Synthesis and spin trapping kinetics of new alkyl substituted cyclic nitrones

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Three new nitrones, 5-*n*-propyl-5-methyl-1-pyrroline-*N*-oxide (PMPO), 5-*n*-hexyl-5-methyl-1-pyrroline-*N*-oxide (HMPO), and 5-*n*-decyl-5-methyl-1-pyrroline-*N*-oxide (DeMPO), amphiphilic versions of the spin trap 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), have been synthesized. A comparative study of the absolute rate constants for formation and decay of the *tert*-butoxyl spin adducts to these cyclic nitrones as well as 3,3,5,5-tetramethyl-1-pyrroline-*N*-oxide (M_4PO) has been undertaken using esr kinetic techniques.

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On a synthétisé trois nouvelles nitrones: le *N*-oxyde de *n*-propyl-5 méthyl-5 pyrroline-1 (OPMP), le *N*-oxyde de *n*-hexyl-5 méthyl-5 pyrroline-1 (OHMP) et le *N*-oxyde de *n*-décyl-5 méthyl-5 pyrroline-1 (ODeMP) qui sont des versions amphiphiles du capteur de spin *N*-oxyde de diméthyl-5,5 pyrroline-1 (ODMP). Faisant appel aux techniques cinétique de rpe, on a entrepris des études comparatives des constantes absolues de vitesse de formation et de désintégration des adduits de spin *tert*-butoxyle de ces nitrones cycliques ainsi que du *N*-oxyde de la tétraméthyl-3,3,5,5 pyrroline-1 (OM_4P).

[Traduit par le journal]

Introduction

Heightened attention has been drawn lately to the intermediacy of free radical species in biological systems. The increased activity has been due in part to the considerable success of spin trapping (see refs. 1 (for biochemical applications) and 2 (for a general review)) with cyclic nitrones (3). The detection and identification of transient bio-radicals includes ·OH (4) and $\cdot O_2^-$ (5) which are difficult to study by other methods. It was realized (6) that effective examination of free radical phenomena in biphasic media such as biological membranes or models thereof required the development of "tailored" spin trapping agents of hydrophilic and/or lipophilic design. A number of these new nitrone (7) and nitroso (8) spin traps have become available. However, 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) counterparts have not yet been reported. The present research was directed towards the synthesis of spin traps wherein hydrocarbon chains of systematically increasing length (*n*-propyl, *n*-hexyl, *n*-decyl) were connected to C-5 of the pyrroline ring to impart increased lipophilic character to the DMPO nucleus.

The general procedures employed in synthesis of the cyclic nitrone spin traps (I, II, III) are outlined in Scheme 1.

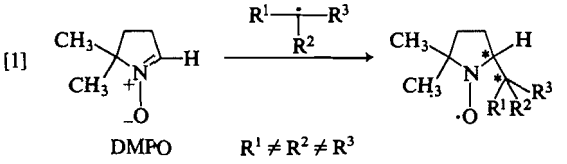
Several years ago (9) it was demonstrated that spin trapping could serve as a quantitative probe for certain free radical reactions in solution. However, only recently has there emerged an increased awareness of the importance of kinetic spin trapping data. Maeda and Ingold (10*a*) have suggested that spin trapping will not fully evolve until rate constants for all ·R's and spin traps become available.

The viability of a given spin trap is dependent to a large extent upon the rates of formation of spin adducts (k_f) and their subsequent decay (k_d). An objective of the present study was to apply kinetic esr spectroscopic techniques to ascertain the effect, if any, of alkyl chains of differing lengths (*n*-propyl, *n*-hexyl, *n*-decyl) at C-5 of the pyrroline ring on the spin trapping and spin adduct decay rate constants relative to those for DMPO.

Results and discussion

Diastereomeric cyclic aminoxyl radicals[1]

The capture of a free radical by DMPO creates an enantiomeric mixture of spin adducts with an asymmetric center located at position 2 of the pyrrolidine ring. Only one esr spectrum is anticipated and this indeed is observed (3*c*), see Fig. 1 (a). When the group that was the radical possesses an element of chirality, however, diastereomeric aminoxyls are produced (eq. [1]). Differences in the hyperfine patterns are expected and may be observed (11).



[1]Note, the term "aminoxyl" was introduced during the spin trapping conference and was deemed more appropriate than "nitroxyl".

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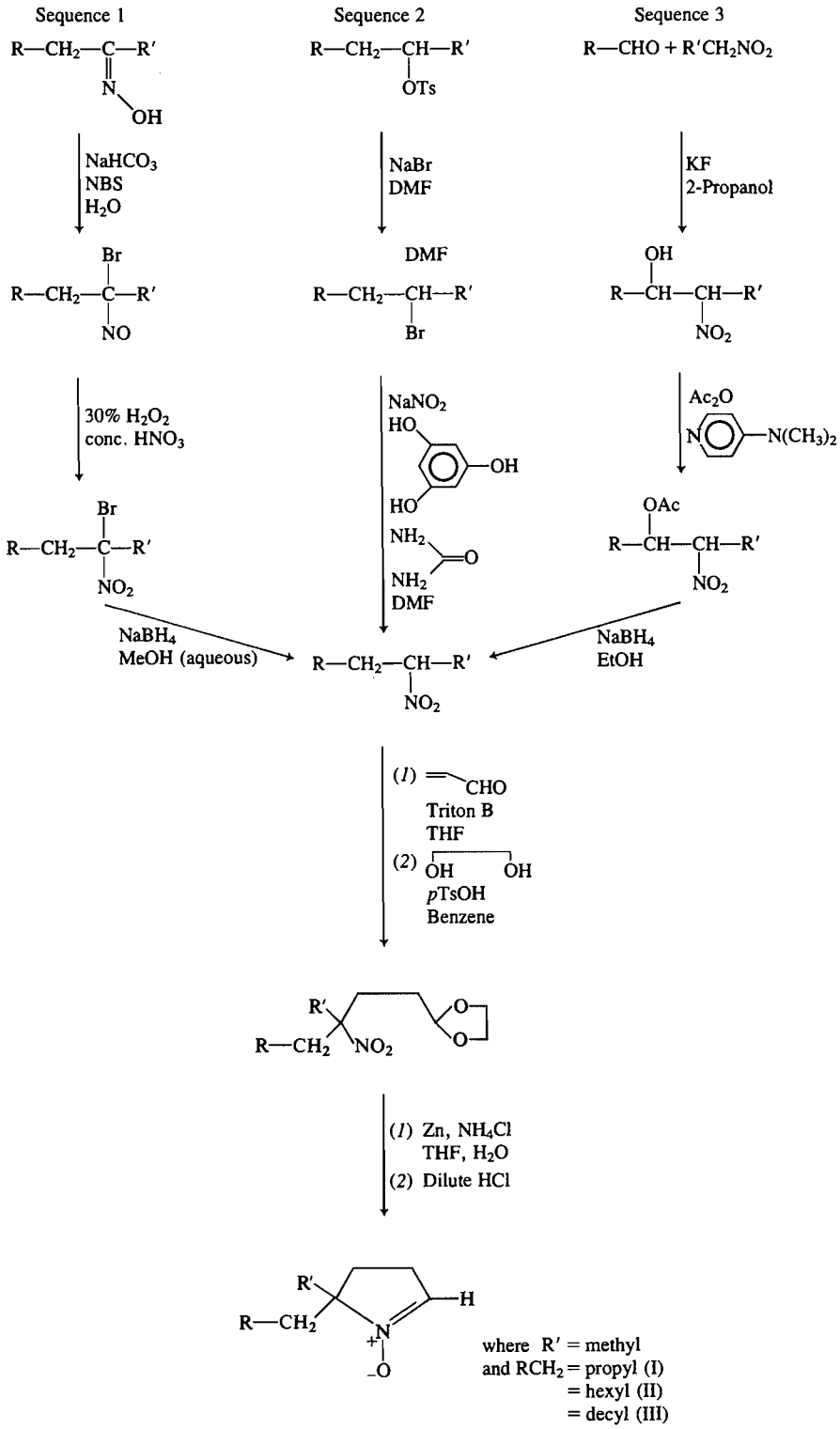


