water molecule to an O(4) atom of the cavity wall was not found in the X-ray structure, and the occupation factors for the disordered $CH_2(6)$–O(6) groups are different. These differences may be due to slight variations in the conditions of crystallization or to the different history after crystallization. They show that even in crystal structures of this size hydrogen-bonding networks may be unique to each individual crystal.

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Supplementary Material Available: Listings of atomic coordinates, equivalent isotropic temperature factors, occupation factors, anisotropic temperature factors, individual bond distances and angles, torsion angles, Cremer and Pople ring puckering parameters for both the neutron and X-ray structures, a list of short O···O contacts not involved in hydrogen bonding, hydrogen bond parameters for the X-ray structure, a list of short contacts of oxygen atoms to O(5) and O(6) of the same glucose for six neutron and two X-ray structures, and figures showing the distributions of D occupation factors and D···D jump distances (37 pages); tables of measured and calculated structure factor amplitudes for the neutron and the X-ray structure (49 pages). Ordering information is given on any current masthead page.

Calibration of a New Horologery of Fast Radical "Clocks". Ring-Opening Rates for Ring- and α-Alkyl-Substituted Cyclopropylcarbinyl Radicals and for the Bicyclo[2.1.0]pent-2-yl Radical[1]

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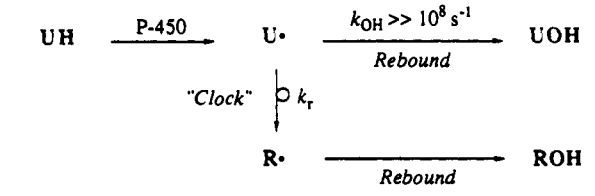
Abstract: Rate constants have been determined at 37 °C for the ring opening of a variety of alkyl-substituted cyclopropylcarbinyl radical "clocks" by nitroxide radical trapping (NRT) using TEMPO. Relative yields of unrearranged and rearranged trialkylhydroxylamines were measured at various TEMPO concentrations, and these data were then combined with absolute rate constants for the reactions of structurally appropriate alkyl radicals with TEMPO as determined by laser flash photolysis. Cyclopropylcarbinyl radicals, including the bicyclo[2.1.0]pent-2-yl radical, were generated by H-atom abstraction from the parent hydrocarbon and, in a few cases, also from the appropriate diacyl peroxide. Twelve substrates yielded sixteen clock reactions because some cyclopropylcarbinyls can undergo two different ring-opening reactions. For six methyl-substituted cyclopropylcarbinyls rate constants ranged from 0.8×10^8 s^{-1} for 1-methylcyclopropylcarbinyl to 47×10^8 s^{-1} for pentamethylcyclopropylcarbinyl. Rate constants for the ring opening of cyclopropylcarbinyl, α-methyl- and α,α-dimethylcyclopropylcarbinyl are 1.2, 0.70, and 0.88×10^8 s^{-1}, respectively. Rate constants for H-atom abstraction by *tert*-butoxyl from various positions in the 12 cyclopropane substrates relative to the rate of H-atom abstraction from cyclopentane have also been determined by using competitive NRT.

In connection with an investigation[3] of the detailed mechanism of the cytochrome P-450-catalyzed hydroxylation of alkanes, we required a number of very fast radical rearrangements ($U^{\bullet} \rightarrow R^{\bullet}$) or clocks[4] with rate constants in excess of 10^8 s^{-1} at the in vivo temperature of 37 °C (Scheme I). The additional requirements were that the rearrangement rate constants could be measured, i.e., that the clocks could be "calibrated", and that hydrogen atom abstraction by the activated cytochrome P-450 ($UH \rightarrow U^{\bullet}$) should lead to simple product mixtures, preferably via a *single* initial radical species. To meet all these requirements we chose symmetrically alkyl-substituted cyclopropanes for our clock substrates (**UH**).

Calibration of the unimolecular ring openings of ring-substituted cyclopropylcarbinyl radicals by competition with a bimolecular radical-trapping reagent requires not only an extremely efficient radical trap but also a radical trap that can be used at high concentrations. For instance, Pereyre, Davies, and co-workers[5]

Scheme I



have shown that ring openings of both the *trans*- and *cis*-2-methylcyclopropylmethyl radicals[6] (**1b**• and **1c**•) are, unlike **1a**•[8] (see Figure 1), too fast to calibrate by the stannane reduction method[9]—only products from the rearranged radicals being observed. Scission of the internal bond of the bicyclo[2.1.0]pent-2-yl

(1) Issued as NRCC No. 32835.
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(3) Bowry, V. W.; Ingold, K. U., following paper in this issue.
(4) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317-323.
(5) (a) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 287-292. (b) Ratier, M.; Pereyre, M.; Davies, A. G.; Sutcliffe, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1907-1915.
(6) These two radicals rearrange too rapidly to be measured by the "conventional"[7] steady-state EPR method.
(7) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1978**, *98*, 7024-7026.
(8) Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902-8015.
(9) However, this method can, apparently, be "pushed" even further, i.e., can be used to calibrate clock radicals which rearrange even more rapidly than **1b**• and **1c**•. See: Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454-5460.

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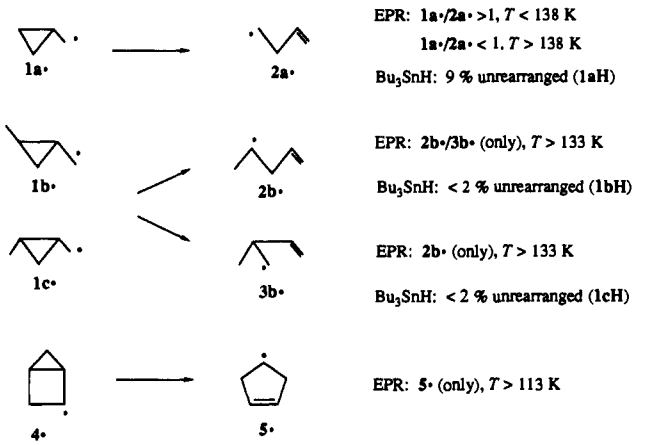


Figure 1. Comparative kinetic data for some cyclopropylcarbinyl radical ring openings. Specified hydrocarbon yields (refs 5 and 9) were obtained by reaction of the neat stannane with **R**Br at 25 °C.

radical ($4^{\bullet} \rightarrow 5^{\bullet}$) was, likewise, too fast for EPR calibration at the lowest attainable temperature (−160 °C).[10]

Fortunately, more recent studies have demonstrated that trapping such radicals with a nitroxide[11,12] (reaction 1) or with benzenethiol[13] (reaction 2) or with bromotrichloromethane[14] (reaction 3) affords sufficient unrearranged products to allow

$$U^{\bullet} + R'_2NO^{\bullet} \xrightarrow{k_T} UONR'_2 \quad (1)$$

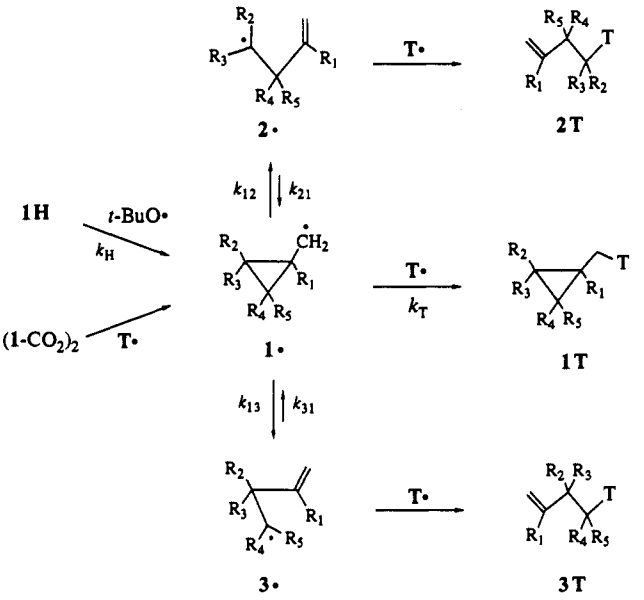
$$U^{\bullet} + PhSH \xrightarrow{k_H} UH + PhS^{\bullet} \quad (2)$$

$$U^{\bullet} + CCl_3Br \xrightarrow{k_{Br}} UBr + {}^{\bullet}CCl_3 \quad (3)$$

reliable measurements of the rearrangement rates. The main advantage of nitroxide radical trapping (NRT) over the other methods used to date[19] is a very large radical trapping rate constant, i.e., $k_T \approx 10k_H \approx 15k_{Br} \approx 1.3 \times 10^9$ M^{-1} s^{-1} for primary alkyl radicals.[11,12,18,20] Moreover, k_T varies much less with radical structure and thermodynamic stability[18,20] than the atom-transfer reactions (e.g., the relative reactivities of benzyl/*n*-alkyl/cyclopropyl radicals are 0.0023/1.0/32 for benzenethiol reduction[21] and 0.011/1.0/28 for CCl_3Br bromination[16,24,25] compared with 0.4/1.0/1.0 for NRT with 2,2,6,6-tetramethylpiperidine-1-oxyl, TEMPO[20,24]). This last attribute of NRT is important when assessing the kinetics of clock radicals for which no compelling nonrearranging model exists (vide infra, $4^{\bullet}$).

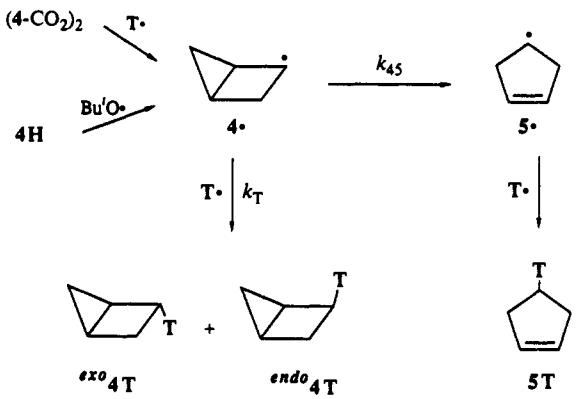
Earlier NRT calibrations[11,18] of radical clocks employed 1,1,3,3-tetramethylisoindoline-2-oxyl (TMIO)[26] as the radical trap because sensitive and uniform detection of the trialkylhydroxylamine products was afforded by HPLC with UV analysis of the isolated aromatic group present in the trap.[11,26] However, because of the limited solubility of TMIO in hydrocarbon solvents, we chose TEMPO as our radical trap for the present work on very fast radical clocks since this nitroxide may, if necessary, even be employed as the neat liquid at 37 °C. The problem of accurate quantitation of the trialkylhydroxylamine products, UONR'$_2$ (**UT**, unrearranged)[27] and RONR'$_2$ (**RT**, rearranged),[27] in the absence

Scheme II[a]

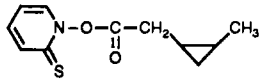


[a] **a**, R_1–R_5 = H; **b**, $R_1 = R_2 = R_4 = R_5$ = H, R_3 = Me; **c**, $R_1 = R_3 = R_4 = R_5$ = H, R_2 = Me; **d**, R_1 = Me, R_2–R_5 = H; **e**, R_1–R_3 = Me, $R_4 = R_5$ = H; **f**, R_1–R_5 = Me.

