Kinetic Applications of Radical-Trapping by a Stable Nitroxide

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by

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DECLARATION

The work described in this thesis is original and has not been submitted for a degree or diploma in any other University or College and, to the best of my knowledge, does not contain material previously published or presented by another person, except where due reference is made in the text.

Vincent W. Bowry
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CONTENTS

Declaration i
Acknowledgements ii
Abstract vi

CHAPTER 1

Stable Nitroxides as Free Radical Traps
1.1 Synthesis 2
1.2 ESR Spin Trapping 3
1.3 Electronic Structure and UV Spectra of Nitroxides 3
1.4 Why are Stable Nitroxides Stable? 5
1.5 Charge Transfer Reactions 8
1.6 The Structure of Nitroxides 9
1.7 Structure of the Trapped Products 10
1.8 Structure and Scavenging Efficiency 11
1.9 Photochemistry 12
1.10 Nitroxides as Radical Reaction Probes 14
1.11 The Radical-Trapping Rate Constant $k_T$ 16
1.12 Miscellaneous Reactions 18
1.13 Conclusions 20

CHAPTER 2

Radical Clock Calibrations of $k_T$ 21

CHAPTER 3

Rearrangements of Ring Substituted Cyclopropylmethyl Radicals 49

CHAPTER 4

Alkoxycarbonyl Fragmentations and Rearrangements of $\alpha$-Substituted Cyclopropylcarbinyl Radicals 65

CHAPTER 5

Alkyl Radical Rearrangements 85
$\omega$-Alkenyl Ring-Closures:
(I) Some 5-Hexenyl Cyclizations 86
(II) 6-Methylene cyclodecyl Radical 94
(III) Two Cyclobutylmethyl Ring-Openings 97
(IV) 1,1-Dideuterio-2-(9-anthracene)-ethyl Radical 100
CHAPTER 6

Solvent Effects
(I) The Effect of Solvents upon the Relative Trapping Rate and Product Stabilities 113
(II) A Kinetic Model for Radical-Trapping and More About Solvent Effects 123

CHAPTER 7

Aryl and Cyclopropyl Radical Rearrangements:
(I) Aryl Radicals: Investigations of a Precursors and Ring-Closure of \( o-(\text{But-3-enyl}) \)phenyl Radical 130
(II) Ring-Closures of \( \varepsilon \)-Alkenyl-cyclopropyl and an \( \varepsilon \)-Alkenyl-cyclobutyl Radicals 139

CHAPTER 8

Calibration of Bimolecular Reactions:
(I) The Direct Method; Phenyl, Cyclopropyl and Alkyl radicals with \( \text{CCl}_4 \) & etc. 150
(II) The Clock-Trap Method Applied to Metathesis, Radical Addition and Radical Coupling Reactions

APPENDIX

Approximations and Kinetic Equations A1

Supplementary Material

REFERENCES AND NOTES R1
ABSTRACT

The stable nitroxyl radical 1,1,3,3-tetramethylisoindin-2-oxyl (T) undergoes very rapid coupling with alkyl, cyclopropyl or aryl radicals (R·) to afford stable hydroxylamine products (R-T); this reaction and its application has been termed radical-trapping. In many cases, species R-T may readily be resolved and quantitated and thus the reaction may be used as a probe for radical reactions. Solomon and his co-workers successfully applied the radical-trapping reaction to elucidate the first steps of several free radical polymerizations of practical and theoretical importance. However, the use of radical trapping as kinetic probe has hitherto been hampered by the lack of reliable estimates of the coupling rate constant $k_T$ (cf. Ch 1.11).

In Chapter 2, the radical clock technique is used to calibrate the $k_T$ for a variety of radical types; i.e. direct competition between the rearrangements of suitable primary (1, 2, 3, 4, and 5), neopentyl (6 and 7), secondary (8), and tertiary (9) alkyl radicals and radical-trapping of these species by T afforded the respective relative trapping rate constants, $k_T/k_C$, and since for radical clocks the rearrangement rate constants, $k_C$, were known, this afforded estimates for the various $k_T$. Fragmentations of acyl (11) and of alkoxy carbonyl (12 and 13) radicals were also used as radical clocks. Data from the radical clock method agreed with those from a concurrent laser flash photolysis investigation and suggest that the rate constant for radical-trapping of unhindered alkyl radicals is about $1.0 \times 10^9$ M$^{-1}$s$^{-1}$ regardless of the fine details of radical structure and of temperature.

In this work, a number of radical rearrangements are investigated through kinetic competition with the radical-trapping reaction. Because of its high rate constant, the latter is particularly well suited for the investigation of very rapid radical reactions (i.e. $k_T > 10^7$ s$^{-1}$). Investigation of the kinetics for the rapid ring-opening reactions of some ring- and $\alpha$-substituted cyclopropylcarbinyl radicals are reported in Chapters 3 and 4 respectively; where these rearrangements were reversible, rate constants for both the forward and reverse reactions could be ascertained (see, e.g., 4h in Ch 4). Investigations of various alkyl radical rearrangements are reported and discussed in Chapter 5; e.g. ring-closure of 5-hexenyl type radicals 16, 17 and 18 are calibrated and compared with similar reactions treated in the radical clock section (Ch 2), the extremely rapid transannular radical addition reaction of 6-methylene cyclodecyl (19), and a mechanistically puzzling neophile type rearrangement of the $\beta$-(9-anthryl)-ethyl radical 21. The effects of salvation on radical-trapping are defined and discussed in terms of a kinetic model which is proposed for the reaction; it appears that the radical-trapping reaction is not diffusion-controlled under ordinary experimental conditions. Radical-trapping calibrations of an aryl and of cyclopropyl radicals are reported in Chapter 7. In the final chapter, the application of radical-trapping to the calibration of bimolecular, i.e. radical/molecule, reactions is described.
CHAPTER ONE

Stable Nitroxides as Free Radical Traps

The stable nitroxides are organic free radicals which are 'stable' in the sense that they can be stored, weighed, and even chemically modified in some cases, without losing their free radical character. The unpaired electron ('spin') of nitroxides allows their orientation, concentration, and movements to be measured by ESR as well as NMR spectroscopy and has led to the development of a large array of spin probes and spin labels for use in studies of biophysics, diffusion motion, and of Magnetic Resonance Imaging (MRI).

In free radical chemistry, nitroxides can be used as radical traps or scavengers for the investigation of reactions with putative free radical intermediates. The term 'spin trapping' is appropriate for this procedure but to avoid confusion with 'ESR spin trapping' (vide infra), the scavenging of radicals (R·) by nitroxides (T) to produce trisubstituted hydroxylamines or, more correctly, alkoxyamines (R-T) will be referred to as 'radical-trapping by stable nitroxides' or simply 'radical-trapping'.

\[
\text{T} + \text{R·} \underset{k_T}{\rightarrow} \text{R-T}
\]

1,1,3,3-Tetramethylisoindolin-2-yloxyl, T, the nitroxide used almost exclusively in the present work, is one of a number of stable organic radicals that may be employed as radical traps; Fig I lists some other examples together with their common acronyms. The literature of radical scavenging by stable organic free radicals has recently been reviewed by Rozantsev and thus does not need to be reiterated here; rather in this chapter I shall attempt to list and speculate upon the properties and known reactions of stable dialkyl nitroxides that are relevant to the radical-trapping method exploited in later chapters.
Figure I. Stable Organic Free Radicals.

**Piperidine Series.**

1. 2,2,6,6-Tetramethylpiperid-1-yloxyl (TEMPO)

2. (TEMPO) $X = \text{OH} \ (4\text{-Hydroxy-TEMPO})$

3. $X = \text{PhCO}_2 \ (4\text{-Benzoyloxy-TEMPO})$

**Pyrrolidine Series ('proxyls')**

4. 2,2,5,5-Tetramethylpyrrolidin-1-yloxyl

5. $X = \text{OH}$

6. $X = \text{CO}_2\text{H}$

**Isoindoline Series**

7. 1,1,3,3-Tetramethylisoindolin-2-yloxyl

8. Di-11metylnitroxide (DBNO)

9. Diphenylnitroxide

10. Diphenylpicrylhydrazyl (DPPH)

11. X = NO$_2$

12. X = NH$_2$

13. X = picryl-NH

14. 'Galvinoxyl'
Chapter One: Background to Radical-Trapping

1.1 Synthesis

General methods for the preparation of the common di-tert-alkyl type nitroxides i.e. the proxyl, doxyl, TEMPO, and isoindoline series (Fig. I), have been reviewed by Rozantsev and Sholle (1971) and their preparation, properties, and applications have been thoroughly reviewed from a biological chemist's perspective by Keana (1978).

The method most often employed for the preparation of nitroxides is the oxidation of secondary amines. Oxidants commonly used are peracids (e.g. meta-chloro-perbenzoic acid - MCPBA), MnO₂, and, with increasing popularity, a solution of sodium tungstate in H₂O/H₂O₂/CH₃CN. The latter oxidizes 1,1,3,3-tetramethylisoindoline to the N-oxyl radical T in greater than 95% yield; the full scheme employed for the preparation of T is shown below.

Nitroxides with a variety of spectral and physical properties can be readily made by acylation of 4-hydroxy-TEMPO (3). For example, benzoylation yields 4-benzoyloxy-TEMPO (4). As explained in later sections it is of great advantage to have a UV chromophore incorporated into the nitroxide radical trap and for this reason 4 would be a possible alternative to the nitroxide used in this work (T).
1.2 ESR Spin Trapping

Another way in which nitroxides are formed is by radical (R·) addition to a nitroso compound (e.g. 18). The nitroxides so formed have much longer lifetimes than the species being 'trapped' and thus the reaction effectively accumulates the 'spin' of the reactive radicals and makes it more readily detectable by ESR. The identity of R· can often be established by the hyperfine splitting pattern (caused by spin delocalization onto the R group) in the ESR spectrum of the resultant nitroxide(s)\textsuperscript{11a-c}.

\[ t-\text{Bu} - \text{N}=\text{O} + R \cdot \rightarrow k_N \rightarrow \text{N}=\text{O} \cdot R \]

\[ 18 \text{ (Nt-B)} \]

\[ KN \]

\[ 2k_D \]

Nitrones R\textsubscript{2}C=\text{N(O)R} trap radicals, though by addition to the vinylic carbon and again nitroxides are formed.

Rate constants (\(k_N\), \(k_D\), and \(k_T\) in the example above) for primary alkyl radicals have been measured by Schmid and Ingold\textsuperscript{11a} by kinetic ESR techniques for a variety of spin-traps (Ch 1.11 and Ch 2.1).

1.3 Electronic Structure And UV Spectra of Nitroxides

ESR measurements\textsuperscript{12} and MO calculations\textsuperscript{13} indicate that the spin density in dialkyl nitroxides is almost equally divided between the nitrogen and oxygen centres. In the valence bond (VB) representation (Fig. II) this implies equal contributions from each of the two main canonical forms.

\[ \text{R}_1 \text{N} - \text{O} \quad \text{R}_2 \text{N} - \text{O} \]

\[ \text{R}_1 \text{N} - \text{O} \quad \text{R}_2 \text{N} - \text{O} \]

It is the dipolar form which gives rise to hyperfine coupling to nuclei in the R groups.
and as might be expected the coupling has been shown to increase with solvent polarity,\textsuperscript{14} i.e. the spin density is shifted to \( N \) by strong solvation.

In the molecular orbital (MO) description of the \( N-O^* \) bond, the bond may be envisaged as arising from the interaction of a \( N^* \) fragment with an oxygen atom (see Fig III). A \( \sigma \)-bond is formed by overlap of a full \( sp^2 \) orbital of \( N \) with a vacant \( \pi \)-orbital (say, \( p_x \)) of \( O \). The unpaired electron is initially in a \( p_z \) orbital of \( N \), which interacts with a full \( p_z \) orbital of \( O \), giving rise to a doubly occupied \( \pi \)-orbital and a singly occupied \( \pi^* \)-orbital.

**Figure III.** MO Description of Bonding in a Nitroxide

The approximately equal distribution of spin between the \( O \) and \( N \) centres implies formal charges of \(+1/2\) e on \( N \) and \(-1/2\) e on \( O \). With a typical bond length of 1.25\( \text{Å} \)\textsuperscript{15} one can calculate that the dipole moment of a nitroxide bond is 1.6 \times 10^{-19} \text{C} \times 0.62 \times 10^{-10} \text{m} = 1.0 \times 10^{-30} \text{mC} = 3.0 \text{Debye} \) (the measured value for TEMPO is 3.1 D\textsuperscript{16a}); thus the nitroxides have a polarity similar to that of ketones (e.g. acetone, 2.9D). Since the dipole moment of the \( NO \) bond is (approximately\textsuperscript{16b}) proportional to the spin density on \( N \), one might expect that solvation of the nitroxy1 group would be indicated by the nitrogen hyperfine coupling constant in the nitroxide. In view of this, it may be significant that it is the electron acceptor ability of solvents (as gauged by the acceptor number \( A_N \)) that correlates closely with the HFC for a wide range of solvents\textsuperscript{11} – the implication being that nitroxides are nucleophilic species.

UV absorption of the nitroxide chromophore arises from a weak "quasi-forbidden"\textsuperscript{17} \( n \rightarrow \pi^* \) transition at 400 - 480nm (Absorptivity, \( A = 2 - 10 \)) and strong \( \pi^* \rightarrow \sigma^* \) and \( \pi \rightarrow \pi^* \)
transitions at 215 - 250nm ($\lambda = 500 - 1000$). The yellow to red colour of dialkyl nitroxides is
due to absorption by the weak forbidden transition and the broad tail of the dipole allowed
transition(s) which sweeps out to about 350nm before merging with the weaker transition. The
fact that solutions of $T$, for instance, are more intensely coloured in polar solvents probably
reflects the mixing of states caused by solvation.

In the products of radical-trapping, viz.the hydroxylamines $R-T$, the near-UV
transitions do not exist; the compounds are normally colourless and exhibit no characteristic
UV absorptions useful for their chromatographic analysis, unless an aromatic chromophore
(for instance) has been incorporated into the trap.

1.4 Why Are Stable Nitroxides Stable?

It has been established that the stable nitroxides do not measurably dimerize by $O-O$
bond formation\textsuperscript{1,18} in the solid state or in solution. In the latter case this is easily shown by the
strict adherence of their UV absorption to Beer's Law over a wide range of nitroxide concen-
trations\textsuperscript{19} and in the solid state it can be shown by X-ray crystallography. This is not
surprising since thermochemical calculations suggest that formation of the $O-O$ bond would be
endothermic by as much as 28 kcal/mol\textsuperscript{19,23} which implies an energy barrier probably greater
than 30 kcal/mol or a rate constant less than $10^{-14}$ s\textsuperscript{-1} (!) for $O-O$ dimerization. When
nitroxides do dimerize it is indicated to occur via a four centred interaction (by analogy with
Fremy's Salt).\textsuperscript{18}

\[ \text{When the nitroxide contains an $\alpha$-C-H bond (e.g. the nitroxides usually formed by}
\text{ESR spin trapping) the dimer can disproportionate giving a nitrone and the reduced nitroxide –}
\text{the kinetics of this process have been investigated by Ingold and his co-workers\textsuperscript{11,18} for several}
\text{nitroxides.} \]
Interestingly when formation of the $N=C$ double bond violates Bredt's Rule even nitroxides with alpha hydrogens can be stable, e.g. 20 is indefinitely stable in the solid state.\(^{20}\)

\[ \text{A 'Bredt Rule Protected' Nitroxide} \]

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{H}
\end{align*}
\]

In di-\text{-}\text{tert}-alkyl nitroxides: (a) the dimerization is more sterically hindered, and (b) there are no readily abstractable hydrogen atoms. However when the $\beta$-C–H group is activated by an electron withdrawing group, a hydrogen transfer reaction may still occur, e.g. when 4-TEMPONE is heated a nitrone (which further decomposes) and an alkoxyamine are formed\(^ {21}\); the proposed\(^ {22}\) initial step is represented below:

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{H} & \quad \text{H}
\end{align*}
\]

The mechanism above indicates electron transfer, possibly occurring within a short lived dimeric form, followed by a conventional acid/base reaction between charged species as the hydrogen transfer step. However, available evidence does not rule out an intermolecular hydrogen atom transfer, i.e. a radical process; a study of solvent effects would probably resolve this point.

Typical nitroxides not only refuse to self-react but they also exhibit remarkable inertness in aliphatic and olefinic solvents and can even be retrieved unaffected from radical-reactive solvents such as acrylic esters and acrylonitriles\(^ {7}\). The reason for their kinetic stability towards even-electron species is no doubt due in the major part to the high delocalization energy in the NO bond which has been thermochemically estimated as 30.4\(^ {23}\) to
Chapter One: Background to Radical-Trapping

32\(^{19b}\) kcal/mol for TEMPO but 4-5 kcal/mol lower for the Bredt Rule nitroxides\(^{19b}\) (e.g. 20). A resonance energy \(E_{\text{res}} = \epsilon\) in Fig. III) of this magnitude makes hydrogen atom abstraction and most radical addition reactions substantially endothermic. For example, based on bond dissociation energies \(D(R-X)\), we can calculate the enthalpy of reaction for a typical hydrogen atom transfer to a nitroxide thus:

\[
R-H + R_2N-O^* \rightarrow R^* + R_2N-O-H + \Delta H^o
\]

\[
\Delta H^o = D(R-H) - D(R_2N-O-H) = D(R-H) - [D(R'O-H) - E_{\text{res}}]
\]

\[
= 95 - (105 - 30) = +20 \text{ kcal/mol (for R-H = cyclohexane).}
\]

(Where \(D(R'O-H)\) is the bond dissociation energy of an ordinary alcohol).