SCHEME 1

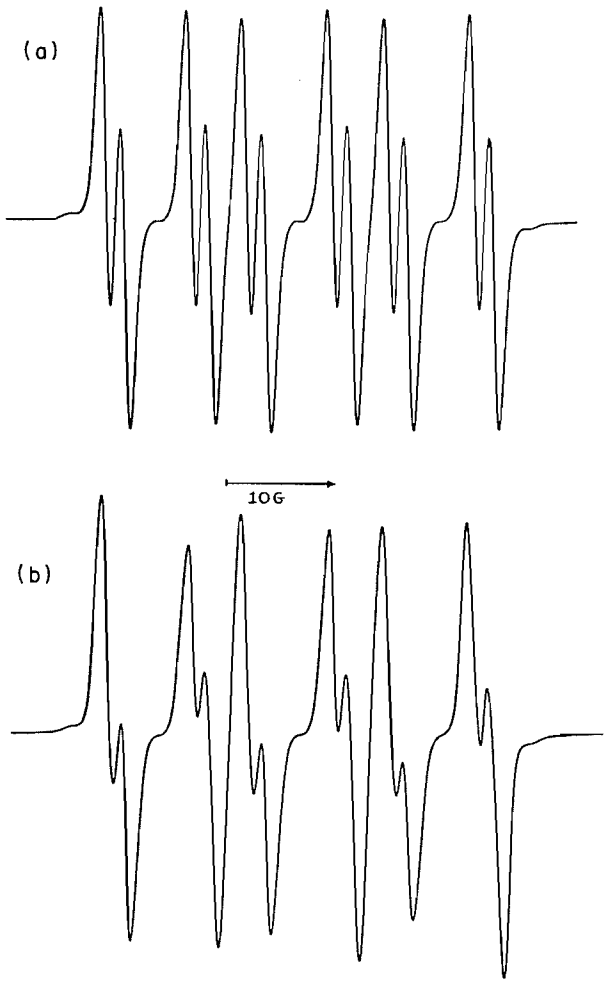
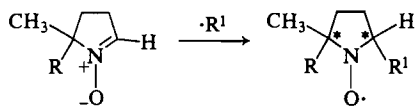


FIG. 1. (*a*) Spectrum from 0.05 *M* DMPO and 0.01 *M* DBPO in benzene (25°C). (*b*) Spectrum from 0.10 *M* HMPO and 0.05 *M* DBPO in benzene (25°C).

The *tert*-butoxyl adduct derived from an RMPO spin trap is diastereomeric. This is due to the presence of the two chiral sites which are incorporated in this case within the pyrrolidine framework at C-2 and C-5 (eq. [2]).

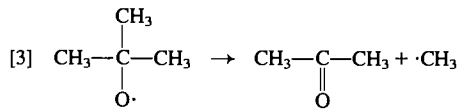
[2] 

RMPO

R = (*n*-propyl, *n*-hexyl, *n*-decyl), $R^1 \neq H$

Linewidths ranging from 0.12 to 0.13 G were observed with all *tert*-butoxyl adducts of DMPO and RMPO. Existence of the relatively wide lines decreases the chances of detecting a distinct esr spectrum for each diastereomer. For this reason the spectra of RMPO BO· adducts might be expected to exhibit dissymmetry when the spectra of diastereomers superimpose, i.e. the typical asymmetric spectral appearance of RMPO *tert*-butoxyl adducts, Fig. 1 (b) may be indicative of diastereomeric cyclic aminoxyls.

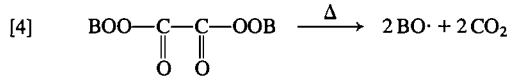
The question of asymmetric spectra arising from impurity radicals rather than diastereomeric spin adducts appears unlikely. *tert*-Butoxyl radicals are known (12*a*) to fragment to acetone and methyl radicals. Asymmetry is definitely not due to spin trapping of methyl or other *C*-centered radicals because the spectra of these adducts are character-

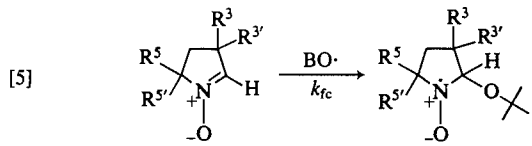
[3] 

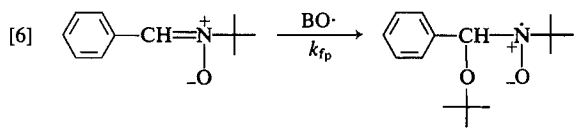
ized by sharp lines and sizably different in their hfsc's; e.g. for the methyl adduct of DMPO in benzene, $a_N = 14.31$ and $a_\beta^H = 20.52$ G (3*d*). The hfsc's for the cyclic nitrone BO· spin adducts are listed in Table 1.

Formation kinetics

The absolute rate constant of *tert*-butoxyl trapping by PBN was determined by correlation with the well established rate constant of hydrogen abstraction from cyclohexane by BO· radicals (12*b*). Rate constants for spin trapping *tert*-butoxyl radicals with cyclic nitrones were obtained by competitive *in situ* scavenging experiments with PBN. *tert*-Butoxyl radicals generated in reaction [4] are trapped by the cyclic nitrone and PBN in reactions [5] and [6] respectively.