Scheme III



(10) Jamieson, C.; Walton, J. C.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1366–1371.
(11) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681–2688.
(12) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 1927–1929.
(13) Newcomb, M.; Glenn, A. G.; Williams, W. *J. Org. Chem.* **1989**, *54*, 2676–2681.
(14) In trial experiments, photolysis of the ((2-thiopyridinyl)oxy)carbonyl precursor[13,15] for **1c**• viz.,



in neat CCl_3Br gave **1b**-Br, **2b**-Br, and **3b**-Br in yields compatible with published kinetic data for this rearrangement[11] and for Br-transfer from CCl_3Br.[16] However, when $4^{\bullet}$ was generated by this method, only **5**-Br was obtained (NMR) possibly because of ionic rearrangement of the bicyclic bromide, **4**-Br → [4^+-Br^-] → **5**-Br; a reaction which has a precedent, see: e.g., Friedrich, E. C.; Holmstead, R. L. *J. Org. Chem.* **1971**, *36*, 971–974.
(15) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275–281.
(16) Mathew and Warkentin[17] give $k_{Br}/k_T = 0.12$ for *n*-butyl radicals in CCl_3Br solvent at 80 °C which, because of the solvent dependence[18] of k_T, suggests that k_{Br}/k_T will be ca. 0.07 in a hydrocarbon solvent and hence, by using the recent and reliable values[18,20] for k_T, we obtain $k_{Br} \approx 1.0 \times 10^8$ M^{-1} s^{-1} at 80 °C.
(17) Mathew, L.; Warkentin, J. *Can. J. Chem.* **1988**, *66*, 11–16.
(18) (a) Beckwith, A. L. J.; Bowry, V. W.; Moad, G. *J. Org. Chem.* **1988**, *53*, 1632–1641. (b) Bowry, V. W. Ph.D. Dissertation, Australian National University, 1988.
(19) (a) A faster H-atom donor than PhSH, viz., PhSeH, has recently been found by Newcomb et al.[19b] to be particularly valuable for calibrating very fast radical clocks. (b) Newcomb, M.; Manek, M. B.; Glenn, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 949–958.
(20) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629–1632.
(21) From data for reaction at 25 °C of PhSH with benzyl radicals,[22] *n*-butyl radicals,[23] and cyclopropyl radicals.[24]
(22) Franz, J. A.; Suleman, N. K.; Alnajjar, M. S. *J. Org. Chem.* **1986**, *51*, 19–25.
(23) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268–275.
(24) Johnston, L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877–4881.
(25) For $k_{Br}^{\alpha\text{-methylbenzyl}}$ see: Kuwae, Y.; Kamachi, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2474–2479.
(26) Moad, G.; Rizzardo, E.; Soloman, D. H. *Macromolecules* **1982**, *15*, 909–916. Griffiths, P. G.; Moad, G.; Rizzardo, E.; Soloman, D. H. *Aust. J. Chem.* **1983**, *36*, 397–401.

of TMIO's aryl chromophore has been overcome by using reversed-phase HPLC coupled with "thermospray" ionization and mass spectral detection, an analytical procedure which has proved to be particularly simple and effective for these products.

We report herein ring-opening rates for a number of cyclopropylcarbinyl species (vide infra, Scheme II) together with more complete data on the ring opening of the bicyclo[2.1.0]pent-2-yl radical, **4**• (vide infra, Scheme III), than were reported in our preliminary communication.[12] For the present study, NRT rate constants (k_T) for relevant model radicals were measured by the laser flash photolysis method when not already available.[20] Finally, since the clock radicals were generated by reaction of appropriate alkylcyclopropanes with the *tert*-butoxyl radical, *t*-BuO• (vide infra, Scheme II), we could readily determine hydrogen atom abstraction rate constants (k_H) for the various substrates simply by incorporating, as cosolvents, hydrocarbons with known reactivities toward *t*-BuO•.

Results

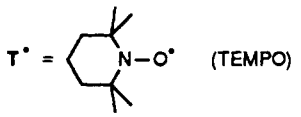
Generation and Trapping of the Cyclopropylcarbinyl Radicals. These radicals were generated either by the TEMPO-induced decay of diacyl peroxides,[28] reactions 4 and 5, and/or by hydrogen atom abstraction from appropriate hydrocarbons using *tert*-butoxyl radicals produced by the thermal decomposition of di-*tert*-butylhyponitrite[30] (TBHN), reactions 6 and 7.

$$(U\text{-}CO_2)_2 + T^\bullet \longrightarrow U^\bullet + CO_2 + [T + U\text{-}CO_2^-] \quad (4)$$

$$U^\bullet + T^\bullet \longrightarrow UT \quad (5)$$

$$t\text{-BuON=NO}t\text{-Bu} \longrightarrow 2t\text{-BuO}^\bullet + N_2 \quad (6)$$

$$t\text{-BuO}^\bullet + UH \longrightarrow U^\bullet + t\text{-BuOH} \quad (7)$$



In the first method, the neat diacyl peroxide (0.1 mol equiv) was added to a nitrogen-flushed, stirred, and thermostatted (37 °C) solution of TEMPO in 2,2,4-trimethylpentane (isooctane), and the reaction mixture was maintained at this temperature until the peroxide was consumed, as determined by TLC.[33] In the second method a solution of TBHN[30] (0.05 mol equiv) and TEMPO in a solvent consisting of the substrate hydrocarbon and a cosolvent (see tables) was freeze/thaw degassed, sealed, and then heated for five reaction half-lives (i.e., 100 h at 37 °C).[32]

Kinetic data obtained from diacyl peroxide precursors suffer the ambiguity that the nitroxide-induced decomposition might afford unrearranged (or rearranged) trialkylhydroxylamine products *without* the intermediacy of *freely* dissociated radicals. This possibility may usually be dismissed on the basis of a sound "kinetic" relationship between product distribution and nitroxide concentration, i.e.

$$[UT]/[RT] \; \alpha [T^\bullet] \quad (I)$$

or for the cyclopropylcarbinyl radicals (Scheme II)

$$[1T]/[2T + 3T] \; \alpha [T^\bullet] \quad (II)$$

The hydrogen atom abstraction method suffers no such ambiguity, and it is especially appropriate, on theoretical[34] as well as practical grounds, for determining the rate constants for "hydroxyl rebound" in cytochrome P-450-catalyzed alkane hydroxylations[3] (see Scheme I) since the P-450 (in microsomes) also generates radicals by hydrogen abstraction. In some cases (e.g., **1e**• and **4**•) both methods of radical generation were used to help resolve questions of solvent effects and product identities.

Product Analyses. Reaction mixtures were analyzed by microbore reversed-phase high-pressure liquid chromatography coupled with thermospray mass spectrometric detection (LC-MS). Satisfactory resolution of trialkylhydroxylamines could generally be achieved by eluting with either aqueous acetonitrile (with 5 mM NH_4OAc added to aid ionization) or aqueous methanol. Thermospray LC-MS with the former solvent system proved particularly effective since the trialkylhydroxylamines were detected almost solely as their protonated parents $(M + 1)^+$ with negligible ion fragmentation; other components in the reaction mixture either were not detected (e.g., hydrocarbons) or had different fragmentation signatures. Products were quantified by LC-MS from either the total ion count or from the "M + 1" ion count peak integration (the latter providing selective detection for isomeric nitroxide-trapped radicals, **UT** and **RT**). Both of these methods were shown, by analysis of standard mixtures, to give accurate product ratios without any need for corrections.

The identities of the trialkylhydroxylamines were established by (a) their molecular masses, (b) their LC retention times which increase with the degree to which the **R** group shields the polar NO group from the solvent, (c) the response of relative peak areas to changes in the nitroxide concentration (cf. eqs I–VI), (d) the NMR spectra of isolated products, or (where preparative isolation was not feasible) (e) NMR analysis of mixtures of trialkylhydroxylamines generated both from concentrated reaction mixtures and from dilute reaction mixtures. In addition, the presence of minor and/or poorly resolved components was checked by (f) co-injection of authentic material (**UT** or **RT**) prepared by reaction of $(U\text{-}CO_2)_2$ or $(R\text{-}CO_2)_2$, respectively, with TEMPO, and by (g) mild bromination of product mixtures, which removes unsaturated **RT** from the $(M + 1)^+$ LC-MS traces.

The reaction of TEMPO with the *tert*-butoxyl radical produced some polar materials (prominent only in the LC-MS of concentrated reaction mixtures) which did not interfere with analyses of the trialkylhydroxylamines. No evidence for reaction of the trapped products with *t*-BuO• was obtained by LC-MS analysis.[35]

NRT Kinetic Data. The initially formed cyclopropylcarbinyl radical, **1**•, may undergo ring opening of either the more or the less substituted ring bond to give radicals **2**• and **3**•, respectively (see Scheme II). The ring-opening reactions compete with trapping of the initial radical by the nitroxide to afford a mixture of trialkylhydroxylamines (**1T**, **2T**, and **3T**). Under conditions where the reverse ring-closing reactions do not compete with radical trapping (i.e., $k_T[T^\bullet] \gg k_{21}$ and/or k_{31}) and where there

(27) For simplicity, stable nitroxides are designated by the generic title T• so that the unrearranged radicals, U• [formed from diacyl peroxides $(U\text{-}CO_2)_2$ or alkanes UH], are trapped to give the unrearranged trialkylhydroxylamines **UT** while the rearranged radicals, **R**• are trapped to give the rearranged trialkylhydroxylamines, **RT**. In the present work, T• is invariably TEMPO though, in trial analyses of TMIO/$(\mathbf{1d}\text{-}CO_2)_2$ reaction products, LC-MS indicated the same component ratios as given by HPLC-UV (270 nm), and moreover these ratios were very similar to those obtained by NRT with TEMPO.

(28) The mechanism of this reaction has been investigated by Moad et al.[29] This reaction has been previously applied to kinetic NRT.[11,12,18a]

(29) Moad, G.; Rizzardo, E.; Soloman, D. H. *Tetrahedron Lett.* **1981**, *22*, 1165–1168. See, also: Kartasheva, Z. S.; Kasaikina, O. T.; Gagarina, A. B. *Kinet. Katal.* **1989**, *30*, 326–333.

(30) TBHN provided a readily available,[31] thermal source of *tert*-butoxyl radicals suitable for the 30 °C ($t_{1/2}$ = 61 h) to 85 °C ($t_{1/2}$ = 5 min) range.[32] Of particular importance for NRT, TBHN is relatively unreactive toward nitroxides, *tert*-butoxyl radicals and alkyl radicals.

(31) Mendenhall, G. D. *Tetrahedron Lett.* **1983**, *24*, 451–452.

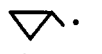
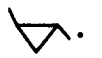
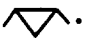
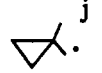
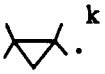
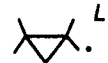
(32) Mendenhall, G. D.; Chen, H.-T. E. *J. Phys. Chem.* **1985**, *89*, 2849–2851.

(33) Preparation of the peroxide-locating spray is described by Mair and Hall: *Organic Peroxides Vol. II*; Swern, D., Ed.; Wiley: New York, 1971; pp 553–557.

(34) The method of radical generation could conceivably influence the measured kinetics and the regiochemistry of very fast radical clocks. For example, excess energy in nascent radicals produced from diacyl peroxides, $(U\text{-}CO_2)_2 \rightarrow U\text{-}CO_2^\bullet \rightarrow U^{\prime\bullet}$, *might* accelerate bond breaking in the clock to form **R**• despite the fact that excess energy of this type is known to be rapidly transferred to the solvent. A conformational effect is also plausible if the rate constant for rearrangement of the radical, k_r, is so great that it makes this process faster than relaxation of the radical's initial conformation, e.g., $k_r > k_{\text{ring flip}}$ or $k_{\text{hindered group rotation}}$. Such effects are not evident for either **1e**• or **4**•, where results obtained from the two methods of radical generation may be compared.

(35) The high reactivity of allylic hydrogens relative to alkane hydrogens makes such a reaction a potential route by which rearranged products may be destroyed. However, the concentrations of the rearranged products were low (<0.03 M) relative to the concentrations of the hydrogen donor solvents (~10 M). Furthermore, no products with two TEMPO moieties could be detected.