Furthermore, if one assumes an activation energy of about 3 kcal/mol for the reverse reaction and a 'normal bimolecular preexponential'\(^{24}\) of \(10^9\) s\(^{-1}\) for the forward reaction the half-life of a nitroxide in cyclohexane should be 80 to 200 hr at 80°C or 1 to 2 hr at 120°C. The fact that \(T\) is stable in cyclohexane at 120°C for over 24 hours (cf. Ch 2) and that it does not react rapidly at ordinary temperatures with olefins which have weaker allylic C-H bonds, suggests that perhaps other factors contribute to the di-tert-nitroxides' kinetic stability, i.e. non-bonded interactions of the bulky 'protective' groups (e.g. the four methyl groups in \(T\), &etc.).

Unlike compounds with allylic C-H bonds [\(D(C-H) = 80-85\) kcal/mol], substrates with substantially weaker bonds to hydrogen, such as mercaptans and stannanes (cf. Ch 7), reduce nitroxides at normal temperatures, as do reducing agents such as hydrazines, \(\text{H}_2/Pd\), and ascorbic acid and biological reductases.\(^{26}\) On the other hand, the hydride type reducing agents LiAlH\(_4\), BH\(_3/\text{SMe}_2\), and NaBH\(_3\)CN apparently do not readily reduce the nitroxyln function; this has been used to advantage in synthesis,\(^{26}\) e.g.\(^{27}\)

\[
\begin{align*}
\text{LiAlH}_4, \text{BH}_3/\text{SMe}_2, \text{and NaBH}_3\text{CN} & \text{ apparently do not readily reduce the nitroxyln function;} \\
\text{this has been used to advantage in synthesis,} & \text{e.g.}\end{align*}
\]

However, one suspects that even if the nitroxide had been reduced it may not have
been detected because of rapid air oxidation of the reduced species (vide supra) i.e.,

$$2R_2NOH + O_2 \rightarrow 2R_2NO^* + 2H_2O_2.$$  

1.5 Charge Transfer Reactions

Although remarkably inert to most even-electron substrates, nitroxides do react with common alkyl and acyl halides at low to moderate rates. With very reactive halides the reaction can be rapid; for instance, triphenylmethyl bromide reacts violently with DBNO (14) at room temperature while benzyl and allyl bromides are affected only when heated in the neat reagent. The products are the oxammonium halide (e.g. 25) and the corresponding N,N,N-alkoxy-tert-butyl-amines. Acyl chlorides react similarly to afford 25 and an N-acyloxy-amine (24).

\[
\begin{align*}
R-CN & \rightarrow R-CN + R-X \\
\text{24} & \quad \text{25}
\end{align*}
\]

The above reactions are thought to proceed by the so called 'homosolvolysis' mechanism. This mechanism has not been thoroughly studied but a charge-transfer reaction is suggested with the general pathway shown below.

\[
\begin{align*}
\text{Homosolvolysis} \\
\begin{array}{c}
R-N^*O \\
R' \quad (T)
\end{array} & \quad + \quad \begin{array}{c}
R-X \\
\text{25}
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
\text{26} \\
\text{27}
\end{array} \\
\begin{array}{c}
R-N^*O \\
R \quad \text{Cl}^-
\end{array} & \quad + \quad \begin{array}{c}
R^* \\
T
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
R-T \\
\text{28}
\end{array}
\end{align*}
\]

Other examples of this type of reaction are the dediazoniation of diazonium salts (see Ch 7) and nitroxide induced decomposition of diacyl peroxides (cf. Ch 3). In both instances the nitroxide probably acts as an electron source (one electron reductant) in the first step, for example reaction of T with phenyldiazonium tetrafluoroborate might proceed as illustrated below.
Dediation with a Nitroxide

\[
\begin{align*}
\text{T}^+ & \quad \text{BF}_4^- \\
\implies & \\
\text{R} & \quad \text{T}^+ \quad \text{BF}_4^- \\
& + \quad \text{N}_2
\end{align*}
\]

The oxammonium salts produced in these reactions, e.g. 25, are very labile and are seldom isolated pure\(^{28}\) (those of T appear to be more stable than others - see Ch 7). Oxammonium salts are strong oxidizing agents, e.g. they can selectively\(^{29,30}\) convert alcohols to aldehydes or ketones and they produce hydrogen peroxide with water (pH>7).\(^{31}\) In inert solvents they disproportionate to nitroso compounds and the acid (H-X) at a rate which apparently depends on the basicity of the counter ion, X\(^-\); the rate is low or negligible if X is a halide but where it is a carboxylate group, the (postulated) salt decomposes too rapidly to be isolated.\(^{32}\) A reaction mechanism involving deprotonation of the nitoxide as its cation has been suggested\(^{32}\): for T:

\[
\begin{align*}
\text{H} \quad \text{O} & \\
\text{O} & \quad \text{C-R} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \quad \text{RCO}_2\text{H}
\end{align*}
\]

This reaction and subsequent reactions of the nitroso compound 26, i.e. radical addition to produce (unstable) nitroxides 27, etc. (Sect 1.2), are probably the main sources of by-products in reactions of diacyl peroxides in the presence of T (see Ch.2 and 3).
1.6 The Structure of Nitroxides

Some members of the pyrrolidinoxyl and TEMPO series and T have been structurally analysed by X-ray crystallography. Features relevant to the reactivity of the nitroxyl function (illustrated in Fig. IV) are:

(a) the 5-membered ring nitroxides 7 and T are flat both about the N-centre and throughout the ring, whereas those of the TEMPO series are distinctly pyramidal at the nitroxide centre with an out of plain angle of 16°;

(b) the CNC angles in the 5-membered ring nitroxides 5 and T are smaller than in piperidinoxyl by 11° and 10° respectively;

(c) the N-O bond lengths in 7 and T are significantly shorter at 1.26Å and 1.24Å than in TEMPO series nitroxide 4 (1.29Å).

Figure IV. Schematic Nitroxide and Product Structures

Features (a), (b) and (c) indicate a more favorable geometry for the N-O π-bond in the 5-membered ring species. A consequence of this might be the high lability of reduced 5-membered ring nitroxides compared with the 6-membered species. For example, reduced TEMPO (TEMPO–H) can be isolated in air whereas T–H is immediately oxidized back to the radical and it has also been demonstrated that proxyl nitroxides, e.g. 5–H, are more readily reduced by ascorbic acid than the piperidinoxyls (in water). Weaker O-H bonding in the 5-membered species would imply a greater resonance energy in the parent radical especially since steric factors in the reduced species would indicate the opposite reactivity trend. It has been suggested that this hypothesis can readily be tested by ESR calibration of the equilibrium established between, say, reduced TEMPO and T, i.e. in reactions such as, T + TEMPO-H ↔ T-H + TEMPO.
Chapter One: Background to Radical-Trapping

The planar nitroxides have full $D_{2h}$ symmetry and thus the ‘visible’ transition $n \to \pi^*$ is more strictly electric dipole forbidden than in the ‘puckered’ 6-membered nitroxides and this is reflected by extinction coefficients for this transition [i.e. $(\lambda_{\text{max}}, \varepsilon_{\text{max}}) = (417\text{nm}, 4)$ for T versus $(460\text{nm}, 16)$ for TEMPO].

1.7 Structure of the Trapped Products

An X-ray crystallographic structure of T-R [R = 5(N-vinylpyrrolidin-2-one)$^{15}$ in Fig. IV] reveals a normal (paraffinic ether$^{25}$) C-O bond length of 1.43Å and a just slightly wider than usual $N-O-C$ angle of 112°. In contrast to T itself, the structure has a distinctly pyramidal nitrogen centre and a puckered ring similar to normal isoindoline compounds. No X-ray data are available for N-alkoxypiperidines but examination of space filling models makes it clear that they suffer larger nonbonded interactions than the corresponding N-alkoxyisoindolines; this is reflected by lower dissociation temperatures for the former species$^{38}$ despite the lower nitroxide resonance proposed above (see next Sect. and Ch. 7).

At first sight it seems curious that bond lengths and angles in T-R are normal despite the fact that the C-O bond must be some 30 kcal/mol weaker than usual. However, it is unlikely that force constants, etc. for the bond would be affected by resonance in the incipient nitrooxyl radical until substantial bond fission had taken place. - for this reason bond lengths and IR data are not very reliable guides to bond strengths in general.

1.8 Structure and Scavenging Efficiency

Of premier importance in this work are the effects of nitroxide structure on reactions with other radicals i.e. radical-trapping. Like other radical-radical reactions, the trapping reaction suffers only a very small energy barrier (≤1.5 kcal/mol) and is highly exothermic ($\Delta H^o = D(\text{NO-C}) = 30-35$ kcal/mol vide supra). The transition state for the coupling reaction must therefore occur very early along the reaction coordinate (by the Hammond Postulate) and small differences in the delocalization energy of the nitroxide or of the transient radical species are unlikely to have an appreciable effect on the coupling rate constant.
Chapter One: Background to Radical-Trapping

Schematic Reaction Profile and Transition State for Radical-trapping by $T$

[Coupling may only occur in the singlet ground state ($^1S$) configuration]

![Diagram of reaction profile and transition state]

An early transition state means that coupling rates are likely to have a greater dependence on face-strain or $F$-strain\(^{39}\) than on bond strengths. This is known to be the case for other extremely exothermic bimolecular reactions; e.g. radical addition to activated double bonds ($\Delta H^o = -30$ to $-35$ kcal/mol) have been shown to be controlled by a combination of steric, polar, and frontier orbital overlap factors\(^{40}\) rather than by product stabilities.

Published X-ray data allows one to compare the steric or spacial requirements for radical coupling for the various nitroxides. For example, in the piperidinoxyl 3 the oxygen to methyl carbon distances can be calculated from X-ray fractional coordinates\(^{33}\) to be 3.06Å and 2.87Å for the axial and equatorial pairs of methyl groups respectively. The analogous distance in $T$ is 3.03Å\(^{15}\) which indicates a small reduction of the overall steric protection of the oxygen centre; the difference is somewhat larger for the O to closest methyl H distance (by ca. 0.1Å by trigonometry). Replacement of the three ring methylene groups by the flat o-phenylene group may also make the nitroxyl function somewhat more accessible to radicals. A less crowded reactive site in $T$ is evidenced by direct calibrations of the trapping rate constants which show that $T$ traps tertiary alkyl, and benzyl radicals 10-15% faster than TEMPO\(^{41}\) (Sect 1.11).

The rate at which the products dissociate should be much more sensitive than the rate of coupling to the effects of strain in the alkoxyamine product species and resonance in the
radical species. This is because, like other bond dissociation reactions, the rate will be
determined almost entirely by the relative thermodynamic stabilities of the products and
reactants; that is, factors which affect the energy of reaction ($\Delta G^\circ$) will affect the dissociation
rate constants by the corresponding amount, viz. $\Delta G^\circ = \Delta G^\dagger = \text{Const} - RT \log k_T$. The degree
of resonance stabilization of the nitroxide (vide supra) is important in this reaction as is any
resonance energy in the transient radical. In addition, because the product species tend to be
quite sterically crowded about the coupling site, non-bonding interactions between the trap's
methyl groups and the R group may also be important.

The effect of strain in product dissociation is exemplified by the observation that
methacrylic ester adduct radicals (see Sect 1.10) form stable products with T (up to 60°C) but
less stable ones with TEMPO and those formed with the tetraethyl-isoindolinoxyI.s, e.g. 11–
13, are unstable even at room temperature. It would be of interest in this respect to ascertain
the product stabilities and trapping rates for the relatively 'open-faced' Bredt Rule nitroxides.

1.9 Photochemistry

In solution most nitroxides react slowly under UV irradiation to give products
apparently derived from hydrogen atom abstraction of the solvent by photo-excited nitroxyI
radicals. For example, 3 in toluene gives the reduced nitroxide and trapped benzyl radical.

$$\text{2} \quad \text{PhCH}_3 \text{OH} \quad \begin{array}{c} \text{318nm} \end{array} \quad \begin{array}{c} \text{H} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{OH} \\
\text{OH} \end{array} \quad + \quad \begin{array}{c} \text{Ph} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{OH} \\
\text{OH} \end{array}$$

By analogy with the reactions of triplet ketones, it is thought that UV excitation of
the $N\text{-}O \pi$-bond leads to excited doublets. For instance, $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ transitions of the
nitroxyI bond leave low lying and hence highly reactive radical orbitals (SOMOs) which may
possess similar or greater reactivity than alkoxy radicals; it is well known that these can rapidly
attack most $C\text{-}H$ bonds. Nelson, Chou, and Spencer have attempted to use this type of
reaction to perform the remote functionalization of a steroid via the appropriate 'doxyl'
derivative; their success was probably limited by an extremely rapid 'reverse' reaction i.e.
\[ R_2\text{NO-H} + R^* \rightarrow R-H + R_2\text{NO}^*. \]

In trial reactions T gave analogous product mixtures, e.g. irradiation of a degassed solution of T in cyclohexane with a 450W Hg vapour lamp through pyrex gave the trapped cyclohexyl radical in 20% yield (by HPLC) after 8 hr. Unfortunately this reaction and a somewhat slower photo-induced decay of the alkoxyisoindolines R-T precluded the use of acyl peroxide photolysis of as a low temperature source of alkyl radicals for kinetic studies.47

1.10 Nitroxides As Radical Reaction Probes

Historically odd-electron traps have often been included in mechanistic studies of reactions with putative radical intermediates, but usually only their capacity to remove radicals from reaction mixtures has been utilized.7 For instance, an effective radical scavenger such as galvinoxyl (15) can be added to a reaction mixture to prevent radical processes such as radical induced diacyl peroxide decay, polymerizations, & etc.47 However, the products of radical coupling with galvinoxyl, verdazyls, and picrazyls (e.g. 14) are usually labile and/or otherwise unsuitable for resolution and analysis so that they can not be readily employed to trap radicals in an identifiable form.

In contrast, nitroxides combine with all but highly stabilized carbon-centred radicals yielding alkoxyamines that are stable at normal temperatures and in most solvents.42,48,49

The earliest example of a quantitative product study with a nitroxide radical trap is Robbins and Eastman's examination50 of the photolysis of dibenzyl ketone in the presence of TEMPO (Scheme IV).

Under irradiation dibenzyl ketone undergoes a Norrish Type I cleavage (i.e. \(\beta\)-fission of the triplet ketone) yielding phenyl-acetyl and benzyl radicals; thus photolysis of the ketone in the presence of TEMPO afforded a mixture of the alkoxyamine products 29 and 30. The relative molar concentrations of these, \([29]/[30]\), were determined by NMR after the TEMPO
had been consumed (since paramagnetic TEMPO would interfere with the NMR determination).

**Scheme IV. Photolysis of Dibenzyl Ketone in the Presence of TEMPO**

Fragmentation of the phenyl-acetyl radical competes directly with its coupling reaction to TEMPO and therefore the molar concentration ratio, $[29]/[30]$, is determined by the rate constant for decarbonylation $k_D$ relative to the radical-trapping rate constant $k_T$. The approximate kinetic equation is $k_D = k_T \times [1]/([29]/[30] - 1)/2$, where $[1]$ is the 'mean' TEMPO concentration during the reaction. By assuming a 'normal diffusion-controlled' rate constant for radical trapping of 'about $10^{10}$ M$^{-1}$s$^{-1}$' Robbins and Eastman estimated $k_D$ to be 'about $10^8$ s$^{-1}$'.

Problems with this technique are clearly that the trapping rate constant is only guessed (see Sect 1.11) and that NMR analysis has limited scope and low precision. Gas chromatography (GC) can be used to resolve the trapped products of small primary radicals (cf. Ch 2) but generally the alkoxyamine products are not sufficiently stable for analysis by GC.$^{51}$

A simple solution to the problem of product analysis has been developed by Solomon and his co-workers.$^{52}$ Incorporation of an isolated UV chromophore into the nitroxide allows products to be readily resolved and quantified by Reversed-Phase High Pressure Liquid Chromatography (RP-HPLC) with UV detection. Solomon's group has used nitroxides such as T and 4 to elucidate the initial stages of many important free radical polymerizations; for instance, the selectivities of various activated vinyl compounds (monomers) towards initiator radicals ($i^*$) can be assessed by 'initiating' the monomers in the presence of a sufficient quantity of nitroxide to prevent extensive telomerization. The generalized scheme below serves
Chapter One: Background to Radical-trapping

to illustrate the facility and effectiveness of the technique.