[4] 

[5] 

[6] 

Due to marked differences in their hfsc's, Table 1, initial formation rate constants of the two adducts may be quantitated by monitoring as a function of time the peaks indicated in Fig. 2. The formation rate constants of the BO· adducts of the cyclic nitrone and PBN are represented by expressions [7] and [8] respectively.

TABLE 1. Hyperfine splitting constants for *tert*-butoxyl spin adducts[a]

Nitrone	a_N	a_β^H	a_γ^H
DMPO	13.19[b]	8.16	1.82 (1H)
	(13.01)[c]	(6.63)	(2.04)
PMPO	13.24	8.17	1.94 (1H)
	(12.92)	(6.91)	(1.98)
HMPO	13.03	7.99	1.87 (1H)
	(12.88)	(6.87)	(1.65)
DeMPO	13.08	7.97	1.77 (1H)
	(12.95)	(6.92)	(2.17)
M_4PO	13.39[d]	5.88	
	(13.16)	(4.90)	
PBN	14.29[e]	1.84	

[a]All spectra were recorded at 25°C in benzene from 0.05 *M* nitrone and 0.01 *M* di-*tert*-butylperoxalate, all hfsc's are in Gauss.
[b]Compare with a_N = 13.11, a_β^H = 7.93, a_γ^H = 1.97 (1H) G, ref. 3*c*.
[c]Bracketed values indicate spectra recorded in di-*tert*-butylperoxide.
[d]Compare with a_N = 13.31, a_β^H = 5.81 G, ref. 3*e*.
[e]Compare with a_N = 14.22, a_β^H = 1.95 G, ref. 9*b*.

[7] $$\frac{d[\text{cyclic adduct}]_0}{dt} = k_{fc}[\text{cyclic nitrone}]_0[BO\cdot]_0$$

[8] $$\frac{d[\text{PBN adduct}]_0}{dt} = k_{fp}[\text{PBN}]_0[BO\cdot]_0$$

Since k_{fp}, $[PBN]_0$, $[\text{cyclic nitrone}]_0$ are known, k_{fc}, the spin trapping rate constant for the cyclic nitrone may be determined by measuring the initial rates of growth of the two spin adducts.

[9] $$\frac{d[\text{cyclic adduct}]_0/dt}{d[\text{PBN adduct}]_0/dt} = \frac{k_{fc}[\text{cyclic nitrone}]_0}{k_{fp}[\text{PBN}]_0}$$

Plots of esr growth for cyclic nitrone and PBN BO·

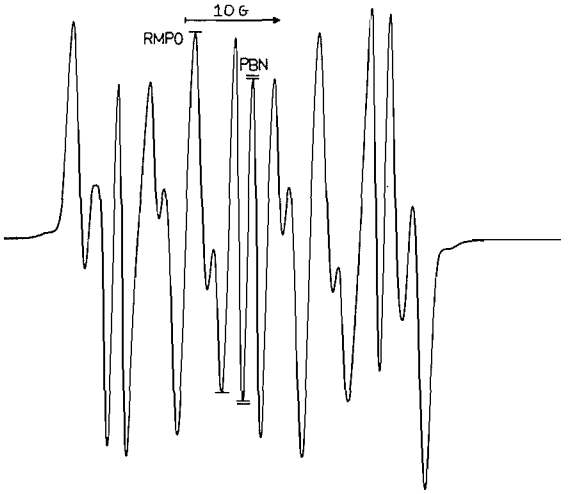


FIG. 2. Spectrum from 0.01 *M* HMPO, 0.30 *M* PBN, and 0.005 *M* DBPO in benzene (25°C).

adducts were characteristically linear (all corr. >0.999) over a 1500 s timescale. A representative plot, i.e. the PMPO adduct, is provided in Fig. 3. Cyclic nitrone adduct growth gradually slowed thereafter causing curvature in the plots due to the onset of spin adduct decay. When the cyclic nitrone concentration was increased from 0.001 to 0.10 *M* nonlinearity effects occurred earlier (~200 s) and were considerably more pronounced. This observation might suggest that spin adduct disappearance was due in some degree to spin adduct reaction with the spin trap. A similar rate constant of *tert*-butoxyl adduct production (within experimental error), 5.2×10^8 vs. 4.1×10^8 M^{-1} s^{-1} (Table 2) was, nevertheless, obtained with 0.10 *M* PMPO. This adds further support (9*b*) to the argument that all BO· radicals generated in this system are scavenged by spin trapping.

Spin trapping rate constants for *tert*-butoxyl are reported in Table 2. Reproducibility of the results, as judged by duplicate runs, was ±10%. The rate constant of *tert*-butoxyl trapping by DMPO was 7.3×10^8 M^{-1} s^{-1}. This is slightly greater than the value of 5.0×10^8 M^{-1} s^{-1} previously reported (9*b*). Rate constants for RMPO (R = *n*-propyl, *n*-hexyl,

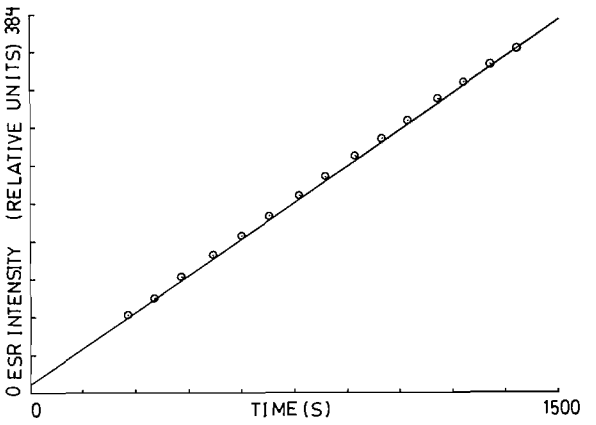


FIG. 3. Plot of the esr signal intensity for the *tert*-butoxyl spin adduct of PMPO versus time in benzene.

TABLE 2. Absolute *tert*-butoxyl spin trapping rate constants of various cyclic nitrones[a]

Spin trap	Spin trapping rate constant $k_{fc} \times 10^{-8}$, M^{-1} s^{-1}
DMPO	7.3[b]
PMPO	4.1
HMPO	3.8
DeMPO	3.3
M_4PO	0.086[c]

[a]All rate constants were determined at 25°C in benzene.
[b]Compare with 5.0×10^8 $M^{-1}s^{-1}$, ref. 9*b*.
[c]Compare with 0.16×10^8 M^{-1} s^{-1}, ref. 3*e*.

n-decyl) BO· trapping of 4.1, 3.8, and 3.3 × $10^8\ M^{-1}\ s^{-1}$ respectively are marginally lower than the DMPO value. Examination of molecular models indicates that the rate constant decrease relative to DMPO might rest in a steric effect wherein a propyl or longer alkyl substituent at C-5 of the pyrroline ring is required to interfere with radical addition at C-2. *tert*-Butoxyl addition to M_4PO, $0.086\ M^{-1}\ s^{-1}$ (compare $0.16 \times 10^8\ M^{-1}\ s^{-1}$ (3*e*)), was decreased 85× with respect to DMPO obviously due to steric interactions caused by the two additional methyl groups located "β" to the nitrone functionality.