Table I. Relative Kinetic Data for 1a·–1f· Calculated from Trialkylhydroxylamine Yields[a]

R·	source[b] [(co-)solvent][c]	$[T^{\bullet}]_m$ (M)[d]	[2T]/[3T][e,f]	k_r/k_T (M)[f]	α[g]	SE[h]
 1a·	DAP [OCT]	0.055	–	0.085		1.0
	DAP [OCT]	0.17	–	0.090		1.0
	DAP [OCT]	0.32	–	0.098		1.0
 1b·	RH	0.13	0.91	0.29		
	RH	0.25	0.93	0.30		
	RH	0.45	0.87	0.32		
	R-H [1eH]	0.45	0.88	0.33	0.23[i]	0.81
	R-H [c-H/1eH]	0.43	0.92	0.29	0.25	0.83
 1c·	RH	0.16	3.1	0.94		
	RH	0.30	3.7	1.00		
	RH	0.86	3.3	1.28		
	RH [c-H]	0.30	3.5	0.98	0.21[i]	
	RH [1eH]	0.31	3.4	1.05	0.23	0.87
 1d·	RH [1eH]	0.12	–	0.06	0.12[i]	0.80
	RH [1eH]	0.28	–	0.07	0.13[i]	0.77
	RH [1eH]	0.94	–	0.09	0.12[i]	0.85
 1e·	DAP [OCT]	0.23	9.8	1.62		1.0
	DAP [OCT]	0.70	9.0	1.76		
	DAP [OCT]	1.0	9.2	1.92		
	DAP [OCT]	1.3	10.4	2.17		
	DAP [OCT]	2.0	10.1	2.49		
	DAP [OCT]	2.9	9.8	3.04		
	DAP [OCT]	4.0	9.1	3.55		
	DAP [RH]	0.93	9.2	3.06		
	RH	0.23	9.9	2.39		
	RH	0.46	10.0	2.56		
	RH	0.92	9.8	2.92		
	RH	1.84	10.5	3.72		
	R-H [c-H]	0.92	9.8	2.80	0.24	
	R-H [c-P]	0.92	10.5	2.68	0.24	
	RH [OCT/RH]	0.92	9.7	2.16		0.97
 1f·	RH [1eH]	0.12	–	4.8	0.29[i]	0.71
	RH [1eH]	0.28	–	5.2	0.26[i]	0.68
	RH [1eH]	0.94	–	6.0	0.25[i]	0.75

[a] 37 ± 0.5 °C unless otherwise noted. [b] Radicals were generated by reaction of appropriate clock hydrocarbon (RH) with di-*tert*-butyl hyponitrite (0.05 mol equiv) or from the appropriate diacyl peroxide (DAP) (0.05 mol equiv). [c] Solvents were cyclohexane (c-H), cyclopentane (c-P), isooctane = 2,2,4-trimethylpentane (OCT) or 1,1,2,2-tetramethylcyclopropane (1eH) or the clock hydrocarbon (RH); cosolvents were added at 10% of the final volumes unless otherwise noted. [d] Mean nitroxide concentration during reaction ($0.95[T\cdot]_{init}$). [e] $[2T]/[3T] = k_{12}/k_{13}$ (scission selectivity). [f] From LC-MS (M + 1 ion) relative yields and kinetic equations. [g] Rate constant for hydrogen abstraction from the clock substrate (RH) relative to the rate constant for abstraction from cyclopentane, i.e., $\alpha = ([c\text{-P}]/[RH])/([1T + 2T + 3T]/[c\text{-PT}])$ where c-PT is trapped cyclopentyl. [h] Solvent effect factor, $SE = (k_r^{1e}/k_T)_{RH}/(k_r^{1e}/k_T)_{OCT}$. [i] Calculated with 1eH ($\alpha = 0.24$) as reference. [j] Approximate data since 1dT and 2dT were poorly resolved. [k] DAP data for 1e· obtained at 35 °C. [l] Solvent [1eH]:[1fH] = 2.1:1.

is a large excess of nitroxide relative to alkyl radicals, the following kinetic equations are obtained:

$$k_{12}/k_T = [T^{\bullet}]_m[2T]/[1T] \quad \text{(III)}$$

$$k_{13}/k_T = [T^{\bullet}]_m[3T]/[1T] \quad \text{(IV)}$$

$$k_r = k_{12} + k_{13} \quad \text{(V)}$$

where $[T^{\bullet}]_m$ is the mean trap concentration during reaction and k_r is the overall ring-opening rate constant.

The bicyclo[2.1.0]pent-2-yl radical (4·) may be trapped at its exo or at its endo face, and thus it gives two unrearranged trialkylhydroxylamines (Scheme III). The appropriate kinetic equation in this case is

$$k_r/k_T = [T^{\bullet}]_m[5T]/[^{exo}4T + {}^{endo}4T] \quad \text{(VI)}$$

Relative yield data obtained for NRT reactions of the ring-substituted and α-substituted cyclopropylcarbinyl radicals and of the bicyclopentyl radical are summarized, in terms of the eqs III–VI, in Tables I–III. Overall yields of trialkylhydroxylamines from diacyl peroxides were in the range of 70–80% based on the stoichiometry of reactions 4 and 5. Hydrogen abstraction afforded high yields of trialkylhydroxylamines (85–90%) in the dilute reaction mixtures but was less efficient at higher [T·] owing to the *t*-BuO·/TEMPO reaction(s) referred to above.

The hydrogen abstraction experiments were carried out in the presence of cosolvents. The cosolvents were incorporated to conserve the clock substrates and to act as internal references for measurement of the reactivity of the clock substrates toward the *tert*-butoxyl radical (vide infra).

Radical-Trapping Rate Constants, k_T. In order to obtain reasonably reliable absolute rate constants for the 12 radical clocks listed in Tables I–III, we require appropriate alkyl radical-trapping rate constants, k_T, for the various radical/solvent combinations employed. Chateauneuf et al.[20] have measured k_T for the trapping

Table II. Relative Kinetic Data for **1g•–1k•** Calculated from Trialkylhydroxylamine Yields

R•[a]	k_r	R'•	temp[b]	$[T•]_m$ (M)[c]	k_r/k_T (M)[c]	α[c]
 **1g•**	→	 [d] **2g•**	37	0.091	0.078	0.25
			54	0.090	0.135	0.27
			54	0.18	0.149	0.30
			54	0.27	0.159	0.32
			85	0.17	0.306	0.32
 **1h•**	→	 **2h•**	37	0.091	0.137	0.56
			54	0.090	0.245	0.63
			54	0.18	0.245	0.72
			54	0.27	0.280	0.67
			85	0.17	0.613	0.85
 **1i•**	k_{12} →	 [e] **2i•**	38	0.34	0.86	1.32
			38	0.62	0.72	1.40
			38	0.97	0.83	1.28
	k_{13} →	 [e] **3i•**	38	0.34	0.14	
			38	0.62	0.12	
			38	0.97	0.16	
 [f] **1j•**	→	 [e,g] **2j•**	40	0.27	0.062	0.35[h]
			40	0.92	0.066	0.41[h]
			40	0.27	0.062	0.37[h]
 [i] **1k•**	→	 **2k•**	37	0.18	0.43	3.9
			37	0.38	0.45	3.6
			37	0.82	0.47	4.4
			37[j]	0.19	0.40	4.6[h]

[a] Generated by hydrogen abstraction with *t*-BuO• from solvents in which the [clock substrate]:[cyclopentane] ratios were 4.5:1 unless otherwise noted. [b] °C ± 0.5 °C. [c] See Table I footnotes. [d] E/Z = 1.88 (37 °C), 1.79 ± 0.08 (54 °C), and 1.68 (85 °C). [e] *E* and *Z* product isomers were not resolved by LC-MS. [f] Solvent [**1jH**]:[**1eH**] = 0.55:1. [g] NMR indicates mainly the *Z* product isomer ($Z/E \approx 5$). [h] Calculated with **1eH** (α = 0.24) as reference. [i] Solvent [**1k**-H]:[c-P] = 0.2:1. [j] Solvent [**1k**H]:[**1eH**] = 1:1.

Table III. Relative Kinetic Data for the Bicyclo[2.1.0]pent-2-yl Radical, **4•**

source (solvent)[a]	temp[b]	[T•] (M)[a]	exo/endo[c]	k_r^4/k_T (M)[d]
DAP (PhCl)	35	1.1	2.6 ± 0.2	4.0 ± 0.3
DAP (PhCl)	35	3.4	2.2 ± 0.1	4.2 ± 0.2
DAP (PhCl)	35	5.2	2.0 ± 0.2	4.6 ± 0.1
DAP (OCT)	35	0.24	2.9	1.5
DAP (OCT)	35	0.42	3.1	1.6
DAP (OCT)	35	0.90	2.6	1.8
DAP (RH)	35	0.42	2.4 ± 0.1	2.5 ± 0.1
RH (c-H)	37	1.17	2.2	2.7
RH (**1eH**)	25	0.42	2.4	1.6/1.96 (0.82)[e]
RH (**1eH**)	37	0.41	2.2	2.2/2.61 (0.84)[e]
RH (**1eH**)	65	0.40	2.6	3.9/4.50 (0.87)[e]
RH (**1eH**)	85	0.39	2.1	5.5/6.18 (0.82)[e]
d_2-RH (c-H)	25	0.29	2.2	1.7
d_2-RH (c-H)	25	0.58	2.0	1.9
d_2-RH (c-H)	25	1.13	2.3	2.0
d_2-RH (c-H)	37	0.13	1.9	2.0
d_2-RH (c-H)	37	0.43	2.2	2.2
d_2-RH (c-H)	37	0.58	2.3	2.4
d_2-RH (c-H)	60	0.27	2.0	4.0
d_2-RH (c-H)	60	0.54	2.3	4.3
d_2-RH (c-H)	60	1.08	2.1	4.6
d_2-RH (c-H)	85	0.26	–	5.8
d_2-RH (c-H)	85	0.52	2.0	6.2
d_2-RH (c-H)	85	1.04	1.7	6.4

[a] See Table I. [b] °C ± 0.5 °C. [c] $[4T_{exo}]/[4T_{endo}]$; where given, standard deviations are from three analyses. [d] From product yields and eq VI. [e] The data represent, in order, $(k_r^4/k_T)/(k_r^{1e}/k_T)$ (ratio), i.e., kinetics of **4•** → **5•** (from eq VI) relative to the internal standard clock, **1e•** → **2e•** + **3e•** (eqs II–IV).

by TEMPO of various alkyl and benzylic radicals by using laser flash photolysis (LFP). The trapping rate constants for the alkyl radicals varied only slightly, viz.,[20] k_T = 1.23, 0.96, and 0.76 × 10^9 M^{-1} s^{-1} in isooctane at 20 °C for *n*-nonyl, neopentyl, and *tert*-butyl, respectively, and should, therefore, provide a fairly reliable basis for deriving rearrangement rate constants from relative NRT kinetic data (k_r/k_T). We consider that the *n*-nonyl,

Table IV. Radical-Trapping Rate Constants by LFP/Probe Method[a]

R•[b]	solvent[c]	k_T (10^7 M^{-1} s^{-1})[d]
	OCT	141 ± 28
	1•H	119 ± 31
	PhH	88 ± 19
	OCT	102 ± 21
	1•H	88 ± 18
	1•H	94 ± 12[e]
	PhH	72 ± 20
	OCT	95 ± 22
	1•H	77 ± 17
n-C_8H_{15}—$\dot{C}H_2$	OCT	138 ± 29 (123 ± 26)[f]
	1•H	109 ± 9
	PhH	108 ± 21
$(CH_3)_3CCH_2$•	OCT	106 ± 35 (96 ± 22)[f]
	1•H	79 ± 16
$(CH_3)_3C$•	OCT	(76 ± 16)[f]

[a] Temp = 19 ± 1 °C unless otherwise noted. Probe = 1,1-diphenylethylene (0.12 M). TEMPO added in 0.7 mM increments (×5). Growth of 329-nm absorption was monitored. [b] Radicals generated by 308-nm LFP of 0.10 M $(RCO_2)_2$. [c] See Table I. [d] Errors represent 95% confidence limits (2σ) but include random errors only. [e] At 30 °C. [f] Reference 20.

neopentyl, and *tert*-butyl radicals are reasonable models[36] for **1a•–1c•**, **1d•–1f•**, and **1h•**, respectively, and the appropriate k_T at 37 °C (extrapolated with an Arrhenius E_a = 1.7 kcal/mol[20]) for TEMPO in isooctane are therefore, 1.4 × 10^9 M^{-1} s^{-1} for **1a•–1c•**, 1.1 × 10^9 M^{-1} s^{-1} for **1d•–1f•**, and 0.9 × 10^9 M^{-1} s^{-1} for **1h•** (see Table IV). Radicals **1g•** and **1i•–1k•** have been *assumed* to have the same reactivity toward TEMPO as cyclopentyl radicals in analogous solvent systems, i.e., taking the solvent effect factor (vide infra), SE, to be 0.8 for these cyclopropylalkanes, k_T = 0.9 × 10^9 M^{-1} s^{-1} at 37 °C.

Both radical clock[18b] and direct LFP measurements[20,39] have demonstrated that k_T can be substantially influenced by the solvent. For instance, it appears that TEMPO is only one-half to one-fifth as reactive toward carbon-centered radicals in aromatic, halogenated, or polar media compared with its reactivity in paraffinic or isoparaffinic solvents, while alicyclic solvents have intermediate values of k_T.[12,39] For an accurate comparison of the radical rearrangement rates in the various media, viz. in the *clock hydrocarbons*, we require some means of measuring or of compensating for these solvent effects.

Uncertainties arising from solvent effects were reduced by a combination of direct and indirect means. The direct procedure was to measure k_T in representative solvents such as isooctane and 1,1,2,2-tetramethylcyclopropane (**1eH**) by LFP. The indirect procedure involved the inclusion of an internal *standard* clock with which to *synchronize* the subject clock reaction. As our standard clock hydrocarbon, we chose **1eH** which was added as a cosolvent to the hydrogen abstraction reactions. The standard (**1e•**) and the subject radical clocks (**1x•**) were thus produced and trapped under identical conditions (temperature, solvent, [**T•**], etc). Comparison of relative rearrangement rates (k_r^{1e}/k_T) measured

(36) There is an excellent correlation[11,37] of kinetic data for the **1a•** → **2a•** rearrangement obtained by using EPR spectroscopy[7] and obtained by using *t*-BuSH,[37] PhSH,[15] Bu_3SnH,[8] and TMIO[18a,38] as radical-trapping agents with the assumption each time that the cyclopropylmethyl radical has a reactivity toward these traps equal to the measured reactivities of *n*-alkyl radicals. This implies that if there is any spin delocalization in cyclopropylcarbinyl radicals it has little or no effect on their reactivities.