**Radical/Monomer Reactions in the Presence of a Nitroxide**

\[
\begin{align*}
\text{(i • = } t\text{-BuO •, PhCO}_2\text{•, CN-i-Pr •, etc.)} \\
\text{(X = Ph, CO}_2\text{Me, CN, etc.)}
\end{align*}
\]

With a few exceptions, the alkoxyamine products indicated by this scheme can be resolved and spectrally identified so that the relative rates of addition to and abstraction from various positions on the monomer unit can be readily gauged from the product distributions.

**1.11 The Trapping Rate Constant \( k_T \)**

Interpretation of experiments employing the reaction scheme above does not require the rate constant \( k_T \) to be known. If on the other hand the radical-trapping reaction is in competition with other radical processes and one wishes from the product data to estimate the latter's absolute rate constants, e.g. for the propagation steps above or for unimolecular reactions (e.g. Scheme IV), then reliable estimates of \( k_T \) are required for a variety of radical types.

As mentioned above, \( k_T \) for the reaction of TEMPO (1) with phenacetyl radicals was assumed to be diffusion controlled – even if true, estimates for such reaction rate constants vary by nearly two orders of magnitude, viz. \( 10^9 \) to \( 5 \times 10^{10} \) M\(^{-1}\)s\(^{-1}\)\(^{202} \). This can hardly be considered a reliable yardstick for kinetic calibrations.

Aleksandrov et al\(^{53} \) tried to measure \( k_T \) for various nitroxides (and for oxygen) essentially by putting the trapping reaction into competition with radical-radical termination in very dilute nitroxide solutions. The reactions were performed with a constant initiation rate and were monitored by the ESR signal of the nitroxide. The latter decreased linearly at first (i.e. where the nitroxide concentration \([T] > 10^{-6} \text{ M}\) but the signal fell less sharply as radical-radical
termination became competitive with trapping \((T < 3 \times 10^{-7} \text{ M})\). By making certain assumptions and by referring to literature termination rates \((2k_t)\) which varied by over two orders of magnitude, the authors estimated \(1-3 \times 10^7 \text{ M}^{-1}\text{s}^{-1}\) for the \(k_T\) of hydrocarbon radicals and somewhat lower values for polymer radicals.

Schmid and Ingold used steady-state ESR to measure the kinetics of spin-trapping of \(n\)-hexyl radical with various nitrones and nitroso-compounds. They were also able to measure rate constants \((k_T)\) for the radical-trapping reaction of the transient nitroxides that were formed by the spin-trapping reactions (Sect. 1.3). Values for \(k_T\) were found relative to the rate constants for the ESR spin-trapping reaction \((k_N)\) which in turn were calibrated by kinetic competition with the hex-5-enyl radical's ring closure. The authors used a rate constant \((k_C)\) of \(1.8 \times 10^6 \text{ M}^{-1}\text{s}^{-1}\) for the last reaction to derive \(k_T = 4-6 \times 10^8 \text{ M}^{-1}\text{s}^{-1}\) at 40°C in benzene but a more recent estimate for \(k_C = 3.9 \times 10^6 \text{ M}^{-1}\text{s}^{-1}\) at 40°C implies a somewhat higher radical-trapping rate constant, viz. \(k_T = 8-12 \times 10^8 \text{ M}^{-1}\text{s}^{-1}\) at 40°C. This estimate is in excellent agreement with the value obtained in the present work by competition between the hex-5-enyl radical clock with radical-trapping with \(T\) \((k_T = 1.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1})\).

Direct measurements of the trapping rate constant have also been made. Asmus and Willson (1976) measured \(k_T\) for several radicals in water by pulse radiolysis and obtained, for example, \(k_T = 5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}\) at 30°C for cyclopentyl radicals with \(3\). More recently Chateauneuf, Lusztyk, and Ingold (1987) measured the \(k_T\) of several radicals in isooctane by laser flash photolysis; an abbreviated list of their results is given in Table I. The data for the isoindolinoxyl \(T\) are less extensive than those for TEMPO but it is clear that the trapping rate constants are very similar, with those for \(T\) being just a shade higher for primary, tertiary and for benzy1 radicals; moreover it has been demonstrated by direct competition experiments (cf. Ch 2), that \(T\) and TEMPO have practically identical \(k_T\)'s for ethyl radicals. The temperature variations of \(k_T\) indicate very low energy barriers for the coupling reactions, viz. 1.8 and 0.8 kcal/mol for nonyl and benzyl radicals, respectively.
Table I. Laser Flash Photolysis Values for $k_T$ in Isooctane at 20°C.41

<table>
<thead>
<tr>
<th>Radical</th>
<th>$k_T$ (10^8 M^{-1}s^{-1})</th>
<th>$k_{TEMPO}$ (10^8 M^{-1}s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclopropyl</td>
<td>--</td>
<td>14</td>
</tr>
<tr>
<td>nonyl</td>
<td>13</td>
<td>12.3</td>
</tr>
<tr>
<td>t-butyl</td>
<td>8.8</td>
<td>7.6</td>
</tr>
<tr>
<td>benzyl</td>
<td>5.5</td>
<td>4.9</td>
</tr>
<tr>
<td>1-phenylethyl</td>
<td>--</td>
<td>1.6</td>
</tr>
<tr>
<td>2-phenyl-2-methylethyl</td>
<td>--</td>
<td>1.2</td>
</tr>
</tbody>
</table>

From the high rate constants and low sensitivity to radical stability (up to the benzyl radical level) one is tempted to conclude that the reaction is diffusion controlled but, as revealed in Ch 6, solvent effect studies indicate otherwise.

1.12 Miscellaneous Reactions

At the foundation of the radical-trapping method is the assumption that nitroxides, in particular T, quench radicals exclusively by coupling with them. Radical disproportionation, i.e. the transfer of a $\beta$-hydrogen atom from one radical to another, is often competitive with coupling in normal radical-radical termination reactions – for tert-butyl, for instance, it is the major pathway.61 However, Bolsman et al.62 concluded from their investigations of the reactions of TEMPO with tert-butyl and 1,1-diphenylethyl radicals that disproportionation between nitroxides and normal alkyl radicals would be negligible. Similar conclusions have been reached regarding galvinoxyl63 and T (Ch 2).

Reaction of $\alpha$-Hydroxy-alkyl Radicals with a Nitroxide

Investigations55 by Asmus et al indicate that $\alpha$-hydroxyalkyl radicals also couple
with nitroxides but that here the product rapidly disproportionates to the reduced nitroxide and the ketone. Mathew and Warkentin's results indicate a similar reaction in organic media.

Though roughly half the spin of dialkyl nitroxides resides on the nitrogen centre, it has been established that coupling occurs at oxygen, even in aqueous media, possibly because of the greater steric protection of the nitrogen centre.

It is generally accepted that oxygen centred radicals do not couple, or otherwise rapidly interact, with dialkyl nitroxides in organic media. For example, radicals (R·) can be produced by hydrogen atom abstraction of suitable substrates (R-H) with tert-butoxyl radicals in the presence of T or 4 without extraneous by-product formation. Contrary to this, Ingold has found that aroyloxyl radicals, which in other ways show reactivity similar to alkoxy radicals, are quenched by TEMPO with very high rate constants i.e. 3 x 10^8 M⁻¹s⁻¹. However, the anomaly may only be apparent because in most situations where hydrogen atom abstraction (or radical addition) is used to generate radicals the substrate is in a huge molar excess over the trap; e.g. if R-H is the solvent and [T] = 40 mM (a typical figure) then [R-H]/[T] = ca. 200 which implies that if the abstraction (or addition) rate constant is in the order of 10⁷ M⁻¹s⁻¹ then the rate constant for the proposed oxy-radical/trap interaction may be as high as ca. 2 x 10⁸ M⁻¹s⁻¹ without having a noticeable effect on the product distribution.

It has been determined by laser flash photolysis that aryl thiyl radicals are quenched by TEMPO or by galvinoxyl with very high rate constants (8-50 x 10^8 M⁻¹s⁻¹). These reactions probably involve charge transfer but product studies are not conclusive in this regard. Certainly the high electron affinity of S- and O-centred radicals and the low ionization potential of the nitroxyl radicals are consistent with a rapid electron transfer. Coupled products, i.e. R₂N⁺(-O-)XR or R₂NOXR (X = O or S) compounds, are unlikely to be stable because the implied O-O or N-O bonds are too weak to provide effective binding when the nitroxyl group's resonance is taken into account (e.g. for RO-OR and RO-NO, ΔH° = 35 and 42 kcal/mol respectively); they can not be discounted, however, as short lived intermediates in the electron transfer process.
In my investigations (see Ch 7), reactions involving stannyl and silyl radicals did not give products identifiable as trapped silicon or tin centred radicals by HPLC but whether this indicates electron transfer reactions or merely that the coupling products are not stable to the analytical/work-up conditions is not clear. In view of very high Si-O and Sn-O bond strengths and the known polar chemistry of stannyloxy and silyl ether compounds, the latter seems more likely.

**Conclusions**

Much is known about the preparations, structures and physical and chemical properties of nitroxides especially in connection with their use as spin labels or probes. However, until recently, reliable data concerning the kinetics of their most characteristic chemical reaction, viz. radical coupling, have not been available.

The lack of reliable kinetic data has hampered the use of nitroxides as kinetic probes. For instance, though Soloman *et al* have successfully employed a radical-trapping technique to investigate the selectivities of several monomer/radical reactions, the interpretation of data involving reactions which proceed in competition with radical-trapping has been severely limited by the paucity of available $k_T$ data. The latter has also been a problem in attempts to apply radical-trapping for the calibration of radical rearrangement or fragmentation rate constants.

In the present work $k_T$ values have been measured by the radical clock method for a number of radical types (Chapter 2) and in several solvents (Chapter 6). With the aid of these data and direct calibration data by Chateauneuf *et al*, the radical-trapping technique has been applied to rearrangements of substituted cyclopropylmethyl radicals (Chapters 3 and 4), to ring closures of $\omega$-alkenyl radicals (Chapter 5), and to radical fragmentation reactions (Chapters 2 and 4). Bimolecular radical reaction rate constants (e.g. for atom transfer reactions) have also been measured: both by direct competition with radical-trapping, and by a more subtle technique employing a radical clock in the presence of the substrate and the nitroxide (Chapter 8).
CHAPTER TWO

Radical Clock Calibrations of $k_T$

Introduction

Stable nitroxides are very efficient radical scavengers or traps and as such have been used to investigate the mechanisms of reactions involving putative free radical intermediates. In this chapter is described a reaction and analysis technique designed to extend the use of nitroxide radical coupling from a qualitative mechanistic probe to a reliable method for evaluating the kinetic parameters and stereochemistry of radical reactions.

2.1 Background to Radical-Trapping. 1,1,3,3-Tetramethylisoindolin-2-yl-oxyl (T) and similar species couple with carbon centred radicals (R), but not with oxygen centred radicals (see Ch 1.12), to give stable alkoxyamine products (RT). Solomon and his co-workers have used this selective coupling reaction to trap and identify reactive intermediates in the initial stages of free radical polymerizations of commercial and theoretical importance (Ch 1.10).

By analogy with other radical-radical termination processes, the rate constant, $k_T$, for nitroxide coupling has been assumed to be at or near the the diffusion-limited value. For example, Robbins and Eastman used an estimated value of $10^{10}$ M$^{-1}$ s$^{-1}$ for the rate constant for coupling of the phenylacetyl radical with TEMPO in their determination of the rate of decarbonylation ($\text{11} \rightarrow \text{11}'$) of the former. More recent literature data suggest a lower value: Schmid and Ingold found the rate constants for coupling of n-hexyl radicals with various nitroxides in benzene to be $3.5 \times 10^8$ M$^{-1}$ s$^{-1}$ at 40°C (see however Ch 1.11) and these values agree well with the results of pulse radiolysis studies on reactions in water. A laser flash
photolysis study\textsuperscript{72} of the coupling of cyclopropyl radicals with TEMPO gave $k_T = 1.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at 25°C. However, ESR measurements using nitroxides in polymerizing mixtures, and nitroxide/oxygen competition experiments\textsuperscript{70} gave values more than an order of magnitude lower.

The use of the nitroxide coupling reaction as an accurate kinetic probe requires the determination of reliable values of $k_T$ for a variety of radical types. In this chapter the use of suitable free radical rearrangements as radical "clocks" is described.\textsuperscript{71} Subsequent to the completion of the major part of the calibration studies described here, Chateauneuf, Lusztyk, and Ingold calibrated $k_T$ for a number of alkyl and arylcarbinyl radicals by a laser flash photolysis (LFP) method in isooctane\textsuperscript{41} (Table 1.1). A comparison of the results suggested that kinetic data for many of the clocks used here could be profitably reevaluated or supplemented by the radical-trapping data. In other words, in addition to measuring $k_T$ the data in this chapter has been used to check and sometimes recalibrate clocks from the so called radical "horlogerie".\textsuperscript{71}

2.2 Calibration with Radical Clocks. The term radical clock has been introduced by Griller and Ingold\textsuperscript{71} for a radical rearrangement or fragmentation (C• $\rightarrow$ C') with a known rate constant. Radical clocks may be used to investigate reactions believed to proceed via free radical intermediates. That is to say, if such radicals are produced in the course of a reaction, they may either be intercepted (e.g. C• + S-Y $\rightarrow$ C-Y) or they may rearrange (C• $\rightarrow$ C') before being 'quenched' in the reaction mixture (C'• + S-Y $\rightarrow$ C'-Y). The presence of the rearranged material (C'-Y) indicates (but generally does not prove) free radical intermediates in the reaction. Moreover, since we have direct competition between the two reactions, viz. quenching and rearrangement, the molar product ratio [C-Y]/[C'-Y] is a measure of the relative rates at which these processes occur.

One of the best known and most accurately calibrated of radical clocks is the irreversible ring closure of the hex-5-enyl radical (1) to the cyclopentylmethyl radical (1').\textsuperscript{72} When this reaction is conducted in such a way that ring closure competes with trapping of the initial radical by T (Scheme I) the relative yields of uncyclized (1T) and cyclized (1'T) products
are related to \([T]\).

\[
\begin{align*}
\frac{1}{2} \left( \begin{array}{c}
\text{O} \\
1P
\end{array} \right) & \xrightarrow{\Delta (-\text{CO}_2)} \begin{array}{c}
\text{O} \\
1
\end{array} \\
& \xrightarrow{k_c} \begin{array}{c}
\text{O} \\
1'
\end{array}
\end{align*}
\]

\[
\begin{align*}
T & \xrightarrow{k_T} \begin{array}{c}
\text{O} \\
1T
\end{array} \\
& \xrightarrow{T} \begin{array}{c}
\text{O} \\
1'T
\end{array}
\end{align*}
\]

Under pseudo-first-order conditions, i.e. when the initial trap concentration is much greater than that of the precursor,\(^7^3\) the steady-state kinetic equations give eq 2.1 (Appendix A2.2), in which \([1T]/[1'T]\) is the ratio of the total molar concentrations of the alkoxyamine products after decomposition of \(1P\) and \([T]_m\) is the mean trap concentration under reaction conditions.\(^7^3\) Since \(k_c\) is known for this reaction,\(^7^2\) \(k_T\) can be calculated.

\[
\frac{k_T}{k_c} = \frac{[TT]}{[T][T]_m^{-1}}
\] (2.1)

The literature provides a wealth of radical rearrangements which can be used as clocks\(^7^1,^7^4\) - the best represented being 1,5-cyclizations for the primary alkyl radicals. However, the clock reactions preferred for the present purpose were those which (a) have been reliably calibrated in the experimental temperature range, (b) give stable coupled products which can be readily resolved by liquid chromatography and identified by their spectral/analytical data, and (c) have accessible rate constants, viz. \(10^5 \text{ s}^{-1} < k_c < 10^9 \text{ s}^{-1}\) - the limits being set by a practical working range of \(10^{-4}\) to 0.3 M (= solubility in cyclohexane) for the concentration of \(T\). The clocks employed are listed in Table 2.1. For convenience each radical has been assigned a number \(N\), the corresponding radical arising from the clock reaction is designated \(N'\), the respective products from coupling with the nitroxide \(T\) are \(NT\) and \(N'T\), and the radical precursor is \(NP\), e.g. see the scheme above.
Table 2.1. Clock Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Precursor&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Reaction</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diagram" /></td>
<td>DAP (60-125°C)</td>
<td><img src="image2" alt="Diagram" /></td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td><img src="image3" alt="Diagram" /></td>
<td>DAP (60-125°C)</td>
<td><img src="image4" alt="Diagram" /></td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td><img src="image5" alt="Diagram" /></td>
<td>DAP (60-125°C)</td>
<td><img src="image6" alt="Diagram" /></td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td><img src="image7" alt="Diagram" /></td>
<td>DAP (60-125°C)</td>
<td><img src="image8" alt="Diagram" /></td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td><img src="image9" alt="Diagram" /></td>
<td>DAP (40-80°C) BPE (60-125°C)</td>
<td><img src="image10" alt="Diagram" /></td>
<td>PhCH₂CHO with DBPO (40-80°C), TBHN (100°C)</td>
</tr>
<tr>
<td><img src="image11" alt="Diagram" /></td>
<td>DAP (80°C)</td>
<td><img src="image12" alt="Diagram" /></td>
<td>see text</td>
</tr>
<tr>
<td><img src="image13" alt="Diagram" /></td>
<td>DAP (60-125°C)</td>
<td><img src="image14" alt="Diagram" /></td>
<td>see text</td>
</tr>
<tr>
<td><img src="image15" alt="Diagram" /></td>
<td>DAP (60-125°C)</td>
<td><img src="image16" alt="Diagram" /></td>
<td>see text</td>
</tr>
</tbody>
</table>

<sup>a</sup> DAP = diacyl peroxide, BPE = tert-butyl perester, DBPO = di-tert-butyl peroxalate, TBHN tert-butyl hyponitrite. <sup>b</sup>Cyclohexane solvent
Chapter 2: Radical Clocks

Results

2.3 The Radical-Trapping Method. Accurately determined mixtures of the nitroxide, T, and the radical precursor in cyclohexane or benzene were degassed by four freeze/thaw cycles and sealed in vacuo in ampoules which were then immersed in constant temperature (±0.3°C) oil baths for about ten to twenty reaction half-lives. Where the reaction was very rapid (e.g. reactions involving tert-butyl peroxyoxalic esters above 80°C) the precursor was injected through a septum into a small vial containing a purged preheated solution of T. Product mixtures were analysed by reversed-phase high performance liquid chromatography (RP-HPLC) with isocratic or gradient elution (methanol/water). Since T contains an aromatic chromophore isolated from the coupling site, UV detection at 270 nm was uniformly sensitive to the trap and trapped products (except 11T, see product spectral data). Hence, the ratios of HPLC peak areas were equal to the ratios of molar concentrations of trapped products. Small samples of the substituted alkoxyamines produced by trapping were obtained by preparative reverse or normal phase HPLC or by MPLC (medium pressure liquid chromatography), and were identified by their spectral and analytical data.