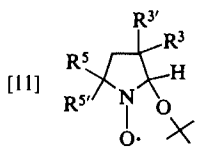
Decay kinetics

Rate constants for the decay of the *tert*-butoxyl adducts of the various nitrones are listed in Table 3. Duplicate experiments indicated a reproducibility of ±20%. Ultraviolet photolysis of di-*tert*-butylperoxide (BOOB) over approximately five minutes produced $\sim 1.5 \times 10^{-6}\ M$ steady-state *tert*-butoxyl adduct concentrations according to reactions [5] and [10].

[10] $\text{BOOB} \xrightarrow{\hbar\nu} 2\,\text{BO}\cdot$

Solubilization of each of the cyclic nitrones (except M_4PO) at 25°C in di-*tert*-butylperoxide produced an exceedingly weak yet persistent triplet (a_N = 15.29). The anomalous signal situated midway between doublets 1 & 2, 3 & 4, 5 & 6 (Figs. 1 (a) and (b)), presumably of a di-*tert*-alkyl aminoxyl, was completely unaffected by photolysis and remained unchanged even days later. This aminoxyl does not appear to interfere with the spin trapping system chemically or spectrally (i.e. the triplet does not overlap the BO· adduct peaks). Hence the kinetic data reported here should remain valid.

Simple dialkyl aminoxyls bearing at least one β-H substituent, such as diethylaminoxyl, are known to decay via disproportionation to the respective hydroxylamine and nitrone.[2]

[11]  $\xrightarrow{k_d}$ nonradical products

[2]For the mechanism of diethylaminoxyl decay,

$$(CH_3CH_2)_2NO\cdot \xrightarrow{k_d} (CH_3CH_2)_2NOH + CH_3CH{=}\overset{+}{N}(-O)CH_2CH_3$$

see ref. 10*b*. Further examples exhibiting the second order decay of dialkylaminoxyls are presented in ref. 10*c*.

TABLE 3. Absolute rate constants for the second order decay of the various cyclic *tert*-butoxyl adducts[a]

Spin trap[b]	Initial radical concentration (*M*)	Decay rate constant $k_d \times 10^{-2}$, $M^{-1}\ s^{-1}$
DMPO	1.8×10^{-6}	5.1
PMPO	1.8×10^{-6}	3.9
HMPO	1.3×10^{-6}	5.5
DeMPO	1.2×10^{-6}	4.1
M_4PO	1.5×10^{-6}	0.65

[a]All rate constants were determined at 25°C in di-*tert*-butylperoxide.
[b]All nitrones were 0.20 *M*.

Best fits were obtained with second order plots (all corr. >0.99). The decay of the DeMPO *tert*-butoxyl adduct is representative (Fig. 4). A degree of first order character may also be present because these plots were also reasonably linear (all corr. 0.90–0.95).

The decay rate constants of the RMPO *tert*-butoxyl adducts are effectively equal within experimental error. This suggests that despite the increased number of methylene hydrogens (due to the longer alkyl substituents in the RMPO adducts) their persistence remains essentially the same as DMPO adducts. The rate constant of decay for the BO· adduct of M_4PO, $0.65 \times 10^2\ M^{-1}\ s^{-1}$, is 8× slower than that of DMPO. Decay rate constants for all the cyclic nitrone adducts are of comparable magnitude though slightly smaller than that reported for a *C*-radical spin adduct of related structure, i.e. the $\cdot CH_2OH$ adduct of DMPO decayed at $184\ M^{-1}\ s^{-1}$ (4*c*).

Summary

In this study the viability of five cyclic nitrone spin traps (DMPO, PMPO, HMPO, DeMPO, and M_4PO) as scavengers of BO· radicals has been

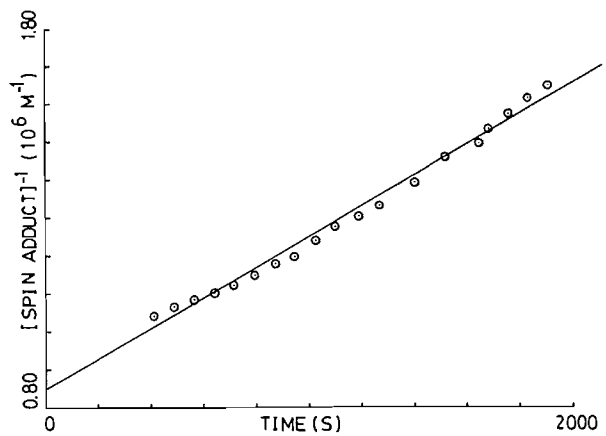


FIG. 4. Plot showing decay of the *tert*-butoxyl adduct of DeMPO is second order at 25°C in di-*tert*-butylperoxide.

evaluated. We find that the RMPO spin traps offer the following advantages in spin trapping.

(a) There is potential for preferentially probing radical reactions in lipid-like regions of mixed phase media.

(b) The spin trapping rate constants for radicals are fast, Table 2, e.g. *tert*-butoxyl ($\sim 3.7 \times 10^8\ M^{-1}\ s^{-1}$).

(c) The spin adducts, e.g. *tert*-butoxyl, are persistent, Table 3, ($\sim 4.5 \times 10^2\ M^{-1}\ s^{-1}$).

(d) Isotropic esr spectra are obtained which are (in addition) sensitive to the nature (polar versus nonpolar) of the radical trapped, Fig. 1 (b) (also refs. 3*c*, 3*d*).

Interpretation of esr spectra of RMPO adducts thus far has not been hampered by the existence of diastereomers because differences in hfsc's have been less than the linewidths. Detailed examination of RMPO adducts by ENDOR spectroscopy is planned. Preliminary experiments with the RMPO spin adducts in model membrane systems are currently in progress.

Synthetic methodology

Synthesis involved essentially the conversion of secondary aliphatic nitroalkanes to nitrones via a procedure developed by Todd and co-workers (13). Several variations in experimental conditions for these reactions were required. Details are given in the Experimental.