(37) Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem.* **1989**, *54*, 4603–4606.

(38) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981–7984.

(39) Solvent effects for the TEMPO/benzyl radical and the TEMPO/neopentyl radical reactions have also been measured by LFP. Solvent polarity was important for both radicals, but viscosity had only a minor effect (Bowry, V. W., unpublished results).

in the mixed clock hydrocarbons with those measured in isooctane allowed solvent effect factors (SE, relative to isooctane) to be assessed (Table I) and applied to the kinetic data for the clock reaction of interest, **1x**$^{\bullet} \rightarrow$ **2x**$^{\bullet}$ (+ **3x**$^{\bullet}$). The variation of k_r^{1e}/k_T between the solvents employed in this work is significant but not large. That is, if one assumes that k_r^{1e} is unaffected by the solvent, our results imply that k_T is about 20% smaller in the alkylcyclopropanes (**1xH**) or ca. 30% lower in bicyclopentane (**4H**) compared with isooctane.

For some additional model radicals k_T values were measured by the LFP method[20] which is now briefly described. The 308-nm LFP of a diacyl peroxide (reaction 8) in the presence of the carbon-centered radical "probe", 1,1-diphenylethylene, gives a UV-absorbing adduct radical (reaction 9) which can be monitored at 329 nm. Addition of a nitroxide gives a lower final (plateau) absorption (since NRT, reaction 10, competes with the probe for **R**$^{\bullet}$), but this plateau is reached more rapidly than without **T**$^{\bullet}$.

$$(RCO_2)_2 \xrightarrow[308\ nm]{h\nu} 2R^{\bullet} + 2CO_2 \qquad (8)$$

$$R^{\bullet} + Ph_2C{=}CH_2 \xrightarrow{k_{probe}} RCH_2\dot{C}Ph_2 \quad (\lambda_{max} = 329\ nm) \qquad (9)$$

$$R^{\bullet} + T^{\bullet} \xrightarrow{k_T} RT \qquad (10)$$

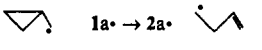
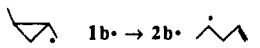
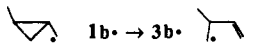
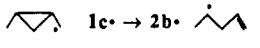
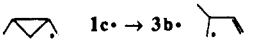
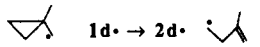
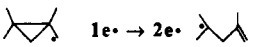
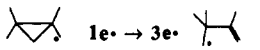
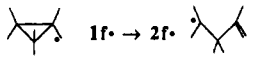
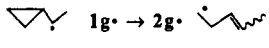
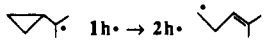
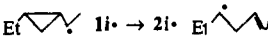
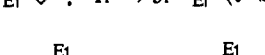
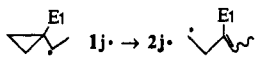
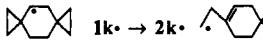
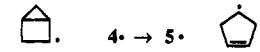
The pseudo-first-order grow-in rate constant for adduct radical formation, k_{expt1}, reflects the lifetime of **R**$^{\bullet}$ and can be described by eq VII. Thus, k_T is obtained from the slope of k_{expt1} vs [**T**$^{\bullet}$] plots.

$$k_{expt1} = k_0 + k_{probe}[Ph_2C{=}CH_2] + k_T[T^{\bullet}] \qquad (VII)$$

Measurements of k_T made by this method for various model radicals in isooctane and 1,1,2,2-tetramethylcyclopropane (**1eH**) are listed in Table IV. Random errors are considerable, but internal consistency[40] and the good agreement between the new data and the earlier results[20] for *n*-nonyl and neopentyl radicals give us confidence that the order of alkyl radical reactivities suggested by Table IV is reliable. The solvent effects measured by LFP corroborate the solvent effect factors (SE) calculated from the standard clock reaction, **1e**$^{\bullet} \rightarrow$ **2e**$^{\bullet}$ + **3e**$^{\bullet}$, which supports the assumption that the observed solvent effect[39] on product ratios (and hence on k_r/k_T) reflects changes in k_T rather than in k_r.

Another potential problem arises from the high nitroxide concentrations which are required to calibrate the very fast rearrangements since the nitroxide itself necessarily becomes a significant component of the solvent mixture and, consequently, creates its own solvent effect. This particular solvent effect[41] is most obvious in the kinetic data for **1e**$^{\bullet}$ in isooctane (Table I) for which k_r/k_T increases significantly with increasing nitroxide concentration, especially for [**T**$^{\bullet}$] > 1 M. Fortunately, the variation in k_r/k_T with [**T**$^{\bullet}$] is approximately linear so that the solvent effect of the nitroxide can be eliminated by extrapolating to "zero nitroxide concentration" (it has been shown[18a] that k_r/k_T is sensibly constant in the range [**T**$^{\bullet}$] = 0.001–0.05 M). This extrapolation procedure, in effect, provides the rate constant ratio k_r/k_T under conditions comparable to those in which k_T was measured by LFP

Table V. Rate Constants at 37 °C and Estimated Arrhenius Parameters for Cyclopropylcarbinyl Radical Rearrangements

rearrangement	k_r[a] ($10^8 s^{-1}$)	log (A/s^{-1})[b]	E_a (kcal/mol)
 **1a**$^{\bullet} \rightarrow$ **2a**$^{\bullet}$	1.2	13.15 (13.31)[c] (13.15)[d]	7.05 (7.26)[c] (7.05)[d]
 **1b**$^{\bullet} \rightarrow$ **2b**$^{\bullet}$	1.6	12.85 (13.5)[c]	6.6 (7.5)[c]
 **1b**$^{\bullet} \rightarrow$ **3b**$^{\bullet}$	1.8	12.85 (14.2)[c]	6.5 (8.4)[c]
 **1c**$^{\bullet} \rightarrow$ **2b**$^{\bullet}$	8.0	12.85 (13.0)[c]	5.6 (6.1)[c]
 **1c**$^{\bullet} \rightarrow$ **3b**$^{\bullet}$	2.3	12.85 (13.5)[c]	6.4 (7.5)[c]
 **1d**$^{\bullet} \rightarrow$ **2d**$^{\bullet}$	0.8	13.15	7.4
 **1e**$^{\bullet} \rightarrow$ **2e**$^{\bullet}$	20	12.85	5.0
 **1e**$^{\bullet} \rightarrow$ **3e**$^{\bullet}$	2.05	12.85	6.4
 **1f**$^{\bullet} \rightarrow$ **2f**$^{\bullet}$	47	13.15	4.9
 **1g**$^{\bullet} \rightarrow$ **2g**$^{\bullet}$	0.70	13.15 (11.0)[e]	7.5 (5.3)[e] (7.9)[f]
 **1h**$^{\bullet} \rightarrow$ **2h**$^{\bullet}$	0.88	13.15 (14.5)[e]	7.4 (10.4)[e]
 **1i**$^{\bullet} \rightarrow$ **2i**$^{\bullet}$	8.6[g]	12.85	5.6
 **1i**$^{\bullet} \rightarrow$ **3i**$^{\bullet}$	1.4[g]	12.85	6.7
 **1j**$^{\bullet} \rightarrow$ **2j**$^{\bullet}$	0.54[g]	13.15	7.7
 **1k**$^{\bullet} \rightarrow$ **2k**$^{\bullet}$	4.1[g]	13.15	6.4
 **4**$^{\bullet} \rightarrow$ **5**$^{\bullet}$	21	13.05[h]	5.2[h]

[a] Calculated from relative kinetic data in Tables I–III with "appropriate" k_T (see text). [b] Arrhenius activation energies (E_a) were calculated from $k_r^{37°C}$ by assuming log (A/s^{-1}) = 12.85 for ring opening *per bond* (see text). [c] Reference 11. [d] Reference 15. [e] Reference 57. [f] Activation energy calculated from 0 °C stannane data (ref 58) with log (A/s^{-1}) assumed equal to 13.15. [g] These may be slightly overestimated since the rearranging radicals would appear to be more hindered than cyclopentyl, the chosen model radical. [h] See text.

(40) The trend toward larger k_T values for the alicyclic radicals as ring size decreases from C_6 to C_4 and continues to C_3 (the cyclopropyl radical) for which a value of 1.2 (± 0.3) × 10^9 M^{-1} s^{-1} was obtained earlier in benzene,[24] a value which may be compared with the 8.8 (±1.9) × 10^8 M^{-1} s^{-1} found for cyclobutyl in this solvent (see Table IV).

(41) The most probable reason for the increase in k_r/k_T with an increase in the nitroxide concentration is a "simple" solvent effect analogous to the isooctane vs benzene solvent effect (see Table IV) whereby, as the polarity or polarizability of the solvent is increased k_T is decreased. Such a decrease in k_T can be ascribed to the necessity for the nonpolar and relatively nonpolarizable carbon-centered radicals employed in this study to break the 1:1 association[42] between the dipolar[43] nitroxide radical and a polar or polarizable solvent molecule, including a second nitroxide radical.[44] Such a requirement for the desolvation of nitroxide radicals has been invoked to explain solvent-induced changes in the rate constants for the bimolecular self-reactions of sterically unhindered nitroxides.[45,47]

(42) Redock, A. H.; Konishi, S. J. *J. Chem. Phys.* **1979**, *70*, 2121–2130.

(43) The bulk dipole moment of TEMPO is 3.14 D, see: Rosantsev, E. G.; Gur'yanova, E. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1966**, 979–983.

(44) Sterically unhindered nitroxides have been shown to dimerize reversibly in relatively nonpolar and nonpolarizable solvents at low temperatures; however, this dimerization does not occur in more polar solvents.[45,46] TEMPO does not dimerize appreciably in benzene at 25 °C.[46]

(45) Adamic, K.; Bowman, D. F.; Gillan, T.; Ingold, K. U. *J. Am. Chem. Soc.* **1971**, *93*, 902–908. Bowman, D. F.; Gillan, T.; Ingold, K. U. *J. Am. Chem. Soc.* **1971**, *93*, 6555–6561.

(46) Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 6390–6394.

(47) Bowman, D. F.; Brokenshire, J. L.; Gillan, T.; Ingold, K. U. *J. Am. Chem. Soc.* **1971**, *93*, 6551–6555.

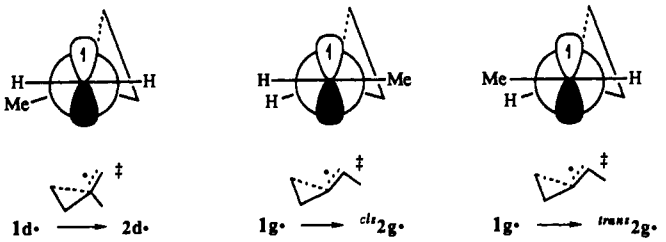


Figure 2. Suggested transition-state geometries for the ring opening of two cyclopropylcarbinyl radicals viewed down the C_α–C_1 bond.

for the model radical and should therefore afford reliable values for k_r. Accordingly, the final kinetic data which are presented in Table V are derived from $(k_r/k_T)_{T\bullet\to 0}$ values and have been corrected for solvent effects by using the standard clock procedure (vide supra).

Discussion

Cyclopropylcarbinyl Radicals (1a•–1k•). Rearrangement kinetics of radicals **1a•–1k•** were derived from the NRT data in Tables I and II with the above corrections and with the model radicals *n*-nonyl for **1a•–1c•**, neopentyl for **1d•–1f•**, cyclopentyl for **1g•**, and **1i•–1k•** and *tert*-butyl for **1h•** (see Table IV).

Table V gives kinetic data at 37 °C and temperature dependencies based on the *assumption* that the *per bond* Arrhenius preexponential factor, A, is the same for each of the cyclopropylcarbinyl ring openings. The A factor used is that derived for **1a•** from combined EPR and product studies covering a 280 °C range of temperature and recommended by Newcomb and Glenn,[15] viz., log (A/s^{-1}) = 13.15 for **1a•** → **2a•** or 12.85 *per bond* (at ordinary temperatures). This is also the value of log A expected on theoretical grounds.[7,48] In terms of Eyring parameters, this assumption is equivalent to saying that all variations in rate constant arise in the enthalpy term $(\Delta H^\ddagger)$ and that entropy of activation is constant $(\Delta S^\ddagger = -1.9$ eu).[49] We are of the opinion that cyclopropylcarbinyl ring-opening rate constants calculated at temperatures other than 37 °C will be more reliable if they are based on an accurate, 37 °C rate constant and an assumed log (A/s^{-1}) = 12.85 per bond than would be rate constants calculated from individually measured Arrhenius parameters which are based only on an "isolated" kinetic study using only a single technique. Of necessity, a single kinetic technique normally will only include measurements over a severely limited range of temperatures. Certainly, our procedure should give fairly accurate ring-opening rate constants in the general vicinity of our experimental temperature.