2.4 Product Stabilities. The thermal stabilities of the product mixtures were tested by the prolonged heating of duplicate ampoules (cf.Ch 6 Exp.). Radical product ratios were unaffected below 120°C except for 10T and for those containing trapped tertiary alkyl radicals (5'T, 7'T, 9T, 12'T and 13'T). However, in the range 115-130°C the rate of change was slow (e.g. \( k = 2.5 \times 10^{-5} \text{s}^{-1} \) for 7T/7'T in cyclohexane at 125°C) compared with the peroxide decomposition rates (\( k = 2 \times 10^{-3} \text{s}^{-1} \) for 7P at 125°C). Consequently, accurate kinetic data were available up to about 130°C for all of the rearrangements studied here. The stabilities of the products under the conditions used for analysis were tested by the analysis of solutions of product mixtures in the HPLC mobile phase (80%-95% methanol) at intervals of time. Only 10T was significantly labile, presumably by solvolysis of this acetal-like product; this problem was overcome by buffering the mobile phase with 0.5% sodium acetate.

2.5 Generation of Radicals. Alkyl radicals were generated by thermolysis of appropriate diacyl peroxides (eq 2.2) or tert-butyl peresters (eq 2.3) as indicated in Table 2.1.
Chapter 2: Radical Clocks

The latter, which were used when the corresponding diacyl peroxides could not be prepared or decomposed too rapidly to give accurate kinetic data (e.g. those giving tert-alkyl radicals\textsuperscript{75}), gave more complex product mixtures because of the production of tert-butoxyl radicals (eq 2.3). When the solvent (S-H) was a good hydrogen donor (e.g. cyclohexane) it underwent hydrogen atom abstraction by tert-butoxyl radicals to afford S-. Hence in such solvents the peresters gave S-T together with the expected products, R-T and R'-T. With benzene as solvent a complex mixture of products arose via β-fission of tert-butoxyl, by reactions of the solvent, and by hydrogen atom abstraction from the precursor, products, and trap.\textsuperscript{77}

\[ \text{RCO}_2\text{H} \rightarrow 2\text{R}^* + 2\text{CO}_2 \text{ (2.2)} \]

\[ \text{RCO}_2\text{OBu}^t \rightarrow \text{R}^* + \text{CO}_2 + \text{^tOBu}^t \text{ (2.3)} \]

The yields of trapped products were usually in the range 50-90%, with diacyl peroxides generally being less productive than peresters. Low yields reflect the tendency of peroxides to: (a) decompose by polar routes,\textsuperscript{78} (b) give solvent cage radical recombination products, and (c) undergo nitroxide induced decomposition.\textsuperscript{20}

2.6 Determination of Kinetic Parameters. For all of the irreversible rearrangements studied here the experimental data were consistent with eq 2.1. Illustrative data obtained for the 5-hexenyl ring closure (1 → 1') are given in Table 2.2 (over); application of eq 2.1 to these data yields \( k_T/k_c \) (1) = 1030±20 M\(^{-1}\) at 80°C. Substitution of the literature value\textsuperscript{72} of \( k_c \) of 1.38 \times 10\(^6\) s\(^{-1}\) gives \( k_T = 1.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} \) at 80°C in cyclohexane. Data, including analytical conditions, for the other radical clocks can be found in the Supplementary Tables at the end of this Thesis.

The temperature dependence the rate ratios \( k_T/k_c \) were investigated by thermolysis of sets of identical reaction mixtures at various temperatures. To optimize analytical precision over the temperature range, the trap concentrations were chosen to give approximately equal concentrations of trapped initial and rearranged radicals ([1T] = [1'T]) at an intermediate temperature. The usual Arrhenius treatment of the data obtained in this way for \( 1 \rightarrow 1' \) (Table 2.3) gives eq 2.4 in which \( \theta = 2.3RT \text{ kcal/mol} \) and \(<\tau>\) is the operational correlation coefficient.

\[ \log(k_T/k_c) = -0.65 + 5.93/\theta, \ <\tau> = 0.9985 \text{ (4)} \]
**Chapter 2: Radical Clocks**

### Table 2.2 Yields of Alkoxyamines from Hex-5-enyl Radical in Cyclohexane at 80°C.

<table>
<thead>
<tr>
<th>[T]a, mM</th>
<th>[T]b, mM</th>
<th>%(1T + 1'T)c</th>
<th>1T(%)/1'T(%)d</th>
<th>k_T/k_C, M⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.465</td>
<td>0.437</td>
<td>9.3</td>
<td>0.451(22)</td>
<td>1030(50)</td>
</tr>
<tr>
<td>0.931</td>
<td>0.875</td>
<td>10.4</td>
<td>0.874(39)</td>
<td>1000(40)</td>
</tr>
<tr>
<td>1.86</td>
<td>1.75</td>
<td>11.5</td>
<td>1.84(8)</td>
<td>1050(40)</td>
</tr>
<tr>
<td>4.19</td>
<td>3.94</td>
<td>10.2</td>
<td>4.09(12)</td>
<td>1040(30)</td>
</tr>
</tbody>
</table>

*a* Stock solutions were 0.500, 1.00, 2.00, and 4.50 mM in T; these figures were corrected for thermal expansion based on a coefficient of 0.00124°C⁻¹. *b* Mean concentrations during the reactions were calculated from [T] = [T]₀(100 + %T)/200, where %T is the %HPLC area assigned to T in the product mixture. *c* Percentages of total integrated area using UV detection at 270 nm; actual yields based on 1P were in the range 60-80%. *d* Product ratios were averaged from three runs; the standard deviation is in units of the last significant figure.

### Table 2.3 Temperature Variation of k_T/k_C for Hex-5-enyl Radical (1).

<table>
<thead>
<tr>
<th>temp,a °C</th>
<th>[T], mMb</th>
<th>yield 1T, %</th>
<th>yield 1'T, %</th>
<th>k_T/k_C, M⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.4</td>
<td>0.91</td>
<td>3.84</td>
<td>2.53</td>
<td>1670</td>
</tr>
<tr>
<td></td>
<td>1.83</td>
<td>0.34</td>
<td>1.46</td>
<td>1620</td>
</tr>
<tr>
<td>80.8</td>
<td>0.87</td>
<td>4.87</td>
<td>5.57</td>
<td>1010</td>
</tr>
<tr>
<td></td>
<td>1.75</td>
<td>6.81</td>
<td>3.70</td>
<td>1050</td>
</tr>
<tr>
<td>100.0</td>
<td>0.84</td>
<td>6.91</td>
<td>3.74</td>
<td>645</td>
</tr>
<tr>
<td></td>
<td>1.69</td>
<td>6.23</td>
<td>5.76</td>
<td>640</td>
</tr>
<tr>
<td>123.5</td>
<td>0.83</td>
<td>3.47</td>
<td>10.87</td>
<td>385</td>
</tr>
<tr>
<td></td>
<td>1.53</td>
<td>6.74</td>
<td>11.84</td>
<td>372</td>
</tr>
</tbody>
</table>

*a* Temperatures are ±0.3°C. *b* Stock solutions were 1.00 and 2.00 mM in T at 22°C; the concentrations were corrected for thermal expansion.
When combined with the literature expression for $\log k_c$,\textsuperscript{13} this gives the temperature dependence of $k_T$:

$$\log k_T = 9.7 - 0.9/\theta$$

(2.5)

Hence at 25°C in cyclohexane, $k_T = 1.1 \times 10^9$ M\textsuperscript{-1}s\textsuperscript{-1}.

### 2.7 Alkyl Radicals

Values of $k_T$ and of the associated Arrhenius parameters, obtained as described above, for the simple alkyl radicals 1–3, 5–9 are listed in Table 2.4. Also included are data for the cyclopropylmethyl radical ring opening ($4 \rightarrow 4'$), discussion of which is presented separately below.

By far the best represented types of radical clock are the rearrangements, especially cyclizations, of primary alkyl radicals. Each primary alkyl clock listed in Table 2.2 satisfied the criteria listed in the introduction except that alkoxyamines 5T and 5'T were not separable by RP-HPLC – these were quantified by NMR of the mixed isomers. As the rate constants for the clock reactions for primary alkyl radicals 1 to 6 span a large range of values,\textsuperscript{71,79-81} the required trap concentrations vary from about 10\textsuperscript{-4} M for 1 to concentrated solutions in benzene (=1 M) for 4.\textsuperscript{80} The clocks used also cover a range of radical size from C4 to C8 and of structure from unhindered to neopentyl.

The secondary and tertiary alkyl 'horlogerie'\textsuperscript{71} is much less well stocked than the primary. The literature provides few rearrangements which meet all the criteria listed in the Introduction: the ring opening of 13' was too slow\textsuperscript{82,83} to be useful, while experimental difficulties\textsuperscript{84} (viz. inseparable alkoxyamine products and low rate constants) precluded the use of the calibrated 1-methylnex-5-enyl and 1,1-dimethylnex-5-enyl radical ring closures. However, the ether analogues of the latter, i.e. 8 and 9, provided clocks with convenient rates and separable products. Ring closure of radical 8 has been previously reported to favour formation of the cis product ($k_c(cis)/k_c(trans) = 2.3$ at 65°C)\textsuperscript{85b}. In accord with this observation formation of the cis stereoisomer of the trapped product 8'T was found to be preferred over the temperature range 60-120°C. The observed ratios of product concentrations fit the expression (Sup. Table 2.8),
Table 2.1. Clock Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Precursor&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Reaction</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DAP (60-125°C)</td>
<td>8</td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td>2</td>
<td>DAP (60-125°C)</td>
<td>9</td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td>3</td>
<td>DAP (60-125°C)</td>
<td>10</td>
<td>BPE (60-122°C)</td>
</tr>
<tr>
<td>4</td>
<td>DAP (40-80°C) BPE (60-125°C)</td>
<td>11</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CHO with DBPO(40-80°C), TBHN(100°C)</td>
</tr>
<tr>
<td>5</td>
<td>DAP (80°C)</td>
<td>12</td>
<td>see text</td>
</tr>
<tr>
<td>6</td>
<td>DAP (60-125°C)</td>
<td>13</td>
<td>see text</td>
</tr>
</tbody>
</table>

<sup>a</sup> DAP = diacyl peroxide, BPE = tert-butyl perester, DBPO = di-tert-butyl peroxalate, TBHN = tert-butyl hyponitrite. <sup>b</sup>Cyclohexane solvent
Table 2.4 Rearrangement and Trapping Rates of Radical Clocks 1 to 13.

<table>
<thead>
<tr>
<th>Radical Clock</th>
<th>Literature Rate Constant(s) ($k_r$)</th>
<th>Experimental $k_T/k_r$</th>
<th>Derived $k_T$ Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ref.</td>
<td>$k_r^{80},10^{-3}$</td>
<td>$A_r/s^{-1}$</td>
</tr>
<tr>
<td>1 $\rightarrow$ 1'</td>
<td>83</td>
<td>1.35</td>
<td>10.37 (32)</td>
</tr>
<tr>
<td>2 $\rightarrow$ 2'</td>
<td>81</td>
<td>2.65</td>
<td>9.9</td>
</tr>
<tr>
<td>3 $\rightarrow$ 3'</td>
<td>79</td>
<td>19.1</td>
<td>10.5 (2)</td>
</tr>
<tr>
<td>4 $\rightarrow$ 4'</td>
<td>80</td>
<td>44.1</td>
<td>11.3 (17)</td>
</tr>
<tr>
<td>5 $\rightarrow$ 5'</td>
<td>82</td>
<td>7.41</td>
<td>13.03 (36)</td>
</tr>
<tr>
<td>6 $\rightarrow$ 6'</td>
<td>79</td>
<td>9.46</td>
<td>9.7 (2)</td>
</tr>
<tr>
<td>7 $\rightarrow$ 7'</td>
<td>107</td>
<td>19.7</td>
<td>10.49 (24.0)</td>
</tr>
<tr>
<td>8 $\rightarrow$ 8'</td>
<td>83b</td>
<td>11.5</td>
<td>9.6 (6)</td>
</tr>
<tr>
<td>9 $\rightarrow$ 9'</td>
<td>f</td>
<td>34</td>
<td>9.7 (4)</td>
</tr>
<tr>
<td>10 $\rightarrow$ 10'</td>
<td>81</td>
<td>0.42</td>
<td>10.7 (5)</td>
</tr>
<tr>
<td>11 $\rightarrow$ 11'</td>
<td>94</td>
<td>25.6</td>
<td>11.0 (6)</td>
</tr>
<tr>
<td>12 $\rightarrow$ 12'</td>
<td>103</td>
<td>3.6</td>
<td>13.8 (4)</td>
</tr>
<tr>
<td>13 $\rightarrow$ 13'</td>
<td>104</td>
<td>12 (60)</td>
<td>13.4 (10)</td>
</tr>
</tbody>
</table>

\[ a \log k_r = \log A_r - \Delta E_r/2.3RT; \] errors, where available, represent 95% confidence limits (= 2xSD). Figures derived from stannane experiments use the latest values for $k_T$ (ref 56).\(^b \)Units are kcal/mol.\(^c \)Solvent was cyclohexane unless otherwise stated.\(^d \)See Table 2.1 for temperature ranges.\(^e \)Arrhenius expression calculated from published stannane data using $k_T$(neopentyl) (ref 56).\(^f \)Benzene solvent.\(^g \)See text.
Chapter 2: Radical Clocks

\[
\log \left( \frac{k_c(\text{cis})}{k_c(\text{trans})} \right) = -0.7 + 1.8/\theta, \quad \langle r \rangle = 0.96
\]

which gives

\[k_c(\text{cis})/k_c(\text{trans}) = 2.9 \text{ at } 65^\circ C.\]

The rearrangement \(9 \rightarrow 9'\) had not been previously studied but seemed the obvious choice for a tertiary alkyl clock. It was calibrated for this work by the reaction of tributylstannane with the tertiary alkyl chloride 14. For example, neat stannane with 10% (molar) of 14 and a trace of AIBN gave a 31:69 ratio of the uncyclized (15) and cyclized ether (16) products respectively at 80°C.

\[
\begin{align*}
\text{Cl} & \quad \text{Bu}_3\text{SnH, 3M} & \quad 80^\circ C \\
14 & \quad \rightarrow & \quad 15 + 16
\end{align*}
\]

The relative cyclization rate obtained in the usual way\(^7^9\) from the kinetic data (Sup. Table 1.14) over the range 40-90°C is given by

\[
\log \frac{k_c}{k_H} = 1.25(\pm0.70) - 0.45(\pm0.50)/\theta.
\]

The most recent value of \(k_H\)\(^8^6\) (for tert-butyl radicals) then gave the value presented in Table 2.4.

The rate constant at 65°C (2.6 \(\times\) 10\(^7\) s\(^{-1}\)) for ring closure of 9 is slightly greater than for the primary radical 2 (1.7 \(\times\) 10\(^7\) s\(^{-1}\)) and the secondary radical 8 (8.2 \(\times\) 10\(^6\) s\(^{-1}\)).

These results conform to the trend in the analogous all-carbon series\(^2^7\) but run counter to thermodynamic and steric expectations and counter to the trend observed for \(\alpha\)-substituted cyclopropylmethyl\(^8^6\) (Ch 4) and cyclobutylmethyl radical\(^8^2\) (Ch 5) ring openings. However the latter rearrangements (as discussed in the cited chapters) are much less exothermic and hence more likely to be determined by the reaction's thermodynamics than the 5-hexenyl cyclizations.