Three distinct Sequences (1, 2, 3), Scheme 1, to 2-nitroalkanes were examined. A recent Corey modification (14) is evidence that the oxidation of oximes through intermediate halonitroso compounds is still an important route to nitro compounds. The route, however, seems to be limited to the preparation of cyclic and short chain (< 6 carbons) 2-nitroalkanes. Sequence 1 utilized a modified version of the original procedure (15). A major inconvenience inherent in Sequence 2 is the high yield (> 30%) of the side product 2-alcohols. Removal of these impurities from long chain (> 12 carbons) 2-nitroalkanes proved exceedingly difficult. Described in Sequence 3 is the successful extension of a recently developed primary nitroalkane procedure (16) to the synthesis of long chain secondary nitroalkanes.

Experimental

The nmr spectra were recorded on a Varian (T60 or EM 360L) spectrometer and only the characteristic peaks are reported. Chemical shifts were reported in $CDCl_3$ as a solvent in parts per million (δ) downfield from internal tetramethylsilane. The ir spectra were obtained from a Beckman Acculab 6 spectrophotometer. Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario. References to the original literature accompany all known compounds.

Synthesis of nitrones and precursors

I. *Secondary nitroalkanes*

Sequence 1

2-Bromo-2-nitrosopentane

Freshly distilled 2-pentoxime (24.0 g; 237.1 mmol) (94% from 2-pentanone (17)) was added gradually to a vigorously stirred suspension of 63.3 g (355.7 mmol) *N*-bromosuccinimide and 39.8 g (474.2 mmol) sodium bicarbonate in 400 mL of 5°C water. After the reaction subsided, the ice/H_2O bath was removed and stirring was continued for 3 h. The thermally labile bromonitrosoalkane was extracted with pentane (3 × 150 mL), dried over sodium sulfate, and filtered. Approximately 80% of the solvent was removed at atmospheric pressure giving a dark blue oil, (not distillable, lit. (15)), which was used directly in the next step.

2-Bromo-2-nitropentane

30% Aqueous hydrogen peroxide (120 mL) and 50 mL of concentrated nitric acid were added in succession to the crude bromonitrosoalkane. The mixture was heated at 50°C for 4 h, cooled, extracted with 3 × 200 mL pentane, washed with 2 × 120 mL 2% NaOH, dried over sodium sulfate, filtered, and solvent removed under reduced pressure. 2-Bromo-2-nitropentane (27.9 g; 142.3 mmol) was isolated in 60% yield (from the oxime) as a clear colorless oil, bp 72°C/12 Torr (lit. (15) 3-isomer, 3-bromo-3-nitropentane, bp 70°C/10 Torr); ^1H nmr ($CDCl_3$) δ: 2.20–2.60 (s, 3H, Br (NO_2)—C—CH_3), 2.20–2.60 (t, 2H, Br (NO_2)—C—CH_2).

2-Nitropentane

2-Bromo-2-nitropentane (27.9 g; 142.3 mmol) was gradually added to a mechanically stirred solution (0°C) of 20.0 g (528.7 mmol) of sodium borohydride in 270 : 90 (mL) methanol–water. Stirring was continued for 12 h after which the mixture was filtered through sintered glass, methanol was evaporated under reduced pressure, and the resulting aqueous phase acidified by dropwise addition of 15% aqueous hydroxylamine hydrochloride solution. After stirring for 2 h the aqueous mixture was extracted with 3 × 200 mL pentane, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure (25°C) and the residue fractionated to provide 10.0 g (85.4 mmol), 60% yield, of colorless 2-nitropentane, bp 152°C/ 750 Torr (lit. (18) bp 149°C/760 Torr); ^1H nmr ($CDCl_3$) δ: 1.52 (d, 3H, NO_2—C—CH_3), 4.62 (sextet, 1H, NO_2—C—H).

Sequence 2

2-Bromooctane

2-Octyl-*p*-toluenesulphonate (19) was obtained as a thermally labile faint yellow oil in 72% yield by reaction of 56.5 g (433.8 mmol) of dried, freshly distilled 2-octanol with 90.9 g (476.8 mmol) of purified *p*-toluenesulphonyl chloride in 350 mL (4.33 mol) of dry pyridine for 4 h at −5°C. 2-Octyl-*p*-toluenesulphonate (88.7 g; 312.3 mmol) and 32.3 g (313.9 mmol) of anhydrous sodium bromide in 500 mL of dry *N*,*N*-dimethylformamide were stirred for 3.5 days at 25°C. To the mixture were added 200 : 200 (mL) pentane–water. The aqueous DMF portion was extracted with 3 × 150 mL pentane. The combined organic layers were washed with 3 × 150 mL of water, dried over sodium sulfate, filtered, and solvent evaporated under reduced pressure. 2-Bromooctane (57.9 g; 299.8 mmol) (96% yield) was collected as a colorless oil, bp 69°C/12 Torr (lit. (19) bp 87°C/20 Torr); ^1H nmr ($CDCl_3$) δ: 1.70 (d, 3H, Br—C—CH_3), 4.01 (m, 1H, Br—C—H).

2-Nitrooctane

2-Bromooctane (57.9 g; 299.8 mmol), dry sodium nitrite (36.0 g; 521.7 mmol), dry phloroglucinol (37.8 g; 299.7 mmol), and dry urea (39.9 g; 664.6 mmol) were stirred in the dark for 45 h at 25°C in 600 mL of dry DMF. Pentane (300 mL) and 300 mL of water

were added to the mixture. The aqueous DMF layer was extracted with 3 × 150 mL pentane. The combined organic phases were washed with 3 × 150 mL of water, dried over sodium sulfate, filtered, and solvent evaporated under reduced pressure. The crude product was fractionated through a 1 × 20 cm Vigreux column, and 22.9 g (143.9 mmol) of 2-nitrooctane (48% yield) were collected as a colorless oil, bp 70°C/3 Torr (lit. (20) bp 67°C/3 Torr); ^{1}H nmr ($CDCl_3$) δ: 1.52 (d, 3H, NO_2—C—CH_3), 4.60 (sextet, 1H, NO_2—C—H).

Sequence 3

3-Hydroxy-2-nitrododecane

To 58.1 g (371.6 mmol) of freshly distilled decanal and 1.75 g (18.59 mmol) finely ground potassium fluoride dihydrate in 400 mL of 2-propanol at 25°C were added 55.8 g (743.2 mmol) nitroethane. The mixture was stirred for 48 h, dried over magnesium sulfate, filtered, and solvent evaporated under reduced pressure. 3-Hydroxy-2-nitrododecane was obtained in 85% yield as a pale yellow oil; ir (film): 3380–3600 (O—H), 1560, 1390 (NO_2) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.64 (d, 3H, NO_2—C—CH_3), 3.58 (s, 1H, C—OH, D_2O exch.), 4.00 (m, 1H, O—C—H), 4.55 (m, 1H, NO_2—C—H).