The kinetic parameters for the ring opening of **1a•** (included in this study as a reference radical and given in Table V) agree very well with previous estimates made by Newcomb and Glenn[15] and by Beckwith and Bowry.[11] Kinetics and regioselectivities of the ring openings of **1b•** and **1c•** are also in satisfactory agreement with previous data.[5,11] In particular, the slight but unusual preference of **1b•** to yield more of the thermodynamically less stable ring-opened primary radical, **3b•**,[5,11] is now confirmed with the use of an alternative radical precursor.

The 1-methylcyclopropylmethyl radical (**1d•**) undergoes ring opening less readily than **1a•** perhaps because nonbonded interactions between the 1-methyl group and one of the α-H's disfavors the transition-state geometry which is necessary for orbital overlap between the SOMO and the C–C bond which is cleaved (Figure 2).

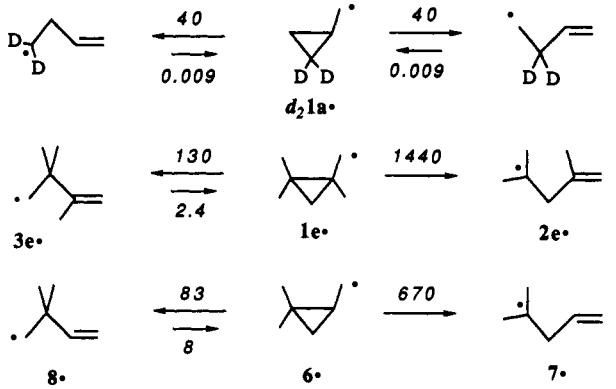


Figure 3. Kinetic data (25 °C) for isomerizations of deuterium-labeled **1a•**(d_2**1a•**) and **1e•** and **6•** in units of 10^6 s^{-1}.

Relatively rapid ring opening of **1e•** to **2e•** (ca. 40-fold faster than **1a•** → **2a•** per bond) no doubt reflects the relief of cis nonbonded interactions in **1e•**. As might be expected, the most substituted cyclopropylcarbinyl radical (**1f•**) is also the shortest lived; with a ring-opening rate constant of 4.7×10^9 s^{-1} at 37 °C (corresponding to 3.6×10^9 s^{-1} at 25 °C). More surprising is our observation that ring opening of **1e•** to give the thermodynamically less favored primary alkyl radical (**3e•**) is, on a per bond basis, about 4-fold faster than the cyclopropylmethyl ring opening (despite the fact that the latter reaction is calculated to be ca. 2 kcal/mol more exothermic[11,48]). This is comparable to reports based on (TMIO) NRT[11] and PhSH[13] trapping studies that the 2,2-dimethylcyclopropylmethyl radical (**6•**) undergoes ring opening to and ring closure of (vide infra) the primary alkyl radical **8•** more rapidly than does the cyclopropylmethyl radical (see Figure 3). Thus, both ring-opening and ring-closing rates are enhanced by the presence of a *gem*-dimethyl group. This fact taken together with the enhanced **1b•** → **3b•** reaction rate (3-fold faster than **1a•** → **2a•** per bond) implies that 2-alkyl substituents (electronically) activate the ring toward β-scission.[5b,11]

The established reversibility of the ring-opening of the dideuteriocyclopropylmethyl radical[52] and of the 2,2-dimethylcyclopropylmethyl radical[11,13] (**6•** ⇌ **8•**) prompted an investigation of the reversibility of the **1e•**/**3e•** radical couple (see Figure 3). Under the conditions employed to study ring opening, viz., [**T•**] = 0.2–4.0 M, the ring-opened products are found in a constant ratio, viz., [**2eT**]:[**3eT**] = 9.8 ± 0.5 at 37 °C. However, when the concentration of the trap, **T•**, was reduced to less than 0.1 M, this ratio is increased. The following data were obtained in dilute solutions of the nitroxide in **1eH** at 37 °C {[**T•**](M)/[**2eT**]:[**3eT**]}: 0.10/10.0, 0.04/10.7, 0.010/15.2, and 0.005/19.6. The kinetic equation which describes the [**2eT**]:[**3eT**] product ratio under these conditions (eq VIII) is consistent with these data (eq IX, $\langle r \rangle$ = 0.997).

$$[\mathbf{2eT}]/[\mathbf{3eT}] = (k_{12}/k_{13})\{1 + (k_{31}/k_T^{3e})[\mathbf{T}^\bullet]^{-1}\} \qquad \text{(VIII)}$$

$$[\mathbf{2eT}]/[\mathbf{3eT}] = 9.7\{1 + 0.005[\mathbf{T}^\bullet]^{-1}\} \quad \text{(at 37 °C)} \qquad \text{(IX)}$$

Substitution of the measured value of k_T for the neopentyl radical in 1,1,2,2-tetramethylcyclopropane (Table IV), affords a ring-closure rate constant for **3e•** of 4×10^6 s^{-1} at 37 °C. The resulting kinetic data are compared with those of related species in Figure 3.[53] It can be seen that the rate of ring closure of **3e•** is about 270 times greater than the rate of the ring closure of 3-butenyl-*1,1*-d_2[52] and that it is three times slower than the ring closure of **8•**. Furthermore, the thermodynamic driving force for the ring closure of **3e•** places it between the thermodynamic driving

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

(49) For comparison, MINDO/3 calculations[50] give $\Delta S^\ddagger$ = −1.0, −2.6, and −1.4 eu for **1a•**, **1g•**, and **1h•**, respectively (25 °C), and high level ab initio calculated ground- and transition-state geometries and energies[51] give $\Delta H^\ddagger$ = 9.2 kcal/mol for **1a•** (cf. E_a = 7.4 kcal/mol, Table V).

(50) Burkhard, P.; Roduner, E.; Fischer, H. *Int. J. Chem. Kinet.* **1985**, *17*, 83–93.

(51) Quenemoen, K.; Borden, W. T.; Davidson, E. R.; Feller, D. *J. Am. Chem. Soc.* **1985**, *107*, 5054–5059.

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

(53) If we assume that the value of log (A/s^{-1}) for the **3e•** → **1e•** ring closure has the mean of the values reported for the **8•** → **6•** reaction, viz., 11.6[11] and 11.0,[13] i.e., 11.3, we obtain an activation energy for the ring closure of **3e•**, E_a = 6.7 kcal/mol and for the vinyl migration, **3e•** → **2e•**, $k_{32} = 2.4 \times 10^6$ s^{-1} at 25 °C.

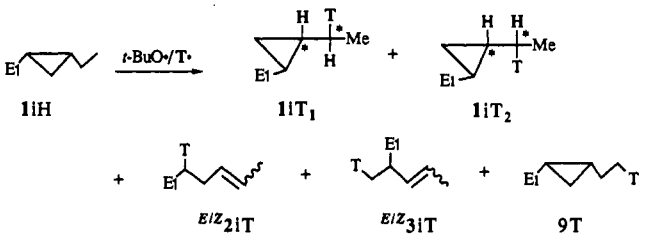
forces for the ring closure of the butenyl radical and of **8**•, i.e., $\Delta G°(\mathbf{2a}^{\bullet} \rightarrow \mathbf{1a}^{\bullet}) > \Delta G°(\mathbf{3a}^{\bullet} \rightarrow \mathbf{1e}^{\bullet}) > \Delta G°(\mathbf{8}^{\bullet} \rightarrow \mathbf{6}^{\bullet})$ by 2.8 and 0.8 kcal/mol, respectively. These data reflect a strong *gem*-dimethyl effect on the rates of ring closure which is tempered somewhat in the **3e**• → **1e**• reaction by cis nonbonded interactions in the ring-closed species, **1e**•.

NRT data indicate that ring openings of the α-substituted cyclopropylcarbinyl radicals **1g**• and **1h**• are nearly as rapid as that of **1a**•.[54] This parallels the situation for cyclobutylcarbinyl radical openings.[55] However, it makes the rate constants for ring opening of **1g**• and **1h**• roughly 4- and 6-fold, respectively, larger than the values which would be estimated at 37 °C from the Arrhenius parameters measured by the muon spin rotation (μSR) method over temperature ranges of ca. 210–265 K (**1g**•) and ca. 230–290 K (**1h**•), viz.,[50,57] $k_r(37\ °C) = 1.8 \times 10^7\ s^{-1}$ for **1g**• and $1.5 \times 10^7\ s^{-1}$ for **1h**•. The reason for this discrepancy is not clear, but we note that for **1g**• our estimated activation energy of 7.5 kcal/mol is in better agreement with an estimate of 7.9 kcal/mol based on earlier triphenylstannane reduction data[58] (cf., footnote f of Table V). Furthermore, we note that the μSR derived Arrhenius preexponential factors for both radicals are out of step with theoretical expectations,[48,49] viz., log $(A/s^{-1}) = 11.0$ for **1g**•[57] and 14.5 for **1h**•[57] vs the expected value of ca. 13.0. This discrepancy serves to emphasize the point we made earlier: viz., that calculated Arrhenius preexponential factors for simple elementary reactions are generally more reliable than *A* factors determined by rate measurements with use of a single experimental technique and a limited temperature range.

The μSR Arrhenius expression for ring opening of **1h**• may readily be checked since the reported high activation energy barrier (10.4 kcal/mol) should prevent this radical from rearranging under the usual steady-state EPR conditions at temperatures below about 170 K ($k_r < 20\ s^{-1}$). Direct UV photolysis in the cavity of a Varian E104 EPR spectrometer of di-*tert*-butyl peroxide with isopropylcyclopropane (**1hH**) in cyclopropane (1:1:3) afforded only a spectrum of the primary radical **2h**• at temperatures above 170 K and only of the tertiary radical **1h**• at temperatures below 130 K. Between 130 and 170 K both radicals were present, and the relative radical concentration ([**1h**•]/[**2h**•]), estimated in the usual way,[7] was similar (ca. 1:1) at 143 K to the [**1a**•]/[**2a**•] ratio obtained by Maillard et al.[7] at ca. 138 K. This demonstrates that the activation energies for the ring opening of **1h**• and **1a**• are not grossly dissimilar which is in accord with the NRT data and our assumption regarding a constant value for the Arrhenius preexponential factors but is contrary to the μSR estimate (see Table V).

The selective formation of the *E* isomer of **2g**• in the ring opening of **1g**• (Table II, footnote d) may be explained[58] in terms of nonbonded interactions between the α-methyl and ring C–H groups in the transition state (Figure 2). The selectivity indicated by NRT (viz.,[59] 2.0 at 0 °C) is in good agreement with an earlier estimate[58] which was based on products from the tri-*n*-butylstannane reduction of **1g**Cl (viz.,[58] 2.2 at 0 °C).

Thermolysis of *cis*-1,2-diethylcyclopropane (**1iH**) with TBHN and TEMPO gave a trialkylhydroxylamine mixture with seven components! At first this appeared to be one product too many, i.e., unrearranged **1iT**, rearranged (*E*)- and (*Z*)-**2iT**, (*E*)- and (*Z*)-**3iT**, and the (minor) product (**9T**), arising via hydrogen abstraction from the methyl groups in **1iH**, add up to only six products. However, further inspection revealed that there are two epimeric forms of **1iT** (ratio 3:1) which were surprisingly well-resolved by HPLC. The selectivity for the ring opening of **1i**• is slightly higher than for **1c**• which is in keeping with the slightly greater bulkiness of the 2-ethyl relative to the 2-methyl substituent.



The dispiro[2.2.2.2]dec-4-yl radical, **1k**•, is of interest because of the scarcity of kinetic data on spiro-fused cyclopropylcarbinyl ring openings[60] and because it provides for the first time a good model for radical traps based on spirocyclopropyl substrates (vide infra). Our kinetic data indicate that **1k**• undergoes ring opening more rapidly than analogous nonspiro species listed in Table V (viz., **1a**•, **1d**•, **1g**•, **1h**• and **1j**•). We note, in particular, that ring opening of **1k**• is nearly an order of magnitude faster (at 37 °C) than its closest nonspiro analogue, **1j**•. Monospirocyclopropylcarbinyl radicals have also been reported to undergo very rapid ring opening.[60] For example,[60] the spiro[2.5]oct-4-yl radical, **10**•, was observed only in its ring-opened form (**11**•) under the usual steady-state EPR conditions even at the lowest attainable temperature of 120 K (at which temperature **1a**• would remain fully ring closed[7]).