The trend can perhaps be rationalized on the basis of Pross\(^8^7\) radical reactivity observations (i.e. tertiary > secondary > primary for nucleophilic radical additions) combined with steric considerations.\(^8^7\)

Further discussion of the 5-hexenyl cyclizations listed in Tables 2.1 and 2.4 will be
Chapter 2: Radical Clocks

undertaken in Chapter Five.

2.8 The Cyclopropylmethyl Radical. Radical 4 was generated from bis (cyclopropaneacetyl) peroxide (40-80°C) and from tert-butyl cyclopropylperacetate (60-125°C). The diacyl peroxide gave low radical yields; for example, at 60°C the yield of 4T plus 4'T was only 15% (HPLC). Other studies have shown that this peroxide decomposes primarily by polar routes 88,89 (cf. Ch 3.1). The perester gave much better yields, especially at higher temperatures (80-90% at 100°C), although the product mixture was contaminated with compounds formed via hydrogen atom abstraction as outlined above. However, molar product ratios 4T/4'T did not depend on the choice of precursor; further evidence that these ratios accurately reflect the dissociated radical's kinetics will be presented in the following chapter.

**Table 2.5. Yields of alkoxyamines formed from Cyclopropylmethyl Radical (4).**

<table>
<thead>
<tr>
<th>temp, °C</th>
<th>reaction time, hr</th>
<th>10⁻³[T]</th>
<th>4T(%)/4'T(%)</th>
<th>k₄/k₄'</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.2</td>
<td>172c</td>
<td>94.9</td>
<td>0.85</td>
<td>9.01</td>
<td>22</td>
</tr>
<tr>
<td>172c</td>
<td>191</td>
<td>1.7</td>
<td>8.67</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>59.4</td>
<td>102</td>
<td>46.5</td>
<td>0.24</td>
<td>5.22</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>93.1</td>
<td>0.46</td>
<td>4.96</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>181</td>
<td>0.86</td>
<td>4.76</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>80.0</td>
<td>19</td>
<td>22.1</td>
<td>0.057</td>
<td>2.53(15)</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>44.6</td>
<td>0.11</td>
<td>2.49</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>89.8</td>
<td>0.22</td>
<td>2.43</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>178</td>
<td>0.46</td>
<td>2.38</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>260</td>
<td>0.63</td>
<td>2.43</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>100.0</td>
<td>5</td>
<td>82.9</td>
<td>0.13</td>
<td>1.59</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>168</td>
<td>0.26</td>
<td>1.57</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>122.0</td>
<td>0.6</td>
<td>83.0</td>
<td>0.07</td>
<td>0.876</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>160</td>
<td>0.14</td>
<td>0.881</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

*a* Temperatures are ±0.3°C. *b* Corrected for trap decrement and thermal expansion of the solvent; stock solutions were 25.0, 50.1, 100, 200 and 300 mM in T at 22°C; in each experiment [T]ᵢ = 13.3[4P]ᵢ. *c* Di(cyclopropylacetyl)peroxide precursor.

Possible changes in the activity coefficient of T at the relatively high concentrations required to study this rearrangement would be detected by deviation from the linear relationship
between the product ratio $4T/4'T$ and the concentration of $T$ implied by eq 2.1. The deviation was shown to be negligible by an excellent least squares fit of data obtained from 0.02 to 0.3 M (saturated) in $T$ to eq 2.1: $4T/4'T = 0.003 + 2.48 [T]_m$ with $<r> = 0.9991$ (5 concentrations) at 80°C in cyclohexane. The Arrhenius expression for $k_T/k_r$ obtained from data over the range 40°C to 122°C (Table 2.5 above) is given in Table 2.4.

The cyclopropylmethyl radical ring opening was studied with a view to testing the trapping technique on a very fast radical clock and one in which the rapid quenching rate of $T$ would provide a great experimental advantage over the conventional reductive techniques. However, its status as a radical clock at near ambient temperatures is open to question because:

(a) ESR data obtained over the range 128-153 K show a large amount of scatter, (b) as pointed out by Mathew and Warkentin the previous data give the corrected Arrhenius expression $\log k_T = 11.3 - 5.9/\theta <r> = 0.851$, from which the calculated rate constant (9.6 x $10^6$ s$^{-1}$ at 25°C) is much lower than those indicated by product studies, i.e. 4-8 x $10^7$ s$^{-1}$ (triphenylstannane), and 1.5 x $10^8$ s$^{-1}$ (tributylstannane), (c) on theoretical grounds the pre-exponential term is too low; a value of at least $10^{13} s^{-1}$ is to be expected since the ring fission is quadruply degenerate and otherwise entropically favourable.

The data presented in Tables 2.4 and 5.5 support this conclusion. Both the corrected Arrhenius coefficients for $k_T$ obtained from Ingold's ESR measurements and those suggested by Warkentin give results for $k_T$ which are out of step with those obtained by the use of other clocks. It appears, therefore, that neither of the available calibrations for the cyclopropylmethyl radical rearrangement is correct; in the Discussion section below an alternative approach will be suggested.

2.9 Alkoxymethyl Radicals. The ring-closure of 3-butenoxymethyl radical, 10, has previously been investigated in these laboratories by steady state ESR and by tributylstannane reduction. Thermolysis of tert-butyl 3-butoxy-peroxyacetate (10P) in the presence of low concentrations of $T$ (0.05 - 0.5 mM) afforded both of the expected products, 10'T and 10T. The former was shown to be identical to 2'T by NMR and by HPLC peak.
enhancement. The uncyclized alkoxyamine, $10T$, was labile above 90°C and was acid sensitive (see above) so that only restricted data were available.

The experimental rate ratio, $k_T/k_e = 3805 \text{ M}^{-1} (\pm 300 \text{ M}^{-1})$ at 60°C, when combined with the extrapolated ESR cyclization rate constant ($k_e = 2.4 \times 10^5 \text{ s}^{-1}$) gave a trapping rate constant $k_T = 9.1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at 60°C. This is consistent with values derived for alkyl radicals in view of the uncertainty in the ESR rate expression and its extrapolation.

2.10 Acyl Radicals. Decarbonylation of the phenylacetyl radical 11 has been studied by ESR93,71 ($k_D = 9 \times 10^2 \text{ s}^{-1}$ at 156 K), CIDNP94 ($k_D = 5-10 \times 10^6 \text{ s}^{-1}$ at 31°C), ESR spin trapping95 ($k_D > 7 \times 10^6 \text{ s}^{-1}$ at 40°C), and more recently by laser flash photolysis96 ($k_D = 5.6 \times 10^6 \text{ s}^{-1}$ at 25°C, log $k_D = 11.0 - 5.8/\theta$). As the data obtained by laser flash photolysis were expected to be the most accurate they were used to calibrate $k_T$ (Table 2.4).

<table>
<thead>
<tr>
<th>[T]i, mM</th>
<th>yield 11T, %</th>
<th>yield 11'T, %</th>
<th>yield MeT, b%</th>
<th>11T(%)/11'T(%) c.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>151 (+5% 11-P)</td>
<td>10.10</td>
<td>2.52</td>
<td>0.30</td>
<td>4.0</td>
</tr>
<tr>
<td>92 (+10% 11-P )</td>
<td>8.17</td>
<td>2.91</td>
<td>0.21</td>
<td>2.8</td>
</tr>
<tr>
<td>55 (+10% 11-P )</td>
<td>5.81</td>
<td>4.21</td>
<td>0.17</td>
<td>1.4</td>
</tr>
</tbody>
</table>

a $[T]_i = 20.[\text{DBPO}]_i$. b Trapped methyl. c HPLC areas corrected for absorptivity difference. d Linear regression gives $11T(\%)/11'T(\%) = 0.08 + 26.7 [T]_i$, $r = 0.983$; thus $k_T/k_D = 26.7 \text{ M}^{-1}$ at 80°C.

The radical 11 was produced by hydrogen atom abstraction from phenylacetaldehyde by the tert-butoxyl radicals generated by thermolysis of di-tert-butyl peroxyxalate (DBPO). The major products, $11T$ and $11'T$, were isolated in 60-80% yield (based on DBPO). However at low concentrations of aldehyde (<5%) significant quantities of Me-T were also detected. Presumably Me-T arises from trapping of the methyl radicals formed by $\beta$-fission of tert-butoxyl radicals. The product formed via hydrogen atom abstraction from the benzylic
position of phenylacetaldehyde (i.e. trapped α-formylbenzyl) was suspected among the minor products but was too labile to be isolated by HPLC.

The results obtained at 80°C are summarized in Table 5.6. If \( \kappa_D = 2.65 \times 10^7 \text{ s}^{-1} \) at 80°C,\(^96\) the trapping rate constant has a value in benzene at 80°C is 8.3 \( \times 10^8 \text{ M}^{-1} \text{ s}^{-1} \). Similar experiments performed over the temperature range 40-100°C gave the rate coefficients presented in Table 2.4.

### 2.11 Alkoxycarbonyl Radicals.

The rate of decarboxylation of the \( \text{tert-} \)butoxycarbonyl radical (12 → 12′) has been measured over a wide temperature range by steady state ESR.\(^97\) However, the absolute rate constant for this clock (and for 13 → 13′) may be about five times faster than that originally reported due to uncertainty in the rate of bimolecular termination of \( \text{tert-} \)butyl radicals.\(^98\) The higher estimates of the decarboxylation rate agree well with Rüegge and Fischer's recent calibration by time-resolved ESR\(^103\) (used in Table 2.4). Decarboxylation 13 → 13′ has also been calibrated by steady-state ESR;\(^104\) the rate is significantly faster than 12 → 12′ and consequently is more convenient for competition with the trapping reaction.

The radicals 12 and 13 were generated from the appropriate \( \text{O,O-} \)tert-butyl monoperoxyxalate esters (\textit{vide infra}) which were readily prepared from the corresponding alcohols (ROH) by treatment with \( \text{tert-} \)butylperoxalylchloride\(^125\) and pyridine (\( R = \text{Bu}^t \) or \( c-C_4H_7.\text{CMe}_2 \)).

Since nitroxides are known to induce decomposition of diacyl peroxides\(^32\) it is conceivable that \( T \) may produce one or both of the products (e.g. 13\( T \), 13′\( T \)) by a pathway not involving dissociated free radicals. Evidence against this hypothesis include the observations that (a) the rate of decomposition of the precursor was independent of of [T] throughout the range 1 mM to 10 mM, (b) there was excellent adherence to eq 2.1, and (c) 13 generated from the formate ester 13\( P' \) by abstraction with \( \text{tert-} \)butoxyl radicals at 60°C and 80°C gave data identical with those obtained when 13 was generated from the peroxyde 13\( P \) (in benzene...
solvent).

\[
\text{O} - \text{C} = \text{O} \quad 12\text{P} \quad \xrightarrow{(-\text{CO}_2)} \quad \text{O}^\cdot + t-\text{Bu-O}^\cdot
\]

2.12 T versus TEMPO. Most other measurements\textsuperscript{11a,58} of coupling rates of radicals with nitroxides have been conducted with TEMPO, or with 4-substituted TEMPO. In order to correlate these measurements with \( k_T \) direct competition experiments between TEMPO and T for ethyl radicals were performed.

Equimolar mixtures of TEMPO and T with 0.2 equivalents of dipropionyl peroxide were heated in cyclohexane then analysed by GC.\textsuperscript{51} The rate ratio \( k_T/k_{\text{TEMPO}} \) over a wide range of concentrations was very close to unity, i.e. \( k_T = 1.05 \pm 0.08 k_{\text{TEMPO}} \). Although the difference in rates may be amplified for more stable and/or sterically hindered\textsuperscript{105} radicals, this result indicates that rates obtained for TEMPO and for T should be more or less interchangeable for coupling with 'normal' alkyl radicals.\textsuperscript{41,106}

2.13 Discussion

The data presented in Table 2.4 reveal no clearcut correlation between the magnitude of \( k_T \) and the stability or geometry of the carbon-centred radicals undergoing nitroxide coupling. For example, \( k_T \) appears to have much the same value at 80\textdegree C for the primary alkyl radicals, 1, 2, 3, 5 and 6, the secondary radical 8, the tertiary radical 9, the alkoxyalkyl radical 10, and the acyl radical 11. This does not necessarily mean that there is no such relationship; indeed the results of current laser flash photolysis studies\textsuperscript{41} indicate that highly stabilized and/or sterically hindered radicals certainly do show lower values of \( k_T \). However, in our case the variations in \( k_T \) are most likely to reflect uncertainties both in the present set of experiments and in those used to determine the kinetics of clock reactions. The most reliable data should be those obtained by...
the use of the well-studied hexenyl system \((1 \rightarrow 1')\). It is noteworthy that the value of \(k_T (1)\) is very close to that reported for the reaction of the nonyl radical with TEMPO.\(^{41}\)

The variations in the Arrhenius parameters presented in Table 2.4 are more pronounced. Once again, they probably reflect, at least in part, the experimental uncertainties in the determination of the kinetics of both the clock and the nitroxide coupling reactions. As before, the data obtained by use of the hexenyl cyclization \((1 \rightarrow 1')\) are likely to be the most reliable. Therefore, until more accurate data become available we suggest that eq 2.6 be used to calculate rate constants for the coupling reaction of the nitroxide, \(T\), in non-polar solvents with all simple primary and secondary alkyl radicals, and with acyl radicals.

\[
\log k_T = 9.7 - 0.9/\theta 
\]  

(2.6)

For alkoxy carbonyl radicals the clock data should be sufficiently reliable to support the expression given in Table 2.4. For neopentyl and tertiary radicals small downward corrections to eq 2.6 are suggested by the direct calibration data (viz. factors of 0.8 and 0.6 respectively - Table 1.1).

As a general guide it is suggested that within the temperature range 0\(^{\circ}\)-80\(^{\circ}\)C no substantial error will be introduced if the value of \(k_T\) for the coupling reactions of \(T\) with all sterically unhindered carbon-centred radicals in non-polar solvents is assumed to be \(1 \times 10^9\) M\(^{-1}\) s\(^{-1}\). Since the direct competition experiment shows that \(T\) and TEMPO are of approximately equal reactivity, the same assumption applies to coupling of the latter.

On the basis of these assumptions it is possible to resolve previous discrepancies in the calibration of some important radical clocks. For example, we have noted above that neither the earlier kinetic data,\(^{80,81}\) nor those recently presented\(^{90}\) for ring-opening of cyclopropylmethyl radical \((4)\) give plausible values of \(k_T\). More acceptable data can be obtained by assuming that \(k_T\) for \(4\) is the same as that for the hexenyl radical, \(1\). The experimental rate ratios, \(k_T/k_i\) (Table 2.5), where \(k_i\) is the rate constant for the reaction \(4 \rightarrow 4'\), were combined with values of \(k_T\) calculated from eq 2.6 to give \(k_i\) from 40\(^{\circ}\)C to 123\(^{\circ}\)C. These data (14 points) were combined with the ESR data (14 points)\(^{80}\) by a least squares fit to the transition state
equation, \( k_i/T = A \exp(-E/RT) \). At around 140 K this gave \( \log k_i = 12.9 - 7.0/\theta \) while at ordinary temperatures

\[
\log k_i = 13.3 - 7.4/\theta
\]  

(2.7)

The overall correlation coefficient was 0.989. This Arrhenius equation is consistent with theoretical predictions and with the experimental pre-exponential for the related cyclobutylmethyl ring opening\(^82\) (eg. \( 5 \rightarrow 5' \)). The rate constant, \( k_i = 8 \times 10^7 \) s\(^{-1}\) at 25°C, agrees well with other estimates for this radical\(^86,91\) and (comparatively) with estimated rates for substituted cyclopropylmethyl radicals.\(^83,107\) It is suggested, therefore, that eq 2.7 be adopted for the calculation of \( k_i \) for the cyclopropylmethyl radical clock (\( 4 \rightarrow 4' \)) within the temperature range 40-130°C.

Discrepancies in the values of the rate constants for decarbonylation of the phenylacetyl radical, \( 11 \), can be similarly reconciled. In earlier work Robbins and Eastman\(^50\) assumed a diffusion controlled coupling rate constant for acyl radicals with TEMPO of \( 10^{10} \) M\(^{-1}\) s\(^{-1}\) to derive a rate of about \( 10^8 \) s\(^{-1}\) for \( k_D(11) \). Substitution of a more reasonable estimate, about \( 1 \times 10^9 \) M\(^{-1}\) s\(^{-1}\), gives \( k_D = 10^7 \) s\(^{-1}\) at 25°C; this brings all of the above estimates for \( k_D \) to agreement to within experimental uncertainties. Extrapolation of the rate expression from flash photolysis gives \( k_D = 750 \) s\(^{-1}\) at 156 K, and by the more exact procedure (for large temperature differences) of extrapolation using the transition state expression gives \( k_D = 980 \) s\(^{-1}\) (at 156 K), in good agreement with the ESR figure.\(^93\)

The Arrhenius parameters for coupling of \( T \) with the alkoxyacarbonyl radical (\( 12 \)) are similar to those determined for alkyl radicals, but the derived trapping rate constant at 80°C (\( 2.2 \times 10^9 \) M\(^{-1}\) s\(^{-1}\)) is a little larger than most of the others in Table 2.4; possibly the reaction is aided by the polar nature of \( 12 \) (cf. Ch 1.6 and Ch 6). However, the results tend to confirm the accuracy of the recently published\(^103\) rate expression for \( 12 \rightarrow 12' \).