3-Acetoxy-2-nitrododecane

3-Hydroxy-2-nitrododecane (73.1 g; 315.9 mmol) was dissolved in 600 mL of anhydrous ether. To this solution was added a mixture of 47.4 g (464.3 mmol) acetic anhydride and 2.27 g (18.59 mmol) 4-dimethylaminopyridine. The mixture was stirred at 25°C for 18 h, dried over magnesium sulfate, and solvent evaporated under reduced pressure at 25°C. Note evaporation under reduced pressure at 45°C caused formation of the highly reactive nitroalkene 2-nitro-2-dodecene identified by ir (film): 1660 (C=C), 1510, 1330 (NO_2) cm^{-1} and ^{1}H nmr ($CDCl_3$) δ: 1.90–2.32 (s and m, 5H, NO_2—C—CH_3 and NO_2—C=C—CH_2), 7.08 (t, 1H, NO_2—C=C—H). 3-Acetoxy-2-nitrododecane was obtained in 85% yield as a light yellow oil; ir (film): 1750 (C=O), 1550, 1375 (NO_2) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.1 (s, 3H, O=C—CH_3), 4.71 (m, 1H, NO_2—C—H), 5.34 (m, 1H, O=C—O—C—H).

2-Nitrododecane

To an ice cooled/mechanically stirred solution of 73.4 g (268.5 mmol) 3-acetoxy-2-nitrododecane in 500 mL of absolute ethanol were added gradually ($T < 30$°C) 28.1 g (742.2 mmol) of sodium borohydride. Stirring was continued for 12 h at 25°C. Acidification was effected by dropwise addition of 10% hydrochloric acid. The mixture was extracted with pentane, dried over sodium sulfate, and solvent evaporated under reduced pressure. The crude product was triply distilled through a 1 × 15 cm Vigreux column affording 34.7 g (161.1 mol) of 2-nitrododecane as a colorless oil, bp 120°C/1.4 Torr (lit. (21) 1-isomer, 1-nitrododecane, bp 128°C/2.0 Torr); ir (film): 1580, 1365 (NO_2) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.53 (d, 3H, NO_2—C—CH_3), 4.55 (sextet, 1H, NO_2—C—H).

II. *Michael addition (4-nitroaldehydes)*

4-Methyl-4-nitroheptanal

2-Nitropentane (10.0 g; 85.4 mmol) and 0.57 mL (1.37 mmol) of Triton B (40% hydroxide in methanol) were dissolved in 75 mL of dry THF. Dropwise addition ($T < 0$°C) of 4.21 g (75.08 mmol) of freshly distilled acrolein in 25 mL of dry THF caused the initially colorless solution to turn brown-green. After stirring for 4 h at 0°C the reaction was quenched with 4.72 mL of 10% aqueous HCl. The mixture was shaken thoroughly with 300 mL of methylene chloride, washed with 3 × 100 mL of saturated NaCl, dried over sodium sulfate, filtered, and solvent evaporated under reduced pressure (25°C). The viscous brown-orange residue was immediately fractionated by distillation; 7.6 g (58% yield) of 4-methyl-4-nitroheptanal were obtained as a faint yellow oil, bp 57°C/ 0.010 Torr; ^{1}H nmr ($CDCl_3$) δ: 1.54 (s, 3H, NO_2—C—CH_3), 9.96 (s, 1H, O=C—H).

Precaution! Thermally unstable residues may form. The product must be distilled over quickly, though preferably with an oil bath temperature < 150°C. Distillation must be halted immediately when black residues appear.

4-Methyl-4-nitrodecanal

Similarly 22.90 g (143.9 mmol) of 2-nitrooctane and 0.96 mL (2.30 mmol) Triton B in 127 mL THF were reacted with 7.09 g (126.5 mmol) acrolein in 50 mL THF. 4-Methyl-4-nitrodecanal (14.71 g; 68.33 mmol) was collected as a faint yellow oil (54% yield), bp 127°C/0.060 Torr; ^{1}H nmr ($CDCl_3$) δ: 1.52 (s, 3H, NO_2—C—CH_3), 9.98 (s, 1H, O=C—H).

4-Methyl-4-nitrotetradecanal

Similarly 34.7 g (161.1 mmol) of 2-nitrododecane and 1.08 mL (2.57 mmol) of Triton B in 150 mL THF were reacted with 7.94 g (141.6 mmol) acrolein in 100 mL THF. 4-Methyl-4-nitrotetradecanal (17.93 g; 66.07 mmol) was isolated as a pale yellow oil (47% yield), bp 145°C/0.050 Torr; ^{1}H nmr ($CDCl_3$) δ: 1.53 (s, 3H, NO_2—C—CH_3), 10.00 (s, 1H, O=C—H).

Note: a heating mantle ($T > 150$°C) was required to distil the product.

III. *4-Nitroacetals*[3]

4-Methyl-4-nitroheptanal (ethylene acetal)

4-Methyl-4-nitroheptanal (7.60 g; 43.88 mmol), 3.23 g (52.04 mmol) of ethylene glycol, and 0.0938 g (0.493 mmol) of *p*-toluenesulphonic acid monohydrate were refluxed in 75 mL benzene (25°C) utilizing a Dean–Stark separator. The cooled mixture was added to 200 mL pentane, washed with 3 × 75 mL of 10% aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and solvent evaporated under reduced pressure. The residue was distilled providing 6.86 g of the nitroacetal (72% yield, 31.59 mmol), bp 90°C/0.10 Torr; ^{1}H nmr ($CDCl_3$) δ: 1.57 (s, 3H, NO_2—C—CH_3), 3.90 (m, 4H, OCH_2CH_2O), 4.85 (t, 1H, $(CH_2O)_2C$—H).

4-Methyl-4-nitrodecanal (ethylene acetal)

4-Methyl-4-nitrodecanal (14.71 g; 68.33 mmol), 5.03 g (80.88 mmol) of ethylene glycol, and 0.1460 g (0.767 mmol) of *p*-toluenesulphonic acid monohydrate were refluxed under similar conditions in 125 mL of benzene to give (70% yield) 12.40 g (47.83 mmol) of nitroacetal, bp 140°C/0.05 Torr; ^{1}H nmr ($CDCl_3$) δ: 1.56 (s, 3H, NO_2—C—CH_3), 3.87 (m, 4H, OCH_2CH_2O), 4.83 (t, 1H, $(CH_2O)_2C$—H).

4-Methyl-4-nitrotetradecanal (ethylene acetal)

Similarly, 17.93 (66.07 mmol) of 4-methyl-4-nitrotetradecanal, 4.86 g (78.30 mmol) of ethylene glycol, and 0.1412 g (0.742 mmol) *p*-toluenesulphonic acid monohydrate in 125 mL benzene gave 13.88 g (44.00 mmol) nitroacetal in 67% yield; ^{1}H nmr ($CDCl_3$) δ: 1.54 (s, 3H, NO_2—C—CH_3), 3.88 (m, 4H, OCH_2—CH_2O), 4.85 (t, 1H, $(CH_2O)_2C$—H).