10• **11**•

The enhancement in the ring-opening rate of spiro compared with nonspiro cyclopropylcarbinyl radicals probably results from a combination of favorable entropy and orbital overlap factors. The ring opening of **1k**• is entropically favorable because it does not entail a loss of rotational freedom about the C_α–C_1 bond[61] as does the ring opening of **1a**• and other nonfused cyclopropylcarbinyl radicals. Orbital overlap is thought to be most favorable for the β-scission of cyclopropylcarbinyl radicals when the SOMO and one of the cyclopropyl ring bonds are eclipsed. The alignment of these elements in **1k**• is determined by the lowest energy conformation of the radical (Figure 4); a twist angle, ψ, in the cyclohexane ring of about 40° eclipses the SOMO and one of the cyclopropyl ring bonds. Dihedral angles calculated from EPR data indicate that in substituted cyclohexyl radicals[62] ψ is

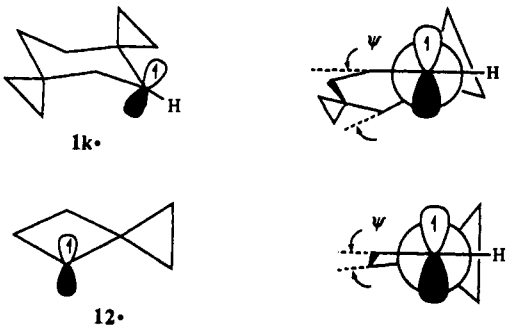


Figure 4. Orbital overlap in **1k**• and in the spiro[2.3]hex-4-yl radical (**12**•).

(54) The thermochemistry of these rearrangements is similar to that of **1a**• → **2a**• since the loss of the secondary and tertiary radical stabilization in the initial species (**1g**• and **1h**•) is almost matched by the greater stability of an internal olefin relative to a terminal olefin.

(55) On the basis of the assumption that the various initial radical species were equally reactive toward tri-*n*-butylstannane, Beckwith and Moad[56] estimated that α-methyl- and α,α-dimethylcyclobutylcarbinyl radicals underwent ring opening less rapidly than the parent radical by factors of 0.23 and 0.75, respectively, at 60 °C.

(56) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083–1091.

(57) Burkhard, P.; Roduner, E.; Hochmann, J.; Fischer, H. *J. Phys. Chem.* **1984**, *88*, 773–777.

(58) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1473–1482.

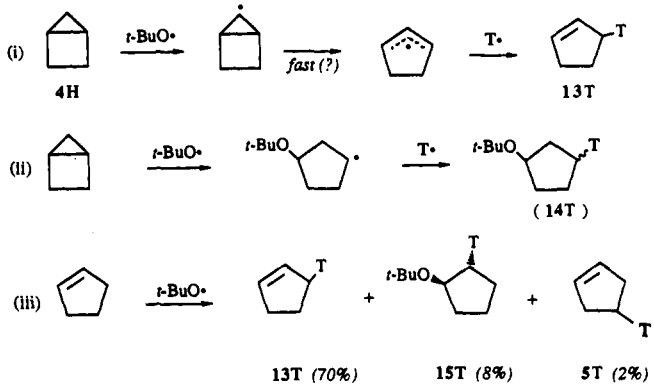
(59) The selectivity data (Table II) may be expressed as log $([^{E}\mathbf{2g}]/[^{Z}\mathbf{2g}]) = -0.09 + 0.5/2.3RT$ which implies an *E*/*Z* ratio of 2.0 at 0 °C.

(60) Roberts, C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 841–846.

(61) Restriction of tortional motion in **1k**• as it undergoes ring opening may somewhat diminish this entropic advantage.

(62) Gilbert, B. C.; Trentwith, M. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1083–1090.

Scheme IV



close to this ideal value (i.e., ψ = 40–45°) unless the substituent (e.g., an oxo group) flattens the ring. NMR evidence[63] suggests that spirocyclopropyl groups do not cause significant ring flattening in the parent hydrocarbons (e.g., $\psi \approx 57°$ for **1kH** and **10H** vs 60° for cyclohexane[63]) so that, all in all, it seems plausible that the ring-opening reactions of **1k**• and **10**• are assisted by favorable orbital alignment in their lowest energy conformations. In contrast, the more rigid spiro[2.3]hex-4-yl radical (**12**•, Figure 4), in which $\psi \approx 0°$, is reported[60] to undergo ring opening with a rate constant of 1.1×10^7 s^{-1} at 25 °C, i.e., rather more slowly than **1a**•.

Bicyclo[2.1.0]pent-2-yl Radical (4•). NRT afforded three trialkylhydroxylamine products arising from **4**•, which were ^{exo}**4T**, **5T**, and ^{endo}**4T** in order of LC elution time (Scheme III). A fourth product (**13T**) of the same molecular mass (M = 223) was present in the products obtained by hydrogen abstraction with *t*-BuO• but not in the diacyl peroxide reaction mixtures. Initially, **13T** was ascribed to abstraction from the cyclopropyl group followed by a cyclopropyl-to-allyl rearrangement[64] and trapping (path i, Scheme IV).[66] However, a further careful analysis revealed an additional *tert*-butoxyl/hydrocarbon reaction product, an *addition/trapping* product [M = 297]. This was initially thought to be **14T** arising from an addition of *t*-BuO• across the bridging bond (path ii). However, this product was soon identified as **15T** since the reaction used to "authenticate" **13T** (viz., hydrogen abstraction from cyclopentene, path iii) afforded **13T** and **15T** in just the same ratio (ca. 9:1) as did the clock substrate. Thus, **13T** and **15T** arise—mainly or solely—from cyclopentene which may well be present as an impurity in **4H**.[67] The relative reactivity data (Figure 5, vide infra) indicate that 0.4% cyclopentene in the bicyclopentane would be sufficient to account for the observed products.[70]

The rearranged product, **5T**, could readily be distinguished from the exo and endo trapped unrearranged radical products, ^{exo}**4T**

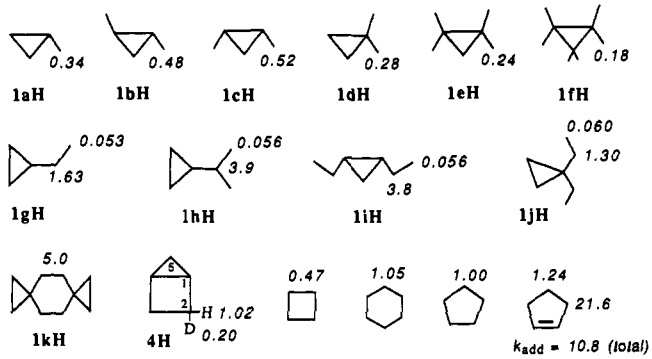


Figure 5. Reactivity *per identical bond* (k_A) for hydrogen atom abstraction relative to cyclopentane at 37 °C by *tert*-butoxyl. Cyclopropyl C–H bonds had $k_A < 0.02$.

and ^{endo}**4T**, by comparison of LC-MS analytical traces from dilute and concentrated solutions (see eq VI) and by co-injection of authentic **5T** prepared from the corresponding diacyl peroxide (**5**-CO_2)$_2$. Exo and endo products were initially[12] distinguished on the basis of their HPLC elution order and the expected steric discrimination in the **4**•/TEMPO reaction; the former predicts that ^{exo}**4T** should be eluted before ^{endo}**4T** [analysis method (b), vide supra] and the latter that the less hindered side should be preferentially trapped. NMR analysis of the mixed trialkylhydroxylamines have since confirmed this; the major α-H resonance is at lower field (δ 3.4 vs δ 4.1) and thus (in view of the ca. 0.6 ppm shielding effect of the cyclopropane ring[71]) we assign ^{exo}**4T** as the major isomer. Experimental uncertainties in the exo/endo ratio were considerable especially in more dilute reaction mixtures where the rearranged species tends to "swamp" the minor unrearranged product; in view of this, we prefer not to overinterpret the exo/endo ratios given in Table III.

It is evident from LFP kinetic data that small angle strain does not strongly affect NRT kinetics since k_T varies only moderately from the strain-free cyclohexyl to the highly strained cyclopropyl radical (cf. Introduction, Table IV, and ref 40). Thus, making the reasonable assumption that **4**• is intermediate in reactivity between cyclopentyl and cyclobutyl radicals and allowing for the solvent effect (i.e., SE ≈ 0.8 for cyclohexane), we estimate that the radical-trapping rate constant which should be applied to the TEMPO/H-atom abstraction data for **4**• is 1.1×10^9 M^{-1} s^{-1} at 37 °C. Combining this value for k_T with an estimate from the TEMPO/H-atom abstraction data that $k_r/k_T = 1.87$ at zero TEMPO concentration at this temperature (based on the relation $k_r/k_T = 1.87 + 0.98_2[T]$, $\langle r \rangle = 0.982$) gives the ring-opening rate constant, k_{45}, at this temperature as $2.0_6 \times 10^9$ s^{-1}. The TEMPO/diacyl peroxide reaction in isooctane (in which solvent k_T is estimated to be 1.42×10^9 M^{-1} s^{-1}) yields $k_{45} = 1.9_6 \times 10^9$ s^{-1} at 35 °C, corresponding to $k_{45} \sim 2.0_7 \times 10^9$ s^{-1} at 37 °C. Rounding off, we therefore take k_{45} to have a value of 2.1×10^9 s^{-1} at 37 °C. If we now make the further assumption that NRT of **4**• has the same activation energy as for a primary alkyl radical (viz.,[20] E_a = 1.7 kcal/mol) and combine this activation energy with the variable-temperature data from Table III we obtain the Arrhenius equations

$$\log (k_T^4/\text{M}^{-1}\ \text{s}^{-1}) = 10.3 - 1.7/\theta \qquad \text{(X)}$$

$$\log (k_{45}/\text{s}^{-1}) = 13.7 - 6.3/\theta \qquad \text{(XI)}$$

where $\theta = 2.3RT$ (kcal/mol). An alternative Arrhenius expression may be derived from the standard clock data, i.e., combination of the reaction rate ratios (see Table III) with the Arrhenius equation for the ring opening of **1e**• gives

$$\log (k_{45}/\text{s}^{-1}) = 13.05 - 5.2/\theta \qquad \text{(XII)}$$

This procedure gives $k_{45} = 2.4 \times 10^9$ s^{-1} at 37 °C and log A and E_a values which are in excellent agreement with the values recently

(63) Lambert, J. B.; Gosnell, J. L.; Bailey, D. S. *J. Org. Chem.* **1972**, *37*, 2814–2817.

(64) Semi-empirical MINDO/3 calculations[65] indicate that the bicyclo[2.1.0]pent-5-yl to 2-cyclopentenyl radical rearrangement may be very rapid since it is highly exothermic ($\Delta H°$ = −34 kcal/mol) and has a relatively small energy barrier ($\Delta H^{\ddagger}$ = 6.2 kcal/mol).

(65) Bews, J. R.; Glidewell, C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1447–1453.

(66) Path (i) was consistent with the product data for abstraction/NRT of the dideuterated bicyclopentane d_2**4H**; i.e., the reaction afforded fully dideuterated **13T** (>95% of M = 225) in nearly twice the relative yield (28% of total nonpolar trialkylhydroxylamine yield) as the reaction of the nondeuterated hydrocarbon (15%) under the same conditions (as might be expected from a deuterium kinetic isotope effect).

(67) In terms of path (iii), the fact that d_2**4H** afforded fully dideuterated **13T**[66] and **15T** suggests (a) that the cyclopentene is dideuterated and must therefore have been formed in the preparation,[68] and/or subsequent thermal (185–190 °C) ring inversion,[69] of **4H** from 1,2-diazabicyclo[2.2.1]hept-2-ene and (b) that one or both of the deuterium atoms in the cyclopentene-d_2 must be in a nonallylic position since otherwise the deuterium abstraction product, d_1**13T**, would have been observed.

(68) Gassman, P. G. *Org. Synth.* **1969**, *49*, 1–6.

(69) See, for example: Roth, W. R.; Enderer, K. *Liebigs Ann. Chem.* **1969**, *730*, 82–90. Baldwin, J. E.; Ollerenshaw, J. *J. Org. Chem.* **1981**, *46*, 2116–2119.

(70) There was insufficient separation on capillary GC and GC-MS to detect cyclopentene at such a low concentration.