The rate of decarboxylation of the alkoxyacarbonyl radical \( 13 \rightarrow 13' \) is less well defined. If we accept that \( k_D(13) \) has the same values as \( k_D(12) \) it is possible to deduce the Arrhenius expression (eq 2.8) for the rate constant \( k_D(13) \).
Chapter 2: Radical Clocks

\[
\log k_D(13) = 13.0 - 10.0/\theta 
\]  

(2.8)

This is close to the original ESR data.\(^{104}\) The marked lowering of \(E_A\) and \(\log A\) relative to those for \(12 \rightarrow 12\)\(^{103}\) (Table 2.4), suggests participation of the cyclobutyl ring bonds in the transition structure for \(C-O\) bond fission. The effects of strain and product radical stabilization upon the decarboxylation of alkoxyacyl radicals will be examined in Chapter Four.

The only other radicals for which the kinetic data deviate significantly from eq 2.6 are the two neopentyl species \(6\) and \(7\). Although in these cases it is possible that the trapping rates are affected by steric hindrance, it seems more likely that the deviations reflect experimental errors in both the calibration\(^ {79,108}\) and trapping experiments. Indeed direct calibration of \(k_{\text{TEMPO}}\) for the neopentyl radical suggests a value just 20% lower than for unhindered primary radicals (nonyl) (Table 1.1) – on this basis, isomerizations of \(6\) and \(7\) are recalibrated in Chapters 5 and 3, respectively.

Finally, it is noteworthy that all of the values of \(k_T\) determined here are about one order of magnitude less than would be expected for a reaction under diffusion control. Since the observed activation energies are less than those expected for diffusion controlled processes, the low values of \(k_T\) are associated with low values of \(\log A\) (9.7 as compared with \(ca\) 11.5 for bimolecular termination of simple alkyl radicals in non polar solvents).\(^ {109}\) Although the basis of this entropic barrier to coupling cannot be identified at present, this author believes that it is associated with the dipolar character of nitroxide radicals, and with the degree of electronic and solvent reorganisaton which must occur when coupling takes place. This aspect of the radical-trapping reaction will be further discussed in Chapter Six.

2.14 Conclusion

The kinetic data discussed above indicate that a wide range of alkyl, substituted alkyl, acyl, and alkoxyacyl radicals couple with the nitroxide radical, \(T\), or with TEMPO at less than the diffusion controlled rates in nonpolar solvents. For many practical purposes the rate constant \(k_T\) can be assumed to be \(ca\) \(1 \times 10^9 \text{ M}^{-1} \text{s}^{-1}\) within the temperature range 0-80°C. More accurate values can be obtained from the Arrhenius expression (eq 2.6). The data are in
satisfactory agreement with the laser flash photolysis experiments of Chateauneuf, Lusztyk, and Ingold, a précis of which was given in Chapter One (Sect.1.10).

These values of $k_{T}$ constitute an important data base for the utilization of nitroxide coupling as a kinetic probe for a wide variety of radical reactions. The method lacks many of the drawbacks of the tin hydride method viz.; reagent reactivity (with air, activated double bonds and carbonyl groups, halocarbons, and with nitro, sulphonyl, disulphide and peroxy groups), and the stannyl by-products which can be very difficult to remove. The nitroxide method also carries the advantage of having a much greater radical quenching rate ($10^9$ M$^{-1}$ s$^{-1}$ versus $10^6$ M$^{-1}$ s$^{-1}$) and less selectivity than tin hydrides.

The value of the method when applied to fast rearrangements has been exemplified by the calibration of the cyclopropylmethyl rearrangement, $4 \rightarrow 4'$. The new data (eq 2.7) now allow this rearrangement to be employed as a reliable kinetic standard for fast radical reactions.$^{110}$

The calibration of $k_{i}$ for the cyclopropylmethyl radical described in this chapter establishes the suitability of radical-trapping for the investigation of very fast radical reactions. Studies of reactions that are practically inaccessible by other methods, e.g. $\beta$-fission of ring substituted cyclopropylmethyl radicals, are described in Chapters Three, Five and Six.

Other valuable kinetic data obtained or confirmed in the course of this work include Arrhenius expressions for the decarbonylation of phenylacetyl radical $^{11}$ and for decarboxylation of the alkoxy carbonyl radicals $^{12}$ and $^{13}$. 
Experimental Section

2.14 Instrumentation. Melting points were determined on a Reichert hot stage microscope. Spectra were recorded on the following instruments: Jeol FX-200, MH-100, and PMX-60 (¹H NMR), Jeol FX-200 (¹³C NMR at 50.1 MHz), Perkin-Elmer 683 (IR), and Varian DMS90 (UV-vis). IR spectra were taken on CCl₄ solutions in 0.5 mm NaCl cells and UV-vis spectra on methanol solutions in 10 mm silica cells. Gas chromatography was performed on a Varian 6000 instrument with a vitreous silica capillary column (25 m) (25QC2/BP5 1.0) and helium carrier gas. Elemental analyses were performed by the ANU Analytical Service unit.

High pressure liquid chromatography (HPLC) was performed with a Spectra Physics SP-8000B ternary proportionating pump, digital integrator, and UV-vis detector (analytical cell). Columns used were: #1, Alltech ODS (5 µ) 4.6 mm x 250 mm; #2, Altex ODS (5 µ) 10 mm x 250 mm; and #3, Dupont C-8 (10 µ) 10 mm x 300 mm.

2.15 Reaction/Analysis Technique. For kinetic studies reaction mixtures were made up volumetrically from common stock solutions of T and the diacyl peroxide. The solutions, in 1 mL pyrex ampoules, were degassed by the freeze/thaw method i.e.; they were successively frozen (liquid N₂ as coolant), evacuated (to < 0.1 mm Hg), thawed, frozen, and evacuated, then {thawed, frozen, evacuated} a further two or three times (according as [T] was high or low respectively) before the ampoules were finally flame sealed under vacuum. Whenever possible, series of reaction mixtures (e.g. for Table 2.2) were heated simultaneously and analyzed under identical HPLC conditions. Solvent loss during degassing was found (by weighing the contents before and after this procedure) to be less than 3%, and peroxide decay up to the heating stage was insignificant (by HPLC analysis). After completion of the reaction, the solvent was evaporated in vacuo and the residue dissolved in MeOH before analysis; product ratios were not affected by this process (which is required because large amounts of solvent, i.e. cyclohexane, are incompatible with the reversed phase HPLC analysis).

All analyses were carried out on column #1 with isocratic H₂O/MeOH elution (1.3
Chapter 2: Radical Clocks

mL/min) and with UV detection at 270 nm (analytical UV cell). Under these conditions and with baseline component separation the analytical precision was better than 7% for yields and 5% for product ratios (1SD). The alkoxyamines 5T and 5'T which had identical HPLC retention times, were isolated by HPLC (column #2) and the product ratios determined by NMR by integrating CH$_2$O on 5T and =CH$_2$ on 5'T; the procedure was rather costly (in HPLC methanol) and time consuming and the precision obtained (=15%) did not warrant a full kinetic study. Other product isolations were readily performed on a small scale with the preparative columns #2 or #3. For difficult separations the different polar selectivities of silica and ODS were used in two step separations, i.e. flash chromatography (2% → 10% ether in pentane on a 300mm x 10mm fine mesh silica column with ca 20psi head pressure) followed by reverse phase HPLC of the fractions.

2.16 Materials. The nitroxyl radical T was made in three steps from N-benzyl phthalimide in 25% overall yield by the procedure of Griffiths et al$^5$ mp 128°C (lit.$^5$ mp 128-129°C) – attempts to improve the yield of the first step (ca 30%) by more thorough work-up etc. were unsuccessful and this author suggests strict adherence to the published method. tert-Butyl hydroperoxide (70% aq) was dried by standing over successive small amounts of 3 Å sieve in the cold (4°C) – the desiccation is very thorough and must be considered far less dangerous than the azeotropic distillation method. Phenylacetaldehyde was distilled twice before use to remove polymers. Other reagents were used without purification. Di-tert-butylperoxyxalate$^{113}$ (DBPO), di-tert-butylhyponitrite$^{114}$ (TBHN), di-tert-butylmonoper oxyxalate$^{113}$ (12P), bis (6-heptenoyl) peroxide$^{114}$ (1P), bis (cyclopropaneacetyl) peroxide$^{115}$ (4P), and 1-methyl-1-cyclobutylethyl formate$^{97}$ were prepared by literature procedures. Allyl isobutyl ether (16) which was required as a GC standard for the stannane calibration of 8 → 8' was prepared by the literature method$^{111}$ while 3,3,4-trimethyltetrahydrofuran (17, 74%), bp 105-107°C, was made by distillation from p-toluenesulphonic acid of the diol obtained by LiAlH$_4$ reduction of trimethylsuccinic acid.$^{112}$

2.17 General procedures. (1) Hydrolysis. Esters were hydrolysed by being stirred in a solution of KOH (1.5 mol. equiv. in a little water) in the appropriate alcohol (e.g.
allyl ester in aqueous allyl alcohol - this avoids cross esterification and mixed ether formation) until the starting material was consumed (GC). The usual workup followed by Kügelrohr distillation afforded the carboxylic acid the purity of which was checked by a small scale diazomethane esterification and GC analysis.

(2) Acid Chlorides. To a solution of the acid in benzene (5 volumes) was added oxalyl chloride (2 mol. equiv.) and then a few µl of DMF. The vigorous reaction was complete after about 15 min at room temperature. The excess of reagent was removed by careful evaporation and by displacement with a further quantity of benzene. Since some of the acid chlorides (e.g. for 4) are low boiling, vigorous evaporation was avoided.

(3) Diacyl Peroxides. The acid chloride and finely powdered Na$_2$O$_2$ (1.2 mol. equiv.) in dry ether (~5 volumes) was treated with small aliquots (~5 ml) of water until the initially vigorous reaction had subsided. The mixture was washed successively with water, saturated aqueous NaHCO$_3$, and brine, then dried (MgSO$_4$) and evaporated to give diacyl peroxides in 60-90% yields and >90% iodometric purity. The carbonyl bands in the IR and the α-protons in the NMR spectra were very useful guides to purity.

(4) tert-Butyl Peresters. The acid chloride in pentane was slowly added to a mixture of anhydrous tert-butyl hydroperoxide (0.95 mol. equiv.) and pyridine (1.8 mol. equiv.) in pentane (10-20 volumes) at <10°C then stirred for one hour longer at room temperature. The mixture was washed successively with water, cold 15% H$_2$SO$_4$, water, saturated aqueous NaHCO$_3$, and brine, then evaporated to give the peresters in 50-80% yields. Purity was checked by NMR, IR, and iodometric titration.

Bis-(3-allyloxypropanoyl) Peroxide (2P). Allyl 3-allyloxypropanoate was converted by procedures 1, 2 and 3 into the required peroxide (53%) of 98% purity (iodometric):

$^1$H NMR δ (CDCl$_3$, 100 MHz); 2.60 (t, 2H), 3.61 (t, 2H), 3.96 (d, 2H), 5.10 (m, 2H), 5.80 (m, 1H); IR $v_{max}$ 1785, 1805 (C=O, Fermi split) cm$^{-1}$.
Bis-(4,4-dimethyl-6-heptenoyl) Peroxide (3P). Diethyl isopropylidenemalonate\textsuperscript{118} (20.0 g) was added to a cooled (-30°C) mixture of allylmagnesium bromide (formed at 0°C from 16.4 g allyl bromide) and CuCl (0.5 g) in ether (200 mL) then allowed to warm slowly to room temperature. The usual work-up gave diethyl 1,1-dimethylbut-3-enylmalonate (20.3 g, 85%), bp 101-104°C at 2.0 mm; \textsuperscript{1}H NMR $\delta$ (CDCl$_3$, 100 MHz); 1.05 (s, 6H), 1.25 (t, 6H), 2.15 (d, 2H), 3.12 (s, 1H), 4.12 (q, 4H), 5.00 (m, 2H), 5.65 (m, 1H); IR $\nu_{\text{max}}$ 1741 cm$^{-1}$. The malonate was decarbethoxylated by Krapcho’s method\textsuperscript{119} to give ethyl 3,3-dimethylhex-5-enoate (6.61 g, 82%), bp 70-72°C at 6.0 mm (91% GC); \textsuperscript{1}H NMR $\delta$ (CDCl$_3$, 100 MHz); 1.00 (s, 6H), 1.22 (t, 3H), 2.04 (d, 2H), 2.10 (s, 2H), 4.03 (q, 2H), 5.01 (m, 2H), 5.70 (m, 1H). The ester was converted via procedures 1, and 2 into the acid chloride (4.0 g) which was added to excess diazomethane in ether (from 23g "Diazald" $=3$ mol. equiv.) at 0°C. After 3 hr at 0°C, evaporation of the mixture yielded 1-diazo-4,4-dimethyl-hept-6-en-2-one (4.1 g, 98%) which was dissolved in methanol (50 mL) and treated (at 50°C) with 0.5 mL portions of a solution of silver benzoate (0.3 g) in triethylamine (3 mL) as previously described.\textsuperscript{20} Filtration and distillation gave methyl 4,4-dimethylhept-6-enoate (3.61 g, 81%), b.p. 80-81°C at 12 mm (91% GC). A sample (1.0 g) was purified by flash chromatography on silica with 2% → 5% ether in pentane and converted by procedures 2 and 3 to the required peroxide (91% from acid chloride) of >97% purity by \textsuperscript{1}H NMR and iodometric titration; \textsuperscript{1}H NMR $\delta$ (CDCl$_3$, 100 MHz); 0.94 (s, 6H), 1.60 (t, 2H), 2.02 (d, 2H), 2.15 (t, 2H), 5.01 (m, 2H), 5.70 (m, 1H); IR $\nu_{\text{max}}$ 1775, 1800 cm$^{-1}$.

Bis-[(2,2-dimethylcyclobutane)acetyl] Peroxide (5P). (−)Methyl (2,2- dimethyl-3-oxo-cyclobutane)acetate (3.4 g) prepared from α-pinene via pinonic acid in five steps,\textsuperscript{121} was treated with BF$_3$ etherate (10 mL) and ethanedithiol (8 mL). After 8 hr the reaction mixture was diluted with pentane and washed successively with water, 5% aqueous NaOH (twice), and brine, then dried and evaporated to give the thioketal (3.8 g) which was desulphurized with Raney-Nickel W2 (20 g) in boiling methanol (200 mL) for 15 min to give, on workup, methyl (2,2-dimethylcyclobutane)acetate (1.66 g, 56%). This ester was purified to 97% (GC) by flash chromatography on silica with 3% ether in pentane: \textsuperscript{1}H NMR (CDCl$_3$, 200 MHz); $\delta$ 1.00 (s, 3H), 1.07 (s, 3H), 1.60 (m, 4H), 1.98 (m, 1H), 2.32 (m, 3H), 3.13 (s, 3H) $\nu_{\text{max}}$ 1738.
Bis-(3,3-dimethylhept-6-enoyl) Peroxide (6P). 3-Butenylmagnesium bromide was conjugatively added to diethyl isopropylidenemalonate at -10°C and the resulting malonate decarbethoxylated as for 3P to give ethyl 3,3-dimethylhept-6-enoate (55% overall), bp 68-72°C at 0.5 mm: \( ^1H \) NMR (CCl\(_4\), 100 MHz) \( \delta \) 1.00 (s, 6H), 1.3 (m, 4H), 2.1 (m, 5H), 4.01 (q, 2H), 5.00 (m, 2H), 5.81 (m, 1H); IR \( \nu_{max} \) 1735 (C=O) cm\(^{-1}\). This was converted by procedures 1, 2, and 3 into the title peroxide (48%) of 94% purity (iodometric): \( ^1H \) NMR (CCl\(_4\), 100 MHz) \( \delta \) 1.05 (s, 6H), 1.50 (t, 2H), 2.10 (m, 2H), 2.35 (s, 2H), 5.00 (m, 2H), 5.78 (m, 1H); IR \( \nu_{max} \) 1778, 1790 (C=O) cm\(^{-1}\).