IV. *1-Pyrroline*-N-*oxides and acetal*-N-*hydroxy intermediates*[3]

5-Propyl-5-methyl-1-pyrroline-N-*oxide*[4] *(PMPO) (I)*

To a mechanically stirred mixture of 7.10 g (32.67 mmol) of 4-methyl-4-nitroheptanal (ethylene acetal) and 1.86 g (34.77 mmol) ammonium chloride in 12:24 (mL) THF–H_2O were added 8.66 g (119.1 mmol) 90% zinc dust keeping $T < 5$°C. Stirring was continued for approximately 4 h at 25°C. The reduction was monitored by analysis of a 0.25 mL aliquot which was filtered, extracted (pentane), dried (Na_2SO_4), filtered, and

[3]The nitroacetals and hydroxylaminoacetals in the text have been named as ethylene acetal derivatives rather than nitrodioxolans and hydroxylaminodioxolans respectively.

[4]5-Methyl-5-propyl-1-pyrroline-*N*-oxide may strictly be the more appropriate nomenclature.

solvent evaporated under reduced pressure. 4-Methyl-4-hydroxylaminoheptanal (ethylene acetal) was detected by ^{1}H nmr ($CDCl_3$) δ: 3.87 (m, 4H, OCH_2CH_2O), 4.83 (t, 1H, $(CH_2O)_2$—C—H), 5.46 (s, 2H, C—NHOH, D_2O exch.). The mixture was vacuum filtered, the filtercake washed with 3 × 40 mL hot (50°C) THF. The filtrate was evaporated under reduced pressure (T < 30°C); 4.9 : 60 (mL) of concentrated HCl – H_2O were added and the mixture stirred for 2 h (70°C). The mixture was cooled (25°C), neutralized with $NaHCO_3$, stirred for 1 h, filtered through sintered glass, extracted with 3 × 75 mL pentane, washed with 3 × 75 mL saturated NaCl, dried (Na_2SO_4), and solvent evaporated under reduced pressure. The residue was distilled, bp 56°C/0.070 Torr. Successive elution on a silica gel column with pentane, benzene, and finally methylene chloride provided 3.0 g (21.24 mmol) of the nitrone (65% yield) as a colorless hygroscopic oil; ir (film): 1560 (C=N), 1242 (N—O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.39 (s, 3H, O—N—C—CH_3), 2.15 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 6.82 (t, 1H, O—N=C—H). The nitrone afforded a complex (1:1) with 2,4,6-trinitrophenol, mp 82°C (from absolute ethanol). *Anal.* calcd. for $C_{14}H_{18}N_4O_8$: C 45.41, H 4.90, N 15.13; found: C 45.98, H 5.00, N 14.93.

*5-Hexyl-5-methyl-1-pyrroline-*N*-oxide (HMPO) (II)*

Similarly, stirring of 12.40 g (47.83 mmol) of 4-methyl-4-nitrodecanal (ethylene acetal), 2.72 g (50.85 mmol) ammonium chloride, and 12.68 g (174.5 mmol) of 90% zinc dust gave 4-methyl-4-hydroxylaminodecanal (ethylene acetal) identified by ^{1}H nmr ($CDCl_3$) δ: 3.85 (m, 4H, OCH_2CH_2O), 4.81 (t, 1H, $(CH_2O)_2C$—H), 5.49 (s, 2H, C—NHOH, D_2O exch.). Acidification followed by distillation, bp 110°C/0.30 Torr, and silica gel chromatography (methylene chloride) provided the nitrone (57%), 5.0 g (27.26 mmol) as a pale yellow oil;[5] ir (film): 1567 (C=N), 1241 (N—O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.39 (s, 3H, O—N—C—CH_3), 2.16 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 6.76 (t, 1H, O—N=C—H).

*5-Decyl-5-methyl-1-pyrroline-*N*-oxide (DeMPO) (III)*

Similarly, reaction of 13.88 g (44.00 mmol) of 4-methyl-4-nitrotetradecanal (ethylene acetal), 2.51 (46.92 mmol) of ammonium chloride, and 11.66 g (160.4 mmol) of 90% zinc dust produced 4-methyl-4-hydroxylaminotetradecanal (ethylene acetal) detected by ^{1}H nmr ($CDCl_3$) δ: 3.88 (m, 4H, OCH_2CH_2O), 4.82 (t, 1H, $(CH_2O)_2$—C—H), 5.44 (s, 2H, C—NHOH, D_2O exch.). Acidification gave the crude nitrone which decomposed upon attempted distillation (110°C/0.05 Torr). The nitrone was purified instead by filtration through Celite and silica gel chromatography (methylene chloride). The isolated yield (53%) was 5.6 g (23.39 mmol) as a pale yellow oil.[5] ir (film): 1564 (C=N), 1244 (N—O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.38 (s, 3H, O—N—C—CH_3), 2.16 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 6.72 (t, 1H, O—N=C—H).

Electron spin resonance (kinetic esr procedure)

The esr spectra were observed with a Varian E-104 spectrometer and were calibrated by comparison with Fremy's salt (22) (a_N = 13.09 G, g = 2.0055). The quartz esr cell was equipped with two adjoining compartments to house separately the radical source and spin trap(s). This arrangement has been amply described previously (23).

Thermally generated tert-*butoxyl radicals*

Di-*tert*-butylperoxalate (DBPO) prepared by Bartlett's method (24) was freshly recrystallized (hexane, −40°C) before kinetic runs. One compartment of the esr cell arrangement was cooled by liquid N_2. Into this sidearm was placed approximately 2.5 mg of DBPO. A 2.0 mL benzene solution (25°C) containing both nitrones, typically (0.01 *M*) in RMPO and (0.30 *M*) in PBN, except M_4PO which was equimolar (0.05 *M*) with PBN, was placed into the other compartment. Deoxygenation was accomplished by purging the esr cell and sidearms simultaneously with dry N_2 gas for 5–10 min. The contents were mixed vigorously and esr spectra recorded immediately thereafter as a function of time. DBPO decomposes at 25°C in benzene according to reaction [4].

Four lines (2 independent doublets) in the middle of the 18-line spectrum due to the cyclic nitrone and PBN adducts were scanned repeatedly at 70 s intervals for 20–25 min. The specific peaks that were evaluated kinetically are depicted in the esr spectrum derived from (PBN/HMPO/DBPO) in benzene, Fig. 2.