(71) Barth, D. E.; Wiberg, K. B. *J. Am. Chem. Soc.* **1969**, *91*, 5124–5130.

obtained by Newcomb et al.,[19b] viz., log (A/s^{-1}) = 13.0, E_a = 5.2 kcal/mol. The log (A/s^{-1}) value given in eq XII is consistent with the ring opening being about neutral entropically.[10,48] We therefore consider eq XII to be more reliable than eq XI. It might be added that eq XII is consistent with the low-temperature EPR data of Jamieson et al.[10] (see Figure 1) from which the authors estimated $k_{45} \geq 10^2\ s^{-1}$ at 113 K and $E_a \leq 5.7$ kcal/mol with an assumed log (A/s^{-1}) = 13.0.[72]

The ring opening of **4•** is some 20-fold faster than the ring opening of **1a•**, but it is not particularly rapid when compared with the polymethyl-substituted cyclopropylmethyl radicals (see Table V). Since the **4•** → **5•** rearrangement is ca. 28 kcal/mol[10] more exothermic than the ring opening of **1a•**, we surmise that the reaction has a very early transition state and that overlap of the semioccupied orbital with the bridging bond is poor.[74] The absence of products arising from the trapping of the cyclobutenylmethyl radical implies that the rate constant for β-scission of the external cyclopropyl ring bond is less than $4 \times 10^7\ s^{-1}$.

Abstraction Kinetics. The reactivity of clock substrates toward *tert*-butoxyl radicals was assessed by including hydrocarbons of known reactivities in the reaction mixtures. For example, a mixture of 1,1,2,2-tetramethylcyclopropane (**1eH**) and cyclopentane (c-C_5H_{10}) reacted with TBHN and TEMPO to yield a mixture of trialkylhydroxylamines derived from the clock substrate (i.e., **1eT**, **2eT**, and **3eT**) and from the reference substrate (i.e., c-C_5H_9**T**). The *per bond relative reactivity*, k_A, is given by eq XIII, in which $k_H^{\mathbf{1eH}}$ and $k_H^{c\text{-}C_5H_{10}}$ are the overall hydrogen abstraction rate constants from **1eH** and cyclopentane, respectively.

$$k_A = (k_H^{\mathbf{1eH}}/12)/(k_H^{c\text{-}C_5H_{10}}/10)$$
$$= (10[c\text{-}C_5H_{10}]/12[\mathbf{1eH}])([\mathbf{1eT} + \mathbf{2eT} + \mathbf{3eT}]/[c\text{-}C_5H_9T]) \quad \text{(XIII)}$$

The relative C–H bond reactivities, k_A (37 °C), estimated in this way are shown in Figure 5. Absolute hydrogen abstraction rate constants may be calculated by using Scaiano et al. kinetic data[76] for *tert*-butoxyl abstraction from cyclopentane (eqs XIV and XV)

$$\log (k_H^{c\text{-}C_5H_{10}}/M^{-1}\ s^{-1}) = 8.47 - 3.47/\theta \quad \text{(XIV)}$$

$$k_H^{c\text{-}C_5H_{10}} = 1.1 \times 10^6\ M^{-1}\ s^{-1} \quad \text{at 37 °C} \quad \text{(XV)}$$

A notable feature of the data in Figure 5 is the high reactivities of α-C–H bonds in the polymethylcyclopropanes compared with ordinary methyl C–H bonds (as exemplified by the terminal group reactivities in **1gH**–**1jH**).[77] The reactivity enhancements (R_α) in the methylcyclopropanes (i.e., $R_\alpha^{\mathbf{1aH}} = k_A^{\mathbf{1aH}}/k_A^{n\text{-alkyl}CH_3} \approx 7$) are smaller than in allylic methyl groups (i.e.,[78] $R_\alpha^{trans\text{-but-2-ene}} = 20$) but are rather similar to the enhancement found for toluene (viz.,[79] $R_\alpha = 10$). The increased reactivity afforded by an adjacent cyclopropyl group has been variously attributed[80] to resonance stabilization of the nascent radical (a pseudoallylic effect),[81] to a polar transition state,[82] or to a ring-strain effect.[83,84] Per bond reactivity of the 1,2-dimethylcyclopropanes (**1bH** and **1cH**) is significantly higher than 1,1-dimethylcyclopropane (**1dH**) or methylcyclopropane, and a similar disparity is evident between the analogous ethyl-substituted species, i.e., **1iH** versus **1jH** or **1gH**. The implication of this, viz., that 2-alkyl (but not 1-alkyl) substitution of the cyclopropane ring kinetically activates α-C–H bonds, is more readily explained as an enhanced polar effect[84,90,91] than in terms of product radical stability. It is interesting to note in this context that the allylic methyl groups in isobutylene (R_α = 12 at 40 °C)[78] are less reactive than those in *trans*-2-butene (R_α = 20 at 40 °C).[78]

The relatively low reactivities of gem-substituted species, **1dH** – **1fH** and **1jH**, might be caused by sterically unfavorable eclipsing of substituents in the transition state. Thus, if reaction enhancement is highest when the breaking bond eclipses or is anti to one of the cyclopropane ring bonds, then the observed substituent effects may be rationalized by conformational analysis. The former situation is shown in Figure 6 where it can be seen that the 1- and α-substituents are partially eclipsed in their (electronically) favored transition-state geometry. The gem-substituted hydrocarbons (e.g., **1dH**) would, it appears, be more

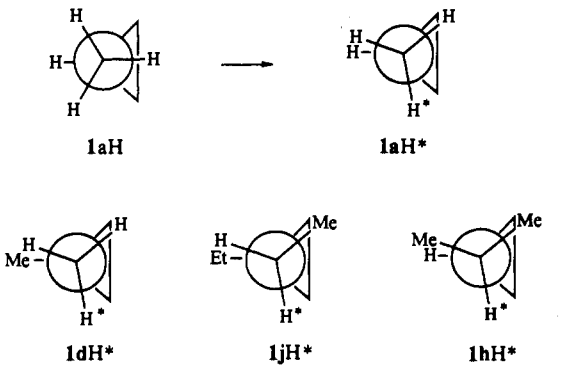


Figure 6. Proposed conformations for cyclopropylalkanes undergoing the abstraction of H*.

(72) Although **4•** should, in principle, be observable by EPR at somewhat lower temperatures,[73] e.g., k_r = 40 s^{-1} at 103 K according to eq XII, the extreme complexity of the EPR spectrum which would be expected for this asymmetric radical may, in practice, preclude its detection.

(73) Photolysis of bicyclo[2.1.0]pentane with di-*tert*-butyl peroxide in cyclopropane (1:1:2 v/v) in the EPR cavity afforded a spectrum of **5•**[10] down to 115 K; at lower temperatures the mixture froze. This problem was not eliminated when ethylene was used as the solvent.

(74) MINDO/3 calculations[65] for **4•** indicate that the radical center is slightly nonplanar and that the SOMO is better aligned to interact with the external (1,5) bond than with the internal (1,4) bond. However, the thermodynamic preference for the 1,4-bond scission overcomes the orbital overlap effect. In contrast, bicyclo[*n*.1.0]alk-2-yl radicals ($n > 2$) are predicted[65] and have been experimentally observed[75] to undergo scission of *external* rather than *internal* cyclopropyl ring bonds.

(75) Roberts, C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1983**, 879–885.

(76) Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 5106–5108.

(77) *tert*-Butyl hypochlorite product data[78] indicate that the methyl groups in *n*-butane have a *per bond* reactivity of 0.065 on our scale (40 °C).

(78) Walling, C.; Thaller, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877–3881.

(79) Walling, C.; Fredericks, P. S. *J. Am. Chem. Soc.* **1962**, *84*, 3326–3331.

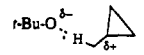
(80) Roberts, C.; Walton, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 1109–1111.

(81) Martin, J. C.; Timberlake, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 978–983.

(82) Huyser, E. S.; Taliaferro, J. D. *J. Org. Chem.* **1963**, *28*, 3442–3445.

(83) Neckers, D. C.; Schnaap, A. P. *J. Org. Chem.* **1967**, *32*, 22–28.

(84) The kinetic effect observed here may arise from radical stabilization in the product radical (i.e., a C_α–H bond weakening effect) or from polarization of the transition state, thus



The low stabilization energy calculated for cyclopropylmethyl radicals (1.8 kcal/mol)[85] and measured by various kinetic methods (0-5 kcal/mol)[81,86–89] versus the large stabilization of the cyclopropylmethyl cation (18 kcal/mol)[88] supports the latter explanation.

(85) (a) Radom, L.; Paviot, J.; Pople, J. A.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1974**, 58–60. (b) Note that Delbecq[85c] has suggested that the delocalization energy of **1a•** may be small or negligible and that the small rotational barrier in **1a•**[85a,85c,87] may not in fact be related to the delocalization energy. (c) Delbecq, F. THEOCHEM **1986**, *136*, 65–75.

(86) See: McMillan, D. F.; Golden, D. M.; Benson, S. W. *Int. J. Chem. Kinet.* **1971**, *3*, 358–374, and references cited therein.

(87) Walton, J. C. *Magn. Reson. Chem.* **1987**, *25*, 998–1000.

(88) For a synopsis of α-cyclopropyl effects in polar and radical reactions, see: de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809–826.

(89) Hart, H.; Cipriani, R. A. *J. Am. Chem. Soc.* **1962**, *84*, 3697–3705.

(90) The carbonium ion character of the cyclopropylcarbinyl group might be enhanced by the electron-releasing effect of a 2-alkyl substituent (transmitted through homoconjugation).

(91) On the basis of a perturbation treatment of hydrogen abstraction reactions, Chandra[92] suggests that "as ionization energy of the donor bonds is decreased, the reaction is accelerated and it is not influenced by the bond strengths of the donor bonds". Evidence that this is at least partially correct has been given by Strong et al.[93]

(92) Chandra, A. K. *J. Photochem.* **1982**, *18*, 151–159.

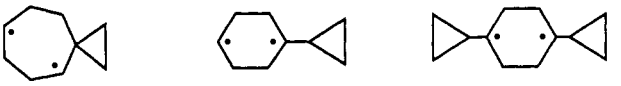
(93) Strong, H. L.; Brownawell, M. L.; San Filippo, J. *J. Am. Chem. Soc.* **1983**, *105*, 6526–6528, and references cited therein.

constrained to a staggered conformation and therefore be less reactive than the nongem-substituted species. In **1jH** a *pseudoanticlinal* arrangement of substituents is required for a C–H bond to eclipse one of the cyclopropyl bonds. The low reactivity enhancement for abstraction of the tertiary hydrogen from **1hH** (R_α = 1.6) may be compared to that for abstraction of the tertiary hydrogen from cumene (R_α = 1.5)[94] and from *o*-cymene (R_α = 0.06)[95,96] where nonbonded interactions also disfavor the reactive conformation in which the tertiary C–H bond is perpendicular to the aromatic ring.[96] A combination of steric inaccessibility and a relatively high rotational energy barrier for the methyl groups in hexamethylcyclopropane (**1fH**) may account for its low reactivity toward H-atom abstraction.

The hydrogen abstraction reactivity of the dispirohydrocarbon, **1kH**, is conspicuously high (cf. ethylcyclopropane, **1gH**[97]). The relative abstraction reactivity of **1kH** may be compared with EPR data[80] for spiro[2.4]octane (**10H**) in which α-C–H bonds were 8.6- and 7.3-fold more reactive than other C–H bonds in the cyclohexane ring at −93 °C and −20 °C, respectively. This extrapolates to a 6.6-fold preference at 37 °C, i.e., a relative reactivity of 6.9 on our scale, a result which is in fair agreement with the value of 5.0 found for **1kH** (Figure 5). It appears that a favorable conformational effect is enhancing the reactivity of **1kH** (cf., the ring opening of **1k**• and the low α-activation reported for spiro[2.3]hexane, **12H**[98]).[99]

The bicyclopentane, **4H**, has a (global[100]) hydrogen abstraction reactivity that is normal for an unstrained cycloalkane but is about twice that found for cyclobutane.[101] The relative smallness of the α-cyclopropyl activating effect in **4H** may reflect poor overlap between the bond being broken and the 1,4- or 1,5-bonds of **4H**.[65] Mass distributions in the LC-MS of **4T** and **5T** generated from d_2**4H** indicate a (global[100]) deuterium isotope effect of 5.3 ± 0.5 on the reactivity of the C_2–H bonds (see Figure 5). As noted above, there is no sign of hydrogen abstraction from the C_1 or C_5 positions, a result which is in keeping with the low reactivity of cyclopropane C–H bonds.