Bis-(3,3-dimethylpent-4-enoyl) Peroxide (7P). 3,3-Dimethylpent-4-enoic acid, was converted by procedures 2 and 3 into the title peroxide (85%) of 95% purity (iodometric): \( ^1H \) NMR (CDCl\(_3\), 60 MHz) \( \delta \) 1.18 (s, 6H), 2.36 (s, 2H), 4.93, (m, 2H), 5.87 (q, 1H); IR \( \nu_{max} \) 1770, 1790 (C=O) cm\(^{-1}\).

tert-Butyl 3-Allyloxy-2-methylperoxypropanoate (8P). \( \alpha \)-Alkylation of propanoic acid with allyl chloromethyl ether using the method of Pffefer et al (with HMPA) gave 3-allyloxy-2-methyl-propanoic acid (76%), bp 80-87°C at 0.3 mm, 95% purity (GC of Me ester): \( ^1H \) NMR (CCl\(_4\), 60 MHz) \( \delta \) 1.11 (d, 3H), 2.52 (m, 1H), 3.35 (m, 2H), 3.75 (d, 2H), 5.05 (m, 2H), 5.65 (m, 1H), 10.35 (s, 1H); IR \( \nu_{max} \) 1752 (C=O) cm\(^{-1}\). It was converted by procedures 2, and 4 into the title perester (80%) with 95% purity (iodometric): \( ^1H \) NMR (CCl\(_4\), 60 MHz) \( \delta \) 0.99 (s, 2H), 1.04 (f, 3H), 2.56 (m, 1H), 3.36 (m, 2H), 3.77 (d, 2H), 5.03 (m, 2H), 5.65 (m, 1H); IR \( \nu_{max} \) 1776 (C=O) cm\(^{-1}\).

tert-Butyl 3-Allyloxy-2,2-dimethylperoxypropanoate (9P). Isobutyric acid was \( \alpha \)-alkylated as above (without HMPA) to give 3-allyloxy-2,2-dimethylpropanoic acid (70%), bp 84-87°C at 0.3 mm, 96% pure (GC of methyl ester): \( ^1H \) NMR (CCl\(_4\), 60 MHz) \( \delta \) 1.18 (d,
Chapter 2: Radical Clocks

6H), 3.35 (m, 2H), 3.85 (d, 2H), 5.05 (m, 2H), 5.45 (m, 1H), 11.35 (s, 1H); IR ν\text{max} 1750 (C=O) cm\(^{-1}\). It was converted by procedures 2 and 4 into the title perester (65%), 98% pure (iodometric): \(^1\)H NMR (CCl\(_4\), 60 MHz) δ 1.13 (s, 9H), 1.21 (s, 6H), 3.38 (s, 2H), 3.87 (d, 2H-6Hz), 5.15 (m, 2H), 5.30 (m, 1H); IR ν\text{max} 1774 cm\(^{-1}\).

tert-Butyl 3-Butenoxyperacetate (10P). 3-Butenol (1.86 g, 30 mmol) was added to a slurry of NaH (1.50 g, 63 mmol) in DMF (15 mL). After 1 hr bromoacetic acid (4.17 g, 30 mmol) in DMF (15 mL plus 1 mL decane to control frothing) was added slowly, and the mixture was then stirred for a further 2 hr. Dilution with water and extraction with CH\(_2\)Cl\(_2\) followed by the usual procedure for isolation of the acidic component, i.e. extraction with aq-NaHCO\(_3\) followed by acidification and ether isolation, gave 3-butenoxyacetic acid (2.10 g, 63%), bp 70-80°C at 0.3 mm: \(^1\)H NMR (CCl\(_4\), 100 MHz) δ 2.42 (q, 2H), 3.61, (t, 2H), 3.97 (s, 2H), 5.00 (m, 2H), 5.75 (m, 1H), 11.2 (br s, 1H). IR ν\text{max} 1760 (C=O) cm\(^{-1}\). It was converted via the imidazolidene into the required perester (0.90 g, 75%), 92% pure (iodometric): \(^1\)H NMR (CCl\(_4\), 100 MHz) δ 1.15 (s, 9H), 2.40 (q, 2H), 3.63 (t, 2H), 4.00 (s, 2H), 5.00 (m, 2H), 5.75 (m, 1H); IR ν\text{max} 1773 (C=O) cm\(^{-1}\).

QQ-tert-Butyl Q-1-Cyclobutyl-1-methylethyl Monoperoxyoxalate (13P).

Treatment of 2-cyclobutylpropan-2-ol\(^{102}\) with an excess of tert-butyl peroxyal chloride\(^{112}\) as described by Bartlett and Pincock\(^{125}\) gave the title compound as a colourless oil (81%) which was pure by NMR and IR but gave erratic results (80-110%) upon iodometric analysis\(^{125}\): \(^1\)H NMR (CDCl\(_3\), 200 MHz) δ 1.25 (s, 9H), 1.44 (s, 6H), 1.6-2.1 (m, 6H), 2.70 (quin, 1H); IR ν\text{max} 1752, 1801 (C=O) cm\(^{-1}\).

2.18 Trapped Products. The alkoxyamine products (TR) were identified by: (a) HPLC relative retention times from which the size and polarity of the addend R could be assessed; (b) kinetic behaviour, since the ratios of conjugate products (e.g. \(1T/1'T\)) varied with [T] as in equation 1; (c) NMR spectra which were readily dissected into trap (T) and addend (R) components and the identity of R could be established by comparison with spectra of authentic ROH, RBr or RCl (which have very similar chemical shifts in the α- and β-positions); (d) UV
and IR (only given for C=O compounds) spectra and combustion analyses. UV spectra did not significantly vary and all products (except 11T, 11'T) in methanol had $\lambda_{\text{max}}$ (log $\varepsilon$), 216 (3.45), 257 (2.71), 264 (2.06), 270 (3.00) nm. Unusual features of the $^1$H and $^{13}$C NMR spectra arising from near and non equivalence of the trap's four methyl groups in the alkoxyamine have been previously reported$^{5,49,52,69}$ and studied.$^{15}$ The methyl protons (centred near $\delta$ 1.45) can appear as a broad singlet, a doublet, or as a triplet (6H + 3H + 3H) of variable peak broadness depending on the steric bulk and symmetry of the carbon centred group at the coupling site (e.g. the above features can be found with primary, tertiary, and some secondary alkyl groups). The splitting is temperature dependent and has been ascribed$^{15}$ to slow inversion at the nitrogen centre which is a common feature of alkoxyamines.

2-(5-Hexenoxy)-1,1,3,3-tetramethylisoindoline (1T): $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.42 (br s, 12H), 1.58 (m, 4H), 2.12 (q, 2H, 7.1 Hz), 3.94 (t, 2H, 6.3 Hz), 5.00 (m, 2H), 5.85 (m, 1H), 7.05 (m, 2H), 7.20 (m, 2H). Anal. Calcd for C$_{18}$H$_{27}$NO: C, 79.07, H, 9.95. Found: C, 78.78, H, 9.71.

2-Cyclopentylmethoxy-1,1,3,3-tetramethylisoindoline (1'T): $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.43 (br s, 12H), 1.58 (m, 4H), 1.85 (m, 4H), 2.22 (tt, 1H), 3.15 (d, 2H, 7.1 Hz), 7.08 (m, 2H), 7.11 (m, 2H). Anal. Calcd for C$_{18}$H$_{27}$NO: C, 79.07, H, 9.95; Found: C, 79.45, H, 9.91.

2-(2-Allyloxyethoxy)-1,1,3,3-tetramethylisoindoline (2T). $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.43 (br s, 12H), 3.6, (m, 2H), 4.0 (m, 4H), 5.16 (m, 1H), 5.80 (m, 2H), 7.01 (m, 2H), 7.21 (m, 2H). Anal. Calcd for C$_{17}$H$_{25}$NO$_2$: C, 74.14, H, 9.15; Found: C, 74.04, H, 8.99.

2-(3-Tetrahydrofuranmethoxy)-1,1,3,3-tetramethylisoindoline (2'T or 10'T): $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.43 (br s, 12H), 2.00 (m, 2H), 2.51 (m, 1H), 3.67 (m, 2H), 3.68-3.95 (m, 4H), 7.01 (m, 2H), 7.21 (m, 2H). Anal. Calcd for C$_{17}$H$_{25}$NO$_2$: C, 74.14, H, 9.15; Found: C, 74.43, H, 8.96.
Chapter 2: Radical Clocks

2-(3,3-Dimethylhex-5-enoxy)-1,1,3,3-tetramethylisoindoline (3T): \(^1\)H NMR

\((\text{CDCl}_3, \text{200 MHz}) \delta 0.91 \text{ (s, 6H)}, \ 1.41 \text{ (t, 2H, 7.3 Hz) overlaps with 1.44 \text{ (br s, 12H)}, \ 1.95 \text{ (d, 2H, 8.3 Hz)}, \ 3.91 \text{ (d, 2H, 7.3 Hz)}, \ 4.94 \text{ (m, 1H)}, \ 5.72 \text{ (m, 2H)}, \ 6.98 \text{ (m, 2H)}, \ 7.16 \text{ (m, 2H)}.\) Anal. Calcd for \(\text{C}_{20}\text{H}_{31}\text{NO}: \) C, 79.68, H, 10.36; Found: C, 79.36, H, 10.25.

2-(3,3-Dimethylcyclopentylmethoxy)-1,1,3,3-tetramethylisoindoline (3'T or 6'T): \(^1\)H NMR \((\text{CDCl}_3, \text{200 MHz}) \delta 1.01 \text{ (s, 6H)}, \ 1.43 \text{ (br s, 12H)}, \ 1.53-1.90 \text{ (m, 6H)}, \ 2.20 \text{ (m, 1H)}, \ 3.14 \text{ (d, 2H, 7.5 Hz)}, \ 7.02 \text{ (m, 2H)}, \ 7.11 \text{ (m, 2H)}.\) Anal. Calcd for \(\text{C}_{20}\text{H}_{31}\text{NO}: \) C, 79.68, H, 10.36; Found: C, 79.36, H, 10.25.

2-(Cyclopropanemethoxy)-1,1,3,3-tetramethylisoindoline (4T): \(^1\)H NMR \((\text{CDCl}_3, \text{200 MHz}) \delta -0.10 \text{ to 0.91 (m, 4H),} \ 1.30-1.49 \text{ (m, 13H),} \ 3.71 \text{ (d, 2H, 7.8 Hz),} \ 6.97 \text{ (m, 2H),} \ 7.13 \text{ (m, 2H)}.\) Anal. Calcd for \(\text{C}_{16}\text{H}_{23}\text{NO}: \) C, 78.32, H, 9.45; Found: C, 78.46, H, 9.44.

2-(3-Butenoxy)-1,1,3,3-tetramethylisoindoline (4'T): \(^1\)H NMR \((\text{CDCl}_3, \text{200 MHz}) \delta 1.39 \text{ (br s, 12H)}, \ 2.30 \text{ (m, 2H)}, \ 3.75 \text{ (t, 2H, 7 Hz)}, \ 4.90 \text{ (m, 2H)}, \ 5.71 \text{ (m, 1H),} \ 6.97 \text{ (m, 2H),} \ 7.13 \text{ (m, 2H).}\) Calcd for \(\text{C}_{16}\text{H}_{23}\text{NO}: \) C, 78.32, H, 9.45; Found: C, 78.54, H, 9.75.

2-(2,2-Dimethylcyclobutanemethoxy)-1,1,3,3-tetramethylisoindoline (5T): \(^1\)H NMR \((\text{CDCl}_3, \text{200 MHz}) \delta 0.92 \text{ (s, 3H)}, \ 1.11 \text{ (d, 3H, 3.4 Hz),} \ 1.41 \text{ (br s, 12H),} \ 1.4-1.8 \text{ (m, 4H),} \ 1.95 \text{ (m, 1H)}, \ 3.63-4.03 \text{ (m, 2H),} \ 7.05 \text{ (m, 2H),} \ 7.21 \text{ (m, 2H):} \) \(^{13}\)C-NMR \((\text{CDCl}_3, \text{50.1 Hz}) \delta 22.5, \ 23.5, \ 25.3, \ 30.3, \ 30.6, \ 32.1, \ 34.9, \ 38.4, \ 42.8, \ 121.6, \ 127.0, \ 145.6.\) Anal. Calcd for \(\text{C}_{19}\text{H}_{29}\text{NO}: \) C, 79.44, H, 9.15; Found: C, 79.31, H, 9.26.

2-(1,1-Dimethylpent-4-enoxy)-1,1,3,3-tetramethylisoindoline (5'T): \(^1\)H NMR \((\text{CDCl}_3, \text{200 MHz}) \delta 1.26 \text{ (2s, 9H),} \ 1.31 \text{ (s, 3H),} \ 1.46 \text{ (s) overlaps 1.48 \text{ (t, 7 Hz, total 8H),} \ 2.20 \text{ (m, 2H),} \ 4.95 \text{ (m, 2H),} \ 5.72 \text{ (m, 1H),} \ 7.21 \text{ (m, 2H).}\) Anal. Calcd for \(\text{C}_{19}\text{H}_{29}\text{NO}: \) C,
79.44, H, 9.15; Found: C, 79.71, H, 8.98.

2-(2,2-Dimethylhex-5-enoxy)-1,1,3,3-tetramethylisoindoline (6T): $^1$H NMR

(CDC$_3$, 200 MHz) $\delta$ 0.95 (s, 6H), 1.35-1.49 (m, 14H), 2.01 (m, 2H), 3.81 (s, 2H), 4.95 (m, 2H), 5.8 (m, 1H), 7.01 (m, 2H), 7.14 (m, 2H). Anal. Calcd for C$_{20}$H$_{31}$NO: C, 79.68, H, 10.36; Found: C, 79.62, H, 10.08.

2-(2,2-Dimethylbut-3-enoxy)-1,1,3,3-tetramethylisoindoline (7T): $^1$H NMR

(CDC$_3$, 200 MHz) $\delta$ 1.05 (s, 6H), 3.82 (s, 2H), 4.8-5.1 (m, 2H), 5.91 (dd, 1H, 17 Hz/10 Hz), 6.98 (m, 2H), 7.10 (m, 2H). Anal. Calcd for C$_{18}$H$_{27}$NO: C, 79.07, H, 9.95; Found: C, 78.78, H, 9.71.

2-(1,1-Dimethylbut-3-enoxy)-1,1,3,3-tetramethylisoindoline (7'T): $^1$H NMR

(CDC$_3$, 200 MHz) $\delta$ 1.22 (s, 3H), 1.31 (s, 3H), 1.40 (s, 6H), 1.51 (br s, 6H), 2.36 (d, 2H), 5.05 (m, 2H), 5.9 (m, 1H), 7.01 (m, 2H), 7.20 (m, 2H). Anal. Calcd for C$_{18}$H$_{27}$NO: C, 79.07, H, 9.95; Found: C, 79.45, H, 9.91.

2-(2-Allyloxy-1-methylethoxy)-1,1,3,3-tetramethylisoindoline (8T): $^1$H NMR

(CDC$_3$, 200 MHz) $\delta$ 1.26 (d, 3H, 8.1 Hz), 1.33 and 1.53 (d + br s, 6H), 3.40 (m, 1H), 3.60 (m, 1H), 4.05 (m, 3H), 5.2 (m, 2H), 5.95 (m, 1H), 7.00 (m, 2H), 7.12 (m, 2H). Anal. Calcd for C$_{18}$H$_{27}$N$_2$O$_2$: C, 74.70, H, 9.40; Found: C, 74.65, H, 9.38.

2-(4-Methyl-3-tetrahydrofuranmethoxy)-1,1,3,3-tetramethylisoindoline (8'T). Cis and trans 8'T could not be preparatively separated (Columns #2 or #3) but adequate analytical separation on column #1 was achieved at high retention times. By the use of the assignments for 4-methyltetrahydrofuran-3-methanol by Bogner et al as a guide, the NMR spectrum of the mixture could be analysed: $\delta$ (CDCl$_3$, 200 MHz) cis 1.05 (d, CH$_3$, 6.8 Hz), 1.44 (br s, 4 CH$_3$), 2.53-2.65 (m, 2CH), 3.47 (m, 2 ring cis-CHH), 3.7-4.1 (m, 2 ring trans-CHH + CH$_2$OH), 7.10 (m, 2 ArH), 7.23 (m, 2 ArH); trans 1.12 (d, CH$_3$, 6.3 Hz), 1.44 (br s, 4CH$_3$), 2.00-2.25 (m, 2 CH), 3.36 (m, ring cis-CHH), 3.61 (m, ring trans-CHH).
trans-CHH), 3.8-4.1 (m, 2 ring CHH + CH₂OH), 7.10 (m, 2 ArH), 7.23 (m, 2 ArH). NMR integration of the separable resonances was consistent with a cis to trans ratio at about 2.5.


2-(2-Allyloxy-1,1-dimethylethoxy)-1,1,3,3-tetramethylisoindoline (9T):

¹H-NMR (CDCl₃, 200 MHz) δ 1.29 (s, 6H), 1.23, 1.31, 1.46 (3s, 12H), 3.36 (s, 2H), 3.99 (dt, 2H), 5.08-5.28 (m, 2H), 5.78-5.97 (m, 1H), 7.10 (m, 2H), 7.21 (m, 2H). Anal. Calcd for C₁₉H₂₉N₀₂: C, 75.21, H, 9.63; Found: C, 75.49, H, 9.31.

2-(4,4-Dimethyl-3-tetrahydrofuranmethoxy)-1,1,3,3-tetramethylisoindoline (9'T):

¹H NMR (CDCl₃, 200 MHz) δ 1.03 (s, 3H), 1.13 (s, 3H), 1.21-1.55 (br m, 12H), 2.27 (m, 1H), 3.39-4.16 (m, 6H), 7.08 (m, 2H), 7.19 (m, 2H). Anal. Calcd for C₁₉H₂₉N₀₂: C, 75.21, H, 9.63; Found: C, 75.61, H, 9.72.

