfield, W. K.; Engelhardt, L. M.; Healy, P. C.; Jenkins, I. D.; Thang, S. H.; White, A. H. *Aust. J. Chem.* **1986**, *39*, 357–365.
(48) Crombie, L.; Wyvill, R. D. *J. Chem. Soc., Perkin Trans. 1.* **1985**, 1983–1995.