Photochemically generated tert-*butoxyl radicals*

Di-*tert*-butylperoxide (Lucidol–Penwalt) was routinely eluted through a silica gel column to remove possible traces of hydroperoxide. Photolysis of BOOB, reaction [10], was accomplished by irradiating the quartz cell with a medium pressure Hg arc equipped with a Pyrex filter.

A 0.20 *M* solution of cyclic spin trap in di-*tert*-butylperoxide scavenged the BO· radicals thus formed. The second doublet in the 12-line pattern was scanned repeatedly at 70 s intervals for 25–30 min. It was important that all decay rates be obtained under as similar experimental conditions as possible since these were direct kinetic measurements. This involved utilization of identical reaction temperatures, esr spectrometer settings, esr cells, and uv lamp intensities for every experiment.

Spin adduct concentrations

Concentrations (or ratios of concentrations) of spin adducts were determined by double integration of nonoverlapping lines (of known degeneracy) in the esr spectra. Area units were calibrated by the use of the stable aminoxyl spin label, 2,2,5,5-tetramethyl-3-carbamidopyrrolidine-1-oxyl (Aldrich). The general procedure has been described elsewhere (9*c*).

[5]Alicyclic nitrones are typically thermally labile hygroscopic oils. Elemental analysis is thus usually restricted to their solid derivatives (13). Unfortunately, HMPO and DeMPO did not form crystalline 2,4,6-trinitrophenol complexes or methiodides; ir, ^{1}H nmr, and tlc (silica gel – acetone, HMPO (R_f 0.6); DeMPO (R_f 0.5)) indicated the nitrones' purity at 99+%.

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1. E. G. Janzen; P. B. McCay, T. Noguchi, K. L. Fong, E. K. Lai, and J. L. Pryor. *In* Free radicals in biology. Vol. IV. Academic Press, New York. *Edited by* W. A. Pryor. 1980. Chapts. 4; and 5, respectively.
2. M. J. Perkins. Advances in physical organic chemistry. Vol. 17. 1980. p. 1.
3. (*a*) M. Iwamura and N. Inamoto. Bull. Chem. Soc. Jpn. **40**, 703 (1967); (*b*) Bull. Chem. Soc. Jpn. **43**, 860 (1970); (*c*) E. G. Janzen and J. I.-P. Liu. J. Magn. Reson. **9**, 510 (1973); (*d*) E. G. Janzen, C. A. Evans, and J. I.-P. Liu. J. Magn. Reson. **9**, 513 (1973); (*e*) E. G. Janzen, R. V. Shetty, and S. M. Kunanek. Can. J. Chem. **59**, 756 (1981).
4. (*a*) J. R. Harbour, V. Chow, and J. R. Bolton. Can. J. Chem. **52**, 3549 (1974); (*b*) E. G. Janzen, D. E. Nutter, E. R. Davis, R. J. Blackburn, J. Lee Poyer, and P. B. McCay. Can. J. Chem. **56**, 2237 (1978); (*c*) P. R. Marriott, M. J. Perkins, and D. Griller. Can. J. Chem. **58**, 803 (1980).
5. J. R. Harbour and L. M. Hair. J. Phys. Chem. **82**, 1397

(1978); E. FINKELSTEIN, G. M. ROSEN, and E. J. RAUCKMAN. J. Am. Chem. Soc. **102**, 4994 (1980).
6. E. G. JANZEN, R. L. DUDLEY, and R. V. SHETTY. J. Am. Chem. Soc. **101**, 243 (1979).
7. E. G. JANZEN, Y. Y. WANG, and R. V. SHETTY. J. Am. Chem. Soc. **100**, 2923 (1978); E. G. JANZEN and R. C. ZAWALSKI. J. Org. Chem. **43**, 1900 (1978); E. G. JANZEN and R. V. SHETTY. Tetrahedron Lett. 3229 (1979).
8. H. KAUR, K. H. W. LEUNG, and M. J. PERKINS. Chem. Commun. 142 (1981).
9. (*a*) L. LUNAZZI, G. PLACUCCI, M. TIECO, and G. ARTELLI. J. Chem. Soc. Perkin Trans. II, 2215 (1972); (*b*) E. G. JANZEN and C. A. EVANS. J. Am. Chem. Soc. **95**, 8205 (1973); (*c*) E. G. JANZEN, C. A. EVANS, and Y. NISHI. J. Am. Chem. Soc. **94**, 8236 (1972).
10. (*a*) Y. MAEDA and K. U. INGOLD. J. Am. Chem. Soc. **101**, 4975 (1979); (*b*) P. R. MARRIOT and K. U. INGOLD. J. Phys. Chem. **84**, 937 (1980); (*c*) K. U. INGOLD. *In* Free radicals. Vol. 1. *Edited by* J. K. Kochi. John Wiley & Sons, New York. 1973. p. 38.
11. Y. KOTAKE, K. KUWATA, and E. G. JANZEN. J. Phys. Chem. **83**, 3024 (1979).
12. (*a*) C. WALLING and P. J. WAGNER. J. Am. Chem. Soc. **86**, 3368 (1964); (*b*) C. WALLING and V. P. KURKOV. J. Am. Chem. Soc. **89**, 4895 (1967); D. J. CARLSSON and K. U. INGOLD. J. Am. Chem. Soc. **89**, 4885 (1967).
13. R. BONNETT, R. F. C. BROWN, V. M. CLARK, I. O. SUTHERLAND, and A. TODD. J. Chem. Soc. 2094 (1959).
14. E. J. COREY and H. ESTREICHER. Tetrahedron Lett. 117 (1981).
15. D. C. IFFLAND and C. X. CRINER. J. Am. Chem. Soc. **75**, 4083 (1953).
16. R. H. WOLLENBURG and S. J. MILLER. Tetrahedron Lett. 3219 (1978).
17. E. W. BOUSQUET. Org. Synth. Coll. Vol. **II**, 313 (1943).
18. G. D. BUCKLEY and E. ELLERY. J. Chem. Soc. 1497 (1947).
19. J. CASON and J. S. CORREIRA. J. Org. Chem. **26**, 3645 (1961).
20. K. KORNBLUM, H. O. LARSON, R. K. BLACKWOOD, D. D. MOOBERRY, E. P. OLIVETO, and G. E. GRAHAM. J. Am. Chem. Soc. **78**, 1497 (1956).
21. C. KIMURA, K. KASHIWAYA, and T. ASAHARA. Chemical Abstr. **53**, 1849 (1959).
22. R. J. FABER and G. K. FRAENKEL. J. Chem. Phys. **47**, 2462 (1967).
23. G. A. RUSSELL, E. G. JANZEN, and E. T. STROM. J. Am. Chem. Soc. **86**, 1807 (1964).
24. P. D. BARTLETT, E. P. BENZING, and R. E. PINCOCK. J. Am. Chem. Soc. **82**, 1762 (1960).