Radical Clocks. Cyclopropylcarbinyl radical rearrangements have long been used to elucidate the mechanisms and kinetics of biological[102] and chemical[103] reactions. However, the lack of sound kinetic data for these radical rearrangements has often led to rather broad uncertainty limits being given to the derived kinetic data. For example, Adam and co-workers[104] have reported the lifetime of the triplet diradical **16** ($^3\tau$) to be in the 0.3–3.3-ns range based on the degree of ring opening of the (spiro) cyclopropyl group observed in the products and on a cyclopropylcarbinyl ring-opening rate constant between 2.2×10^7 and 2.7×10^8 s^{-1}. Likewise, Engel and Keys[105] have calculated lifetimes and other kinetic data for



16 **17** **18**

"spring-loaded"[105] triplet diradicals **17** and **18** based on an estimated ring-opening rate[106–108] for the α,α-dialkylcyclopropylcarbinyl radical moiety. Substitution of the much more appropriate kinetic data for the rearrangements of **1k**• and **1h**• (Table V) gives $^3\tau$(**16**) = 0.3 ns, $^3\tau$(**17**) = 12 ns, and $^3\tau$(**18**) = 8 ns. Other kinetic data for these species and related 1,4-biradicals[109] may similarly be recalibrated by using the more appropriate model radicals shown in Table V.

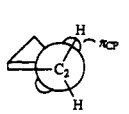
Conclusions

The nitroxide radical trapping technique is a powerful tool for analyzing the kinetics and selectivities of fast radical rearrangements. Alkyl radical trapping rate constants, k_T, are close to the diffusion limit in hydrocarbon solvents for a rather wide variety of radical types (see refs 11, 12, and 20 and Table IV). We estimate that, under favorable conditions, rearrangement rate constants in excess of 10^{10} s^{-1} may readily and reliably be measured by using TEMPO as a radical trap and LC-MS for product analysis.

The substituted cyclopropylcarbinyl radicals **1a**•–**1k**• rearrange with rate constants in the range 5×10^7–3.5×10^9 s^{-1} (25 °C) and thus provide a useful assortment of clocks[4] for kinetic competition with fast radical processes. Within the polymethylcyclopropylmethyl series (**1a**•–**1f**•), ring-opening rate constants (Table V) increase with substitution at the 2-position on the ring, whereas an alkyl group in the 1-position reduces k_r slightly. One or two α-methyl substituents reduce k_r, although to a lesser extent than previously estimated.[50,57,105–107] Ring opening of **1k**• is remarkably rapid which indicates that (nonrigid) spirocyclopropylcarbinyl radicals can provide efficient probes for studying very short-lived radical species (e.g., **16**).[104]

Hydrogen abstraction from hydrocarbons may conveniently be studied by the NRT method because all carbon-centered product radicals are efficiently trapped to give stable, nonvolatile, and easily identifiable nitroxide-coupled products. The NRT data for reactions of *tert*-butoxyl radicals with alkylcyclopropanes, **1bH**–**1kH**, indicate an enhancement of up to nearly a factor of ten in the reactivity of C–H bonds adjacent to the cyclopropyl group relative to comparable "unactivated" C–H bonds. The reactivity enhancement is largest for the spirohydrocarbon **1kH** and for the *cis*- and *trans*-1,2-dialkylcyclopropanes, while the 1,1-dialkyl and

(94) Walling, C.; Jacknow, B. R. *J. Am. Chem. Soc.* **1960**, *82*, 6108–6112.
(95) Sulpizio, A.; Mella, M.; Albini, A. *Tetrahedron* **1989**, *45*, 7545–7552.
(96) Calculated from published data for cumene vs toluene (40 °C, substrate mixture)[94] and *o*-cymene (intramolecular competition at 25 °C in MeCN)[95] by assuming no solvent effect and normal reactivity (k_A = 0.7)[94] for the $ArCH_3$ group in *o*-cymene.
(97) Combining the NRT data with appropriate data for butane,[78] we estimate the α-cyclopropyl reactivity effect, k_A(**1kH**)/k_A(c-C_6H_{12}) = 5.3 vs k_A(**1gH**)/k_A(−CH_2−) = 2.3.
(98) Applequist, D. E.; Landgrebe, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 1543–1550.
(99) For a review of C–H reactivity in bicyclo- and spirocyclopropylalkanes, see: Ingold, K. U.; Walton, J. C. *Acc. Chem. Res.* **1986**, *19*, 72–77.
(100) The present data do not directly distinguish between endo and exo hydrogen abstraction. However, yield data and the isotopic composition of the products indicated that the total *hydrogen* abstraction reactivity of **4H** (vs cyclohexane) was less than twice (1.8 ± 0.1) that of the dideuterated **4H** (67:33 *exo*:*endo*:*cis*-2,3-d_2**4H**), which suggests that the endo C–H bonds are somewhat more reactive than the exo C–H bonds [1.6(±0.3):1.0]. This may be explained as an orbital overlap effect since the endo C–H bonds are better aligned to interact with adjacent cyclopropane (Walsh) π-orbitals (π_{CP}) than the corresponding exo bonds.



(101) An estimate[10] based on relative rates of consumption of **4H** vs cyclohexane by *tert*-butyl hypochlorite gave a value for k_A(**4H**) ca. 30% higher than ours.
(102) For a review, see: Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537–552.
(103) For examples, see: refs 8 and 17. Taylor, K. G.; Govindan, G. K.; Kaelin, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 2091–2099. Barclay, L. R. C.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1982**, *107*, 4964–4975. Beckwith, A. L. J.; Bowry, V. W.; O'Leary, M.; Moad, G.; Rizzardo, E.; Solomon, D. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1003–1004. Tanko, J. M.; Skell, P. S.; Seshadri, S. *J. Am. Chem. Soc.* **1988**, *110*, 3221–3225.
(104) Adam, W.; Grabowski, S.; Scherhag, F. *Tetrahedron Lett.* **1988**, *29*, 5637–5640.
(105) Engel, P. S.; Keys, D. E.; Kitamura, A. *J. Am. Chem. Soc.* **1985**, *107*, 4964–4975. Engel, P. S.; Keys, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 6860–6861.
(106) Engel and Keys[105] based their estimate on kinetic data[7] for **1a**• → **2a**• and analogy with cyclobutylcarbinyl ring openings in which α,α-dimethyl substitution is reported (EPR)[107] to reduce the ring-opening rate constant by a factor of 9 at 25 °C (see, however, ref 55). **Note Added in Proof.** The rate constants for ring opening of the 1-cyclopropylcyclopentyl and 1-cyclopropylcyclohexyl radicals have very recently been reported to be 1.45×10^7 and 1.1×10^7 s^{-1} at 24.7 °C, respectively, see: Engel, P. S.; Culotta, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 2686–2696. On the basis of our study of ring opening by **1h**•, α,α-dialkylcyclopropylcarbinyl radicals should undergo ring opening with a rate constant of 5.3×10^7 s^{-1} at 25 °C. The source of the discrepancy is unknown.
(107) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970–974.
(108) Note that $^3\tau$(**18**) is calculated on the basis of there being two noninteracting cyclopropylcarbinyl groups, each of which may be modelled by **1h**• [i.e., k_r(**18**) = 2k_r(**1h**•)].
(109) Rudolph, A.; Weedon, A. C. *Can. J. Chem.* **1990**, *68*, 1590–1597.

monoalkylcyclopropanes are less activated; we explain these trends in terms of polar and/or conformational effects.

Experimental Section

LC-MS analyses were performed with use of a Hewlett-Packard HP 1090 liquid chromatograph equipped with an HP ODS hypersil (5 μm) 200 mm × 2.1 mm column, thermospray MS interface, and HP 59970C MS data analysis system. NMR spectra were recorded on Brucker AM 400 (400 MHz for ^1H and 61 MHz for ^2H) or Varian EM 360 (60 MHz) instruments with $CDCl_3$ as solvent and tetramethylsilane as an internal standard. The laser flash photolysis apparatus and k_T measurement methods have been adequately described in earlier publications from this laboratory.[20,110]

Starting Materials. TEMPO (Aldrich, WI) was sublimed before use. *tert*-Butyl hyponitrite (TBHN) was prepared from *tert*-butyl bromide, sodium hyponitrite, and anhydrous $ZnCl_2$ in 40% yield by Mendenhall's method[32] and purified by percolation through alumina and low-temperature crystallization from pentane. Alkylcyclopropanes **1aH** to **1eH** and **1gH** to **1jH** (Wiley, OH) were each of >98% isomeric purity (GC) and better than 99.8% olefin free (estimated from LC-MS of abstraction products and relative allylic C–H reactivity). Hexamethylcyclopropane (**1fH**) was prepared by treating a mixture of 2,3-dimethyl-2-butene and 2,2-dibromopropane with *n*-BuLi at −65 °C as described by Fischer and Schaefer[111] and purified by Kügelrohr distillation, preparative GC, redistillation, and fractional crystallization, mp 5 °C (^1H NMR; δ 0.97). Dispiro[2.2.2]decane[112] (**1kH**) was prepared by adding an ether solution of 1,4-dimethylenecyclohexane (3.5 g, 32 mmol) and diiodomethane (25 g, 93 mmol) to an ether suspension of Zn (Cu) couple [prepared by LeGoff's procedure[113] from 7.1 g (110 mmol) of "20 mesh" granular zinc]. After 5 h at reflux, the reaction mixture was decanted into a stirred slurry of concentrated HCl in crushed ice, and the organic layer was washed with H_2O, 20% aqueous ammonia, and brine before being evaporated and distilled to afford the dispiro compound with <3% olefin by ^1H NMR and 97% pure by GC (2.9 g, 65%), bp (Kügelrohr) 110 °C (100 mm), mp 28 °C [^1H NMR; δ 0.1 (s, 8 H), 1.1 (s, 8 H)]; a very pure sample of this compound was obtained for the kinetics experiments by partial crystallization (mp 30 °C). Bicyclo[2.1.0]pentane (**4H**) was prepared by Gasman's method.[68] The deuterium-labeled compound, *cis*-[2,3,-$^2H_2$]bicyclo[2.1.0]pentane (***d*$_2$4H**),[114] which was >95% dideuterated by ^1H NMR and GC-MS (EI) analyses, had an exo:endo ratio of 67:33 as determined by ^2H NMR integration (δ 1.35 = exo, δ 2.08 = endo).

Diacyl peroxides were prepared in 70–75% yield and >90% purity (by iodometric[115] and NMR analyses) from acid chlorides by the Na_2O_2/wetted ether method.[18a] Cyclopropaneacetic acid was purchased from Lancaster Synthesis. 1,2,2-Trimethylcyclopropaneacetic acid (**1e**-CO_2H) was prepared by successive esterification (BF_3/MeOH[116]), cyclopropanation (as above, >98% conversion), and saponification of 3,4-dimethylpent-3-enoic acid.[117] Bicyclo[2.1.0]pentanecarboxylic acid (**4**-CO_2H, endo/exo mixture) was prepared by the method of Brooks et al.[118] The following acids were converted into diacyl peroxides[18a] and treated with TEMPO to assist product identification [(U-CO_2)$_2$ + TEMPO → UT]: cyclopent-3-enoic (**5**-CO_2H),[119] 2-methyl-4-pentenoic acid (**2b**-CO_2H), *trans*-4-hexenoic acid (**^{trans}2g**-CO_2H), *trans*-2-ethyl-4-hexenoic acid (**^{trans}2i**-CO_2H), and *cis*-3-(2-ethylcyclopropyl)propanoic acid (**9**-CO_2H). **^{trans}2i**-CO_2H was prepared by α-ethylation of **^{trans}2g**-CO_2H using Pfeffer's method[120] (LDA/HMPA/EtI). **9**-CO_2H was prepared by cyclopropanation (as above, 65%) of methyl *cis*-4-heptenoate (prepared from *cis*-4-hexenal by Ag_2O oxidation[121] and BF_3/MeOH esterification[116]).

Trialkylhydroxylamines (UT and RT). The trialkylhydroxylamine yield ratios obtained by LC-MS analysis were reproducible (±5%, except for exo:endo **4T**, ±10%) and were not significantly affected by increasing the reaction times nor by prolonged exposure to the buffered (5 mM NH_4OAc) HPLC solvent used for analysis [i.e., MeCN:H_2O, 78:22 (for $C_{4,5}$ radical products), 84:16 (C_7), or 90:10 (C_{10})]. The nonpolar trialkylhydroxylamines were isolated by flash chromatography (10 mm × 150 mm silica column eluted with 0.5% → 2% ether in *n*-pentane) and further resolved (where practical) by preparative HPLC. NMR analysis of the pure or mixed trialkylhydroxylamines (**UT** or **RT**) was straightforward since resonances from the adduct groups (**U** or **R**) were very similar to those reported for the corresponding alcohols (**UOH** or **ROH**).

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