2-(3-Butenoxymethoxy)-1,1,3,3-tetramethylisoindoline (10T):

¹H NMR (CDCl₃, 200 MHz) δ 1.43 (br s, 12H), 2.15 (m, 2H), 3.67 (t, 2H, 7.8 Hz), 4.91-5.21 (m, 2H), 5.75-6.00 (m, 1H), 6.12 (s, 2H), 7.11 (m, 2H), 7.21 (m, 2H). Anal. Calcd for C₁₇H₂₅N₀₂: C, 74.14, H, 9.15; Found: C, 74.41, H, 9.27.

2-Phenylacetoxy-1,1,3,3-tetramethylisoindoline (11T).

Plates from hexane, mp 67-69°C: ¹H NMR (CDCl₃, 200 MHz) δ 1.35 (br s, 12H), 3.77 (s, 2H), 7.05-7.31 (m, 9H); IR νmax 1770, 1720 (C=O) cm⁻¹; UV λmax (log ε) (MeOH), 224 (3.21), 257 (2.93), 264 (3.05), 270 (3.04) nm.

2-Benzylloxy-1,1,3,3-tetramethylisoindoline (11'T).

Plates from aqueous MeOH, mp 90°-91°C (lit. mp 89-91°C) with all spectral data as previously reported. HPLC co-injection showed that 10T and 10'T had identical response factors at 270 nm (about 5% larger than 'alkyl' products).

tert-Butyl 1,1,3,3-Tetramethyisoindolin-2-yl Carbonate (12T). Plates from
aqueous EtOH, mp 61-63°C: \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.41 (s, 6H), 1.51 (s, 6H), 1.53 (s, 9H), 7.10 (m, 2H), 7.21 (m, 2H). IR \(v_{\text{max}}\) 1778, 1750 (C=O) cm\(^{-1}\). Anal. Calcd for C\(_{17}\)H\(_{25}\)N\(_3\)O\(_3\): C, 70.07, H, 8.65, N, 4.81; Found: C, 69.82, H, 8.46, N, 4.47.

**2-tert-Butyl-1,1,3,3-tetramethylisoindoline (12'T):** \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.30-1.52 (m, 21H), 7.05 (m, 2H), 7.23 (m, 2H). Anal. Calcd for C\(_{16}\)H\(_{25}\)N\(_3\): C, 77.69, H, 10.19; Found: C, 77.50, H, 9.90.

**1-Cyclobutyl-1-methylethyl-1,1,3,3-tetramethylisoindolin-2-yl Carbonate (13T).** Plates from pentane, mp 71°C: \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.38 (s, 6H), 1.43 (s, 6H), 1.49 (2, 6H), 1.60-2.10 (m, 6H), 2.70 (quin, 1H), 7.09 (m, 2H), 7.24 (m, 2H); IR \(v_{\text{max}}\) 1773, 1748 (C=O) cm\(^{-1}\). Anal. Calcd for C\(_{20}\)H\(_{29}\)N\(_3\)O\(_3\): C, 71.44, H, 9.15, N, 4.38; Found: C, 71.11, H, 8.94, N, 4.05.

**2-(1-Cyclobutyl-1-methylethyl)-1,1,3,3-tetramethylisoindoline (13'T):** \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.25 (br s, 6H), 1.36 (s, 6H), 1.57 (br s, 6H), 1.4-2.1 (m, 6H), 2.50 (quin, 1H, 7.3 Hz), 7.06 (m, 2H); IR \(v_{\text{max}}\) 2970, 2915, 2960, 1373, 1360, 910 cm\(^{-1}\). Anal. Calcd for C\(_{19}\)H\(_{29}\)NO: C, 79.39, H, 10.17; Found: C, 79.17, H, 10.28.

**Allyl 2-Chloro-2-methylpropyl Ether (14).** Chloroacetic acid (11.7 g) in allyl alcohol (30 ml) was added to a solution of Na (7.5 g) in allyl alcohol (60 mL) at a rate which maintained reflux. 2 hr reflux, neutralization (CO\(_2\)), evaporation, acidification, ether isolation, and distillation afforded allyloxyacetic acid (10.5 g, 74%), bp 81-83°C at 1.0 mm. The acid was converted to the methyl ester with BF\(_3\) in methanol\(^{127}\) then converted with excess MeMgl to 1-Allyloxy-2-methylpropan-2-ol (70% from the acid), bp 75-79°C at 15 mm. \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.20 (s, 6H), 2.42 (s, 1H), 3.22 (s, 2H), 3.99 (d t, 2H), 5.15 (m, 2H), -5.82 (m, 1H). Attempts to make the bromide with conc. HBr and PBr\(_3\) at low temp. failed due to cleavage of the ether. However, treatment of the alcohol at 0°C with conc. HCl/CaCl\(_2\) gave the title chloride (52%), bp 50-52°C at 50 mm, GC purity 96%. \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.55 (s, 6H), 3.44 (s, 2H), 4.02 (d,2H), 5.19 (m, 2H), 5.84 (m, 1H).
2.19 Reaction of 14 with Tributylstannane. Mixtures of tributylstannane (10 mol. equiv.), 14, and a trace of initiator in benzene were heated and analysed by capillary GC (60° to 200° at 10° per min gave baseline separation of all components) following procedures detailed elsewhere. Reproducible kinetic data were difficult to obtain because of the high reactivity towards hydrostannylation of the double bond in 14 and 15. However, slow initiation (with only a trace of AIBN below or di-tert-butyl peroxide above 80°C), short reaction times, and high GC injection port temperature improved the precision. Retention times and kinetic data are given in Sup. Table 2.13.

It has been established through labelling and other products that the migrations occur via distinct cyclopropylmethyl (CPM) radical intermediates (1 and 11). However, unless they are specially stabilized (CP 4), the CPM radicals react very rapidly so that they have much shorter lifetimes than the vinyl and oxy radicals (1). The effect of this is that often the CPM radicals are not isolated as products nor are they detected in ESR studies. Consequently, they are best treated as intermediate species e.g., Scheme 3.2 (in which 1 is the unknown intermediate).

Rearrangements of heterocyclic radicals are very sensitive to conformational influences since the gem dimethyl substituted radical 1e is better than but-3-enyl (1a) and effects of similar magnitude may be seen in rearrangement reactions of cyclic homocyclic radicals. In the present systems, effects such as migration, β-fission rates of the intermediate CPM radicals (12) are measured. β-Fissions of these radicals are often very rapid and difficult in these systems.
CHAPTER THREE
Ring Substituted Cyclopropylmethyl Radicals

Introduction

1,3-Vinyl migrations, both planned and adventitious, are common in free radical chemistry and have been the subject of numerous studies over the last thirty years. Practical interest in these rearrangements has recently been intensified by synthetic and mechanistic studies of the ring-closure reactions of suitably constituted vinyl radicals: addition of vinyl radicals to double bonds produces homoallylic radicals which are converted directly into stable products or which rearrange further according as the reaction conditions.

It has been established through labelling and other product studies that 1,3-vinyl migrations occur via distinct cyclopropylmethyl (CPM) radical intermediates (e.g. Scheme 3.1). However, unless they are specially stabilized (Ch 4), the CPM radicals ring open very rapidly so that they have much shorter life-times than the corresponding homoallylic radicals. The effect of this is that often the CPM radicals neither give rise to appreciable products nor are they detected in ESR studies. Consequently, such rearrangements may be treated as one step reactions e.g. Scheme 3.2 (in which $k_v$ is the ‘vinyl migration’ rate constant).

Rearrangements of homoallylic radicals are very sensitive to substitution, for instance the gem dimethyl substituted radical 1c rearranges some hundreds of times faster than but-3-enyl (1a) and effects of similar magnitude may be expected in the ring contraction/expansion reactions of cyclic homoallylic radicals. In order to clearly define these substituent effects and thus help to predict the outcome of reactions involving plausible vinyl migration, $\beta$-fission rates of the intermediate CPM radicals (2) are required. However $\beta$-fissions of these radicals are often very rapid and difficult to measure e.g. Castaing et al.
Scheme 3.1 Homoallylic Radical Rearrangements.

\[
(1-CO_2)_2 \xrightarrow{k_1+k_c} R_1 R_2 \xrightarrow{k_3} R_1 R_2
\]

Scheme 3.2 Vinyl Migration.

Scheme 3.3 Kinetic Scheme for Homoallylic Rearrangement in the Presence of T

a, \(R_1 = R_2 = H\)
b, \(R_1 = R_2 = D\)
c, \(R_1 = R_2 = Me\)
d_{cis}, \(R_1 = Me\), \(R_2 = H\)
d_{trans}, \(R_1 = H\), \(R_2 = Me\)
e, \(R_1 = H\), \(R_2 = CO_2Et\)
Chapter 3: Cyclopropylmethy1 Rearrangements

found that reduction by neat tributylstannane did not effectively compete with the ring opening of radicals $2d^{cis}$ or $2d^{trans}$ at 40°C and that steady-state ESR also failed to detect unrearranged radicals down to -140°C.

The nitroxyl radical $T$ couples with alkyl radicals with a bimolecular rate constant $k_T$ of about $1 \times 10^9 \text{ M}^{-1} \text{s}^{-1}$ over a wide temperature range. In Chapter Two the coupling of $T$ to $2a$ was found to compete effectively with the latter's ring opening reaction (Scheme 3.3). The unrearranged and rearranged alkoxyamine products (6a and 7a = 5a) could be resolved and quantified to give the ring opening rate constant. In this chapter radical-trapping is used to calibrate the $\beta$-fission reactions of ring substituted CPM radicals $2c$, $2d^{cis}$, $2d^{trans}$, and $2e$ and complete kinetic parameters for homoallylic rearrangements of $1c$ are reported.

Results and Discussion

3.1 Generation and Trapping of Radicals 4c-e. Solutions of diacyl peroxides 4c-e and $T$ (10 mol equiv) in cyclohexane were degassed and sealed in pyrex ampoules then heated in thermostatted baths for the required reaction times, viz. 18 hr at 60°C or 1 hr at 100°C. The product mixtures were resolved and quantitated by Reversed Phase HPLC with UV detection (270 nm) as specified in the previous chapter.

At the high nitroxide concentrations $[T]$ that were required to trap the initially formed CPM radicals before ring opening, peroxides 4c-4e reacted mainly through a nitroxide induced decomposition pathway (Ch.1.5), i.e.

$$T + \text{RCO}_2\text{H}_2 \rightarrow R^* + \text{CO}_2 + \text{RCO}_2\text{H} + 8$$  \hspace{1cm} (3.1)

$$R^* + T \rightarrow R-T$$  \hspace{1cm} (3.2)

In the HPLC analysis a manifold of minor products was eluted just before and after $T$; these probably arose from eq 3.1 and from subsequent reactions of 8 (e.g. radical addition followed by nitroxide decay - Ch.1.5). However, with the large excess of $T$ employed for kinetic determinations by-products from these reactions did not interfere with HPLC analysis of the 'kinetic' products.
It is conceivable that induced decomposition may produce alkoxyamines, e.g. 6, without the intermediacy of dissociated radicals. However, this hypothesis was precluded by the 'correct' kinetic response (viz. eq 2.1) of the product ratios to changes in trap concentration [T], e.g. $6/7 \propto [T]$ over a range of [T]. For 2a$^{57}$ (Ch.2.2) it could be established that the product ratios did not depend on whether a diacyl peroxide (4a) or tert-buty1 perester (or hydroxydiazene$^{63}$) was used to generate the radicals. Unfortunately the tert-buty1 peresters were not useful sources of radicals 2c or 2d in cyclohexane because the trapped cyclohexyl radical (CHT), which was formed by solvent reaction of the tert-butoxy radical, could not be separated from the desired products (e.g. 7c was coeluted with CHT).

The problem of by-products from solvent reactions could be overcome, or at least mitigated, by the addition of 1,4-cyclohexadiene as a co-solvent. The latter undergoes rapid reaction with tert-butoxy radicals (but is much less reactive with alkyl radicals) to afford resonance stabilized cyclohexadienyl radicals; these undergo a disproportionation rather than a coupling reaction with T so that the only solvent derived products are the reduced trap T-H and benzene.

\[
\begin{align*}
\text{RCO}_2\text{Bu}^' & \rightarrow \text{R}^+ + \text{t-Bu-O}^- \\
\text{R}^+ + \text{T} & \rightarrow \text{R-T} \\
\text{t-Bu-O}^+ + \text{H-C}_6\text{H}_4\text{H} & \rightarrow \text{H-C}_6\text{H}_4\text{H} + \text{t-Bu-OH} \\
\text{H-C}_6\text{H}_4\text{H} + \text{T} & \rightarrow \text{C}_6\text{H}_6 + \text{T-H}
\end{align*}
\]

When solutions of the appropriate perester (2c-CO$_2$OBu$^'$ or 2d-CO$_2$OBu$^'$), T (10 mol. equiv.) and 1,4-cyclohexadiene (10% v/v) in benzene were degassed, heated (100°C) and analyzed in the usual manner, product mixtures consistent with the reaction scheme shown above were obtained. The reduced trap T-H was rapidly oxidized to T on exposure to air$^{135}$ but could be identified by HPLC coinjection of authentic 2-hydroxy-1,1,3,3-tetramethyliso-indoline freshly prepared by admixture of ascorbic acid and T in aqueous methanol under
nitrogen. It was found that under these conditions 1,4-cyclohexadiene had no appreciable
effect on product distributions from the diacyl peroxides, i.e. it did not compete with T for the
alkyl radicals. And most importantly, the choice of precursor had no apparent effect on the
observed molar product ratios, viz. \([5]/[6]\) or \([7]/[6]\) (the suffices \(a\), etc. are implicit here and
below).

### 3.2 Kinetic Equations

With steady-state radical concentrations, irreversibility of
\(2 \rightarrow 3\), and pseudo first-order conditions (i.e. a large excess of \(T\)) the relationships eq 3.3, eq
3.4 and eq 3.5 between the alkoxyamine product ratios and the rate constants in Schemes 3.2
and 3.3 can be derived (Appendices A2.3 and A2.4).

\[
\frac{[6]}{[5]} = \frac{k_T}{k_1} \left[ \frac{k_c}{k_T} + [T] \right] 
\]  
(3.3)

\[
\frac{[6]}{[7]} = \frac{k_T}{k_3} [T] 
\]  
(3.4)

\[
\frac{[7]}{[5]} = \frac{k_3}{k_1} \left[ 1 + \frac{k_c}{k_T} [T] \right] 
\]  
(3.5)

Where \(k_T'\) and \(k_T\) are the trapping rate constants of radicals 1 and 2 respectively (radicals 1, 2
and 3 correspond to alkoxyamines 5, 6 and 7 respectively, suffixes \(a, b\), etc. are implicit).

It follows from the definition of \(k_r\) indicated by Scheme 3.2 that \([7]/[5] = (k_r/k_T)[T]^{-1}\); when
this is substituted into the full kinetic equation for Scheme 3.3 (cf. Appendix A2.5) we
obtain the relationship between the cyclization and vinyl migration rate constants, i.e.

\[
k_c = k_r \left[ 1 + \frac{k_1}{k_3} \right] 
\]  
(3.6)

### 3.3 2,2-Dimethylcyclopropylmethyl Radical (2c)

HPLC analysis of reactions of \(4c\) with \(T\) (10 mol. equiv) in cyclohexane at 60°C revealed the alkoxyamine
products \(5c, 6c\) and \(7c\) in the ratios listed in Table 3.1. Yields, based on the usual
stoichiometry for peroxide decay, were low (30-45%) reflecting the extensive nitroxide
induced decay and (at low \([T]\)) polar decomposition which is prevalent in
Chapter 3: Cyclopropylmethyl Rearrangements

Di(cyclopropaneacetyl) peroxides.\textsuperscript{78,136}

Table 3.1. Kinetic Data for 2c at 60°C\textsuperscript{a}

<table>
<thead>
<tr>
<th>[T], mM</th>
<th>6c/5c</th>
<th>7c/5c</th>
<th>6c/7c</th>
<th>k_{3}/k_{T}, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>271</td>
<td>1.00</td>
<td>7.7</td>
<td>0.139</td>
<td>1.9</td>
</tr>
<tr>
<td>270</td>
<td>1.08</td>
<td>7.6</td>
<td>0.152</td>
<td>1.8</td>
</tr>
<tr>
<td>144</td>
<td>0.50</td>
<td>7.8</td>
<td>0.072</td>
<td>2.1</td>
</tr>
<tr>
<td>72</td>
<td>0.32</td>
<td>8.5</td>
<td>0.038</td>
<td>1.8</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td></td>
<td></td>
<td>35.9</td>
<td></td>
</tr>
</tbody>
</table>

Linear regression analysis gives:

\[ 6c/5c = 0.015 + 3.8 \text{[T]}, \langle r \rangle = 0.990 \]
\[ 7c/5c = 6.81 + 0.13 \text{[T]}^{-1}, \langle r \rangle = 0.999. \]

\textsuperscript{a} ±0.3°C, cyclohexane. \textsuperscript{b} Corrected for thermal expansion and consumption of the nitroxide. \textsuperscript{c} Calculated from data of the previous column with eq 3.5.

Molar ratios of ring opened to closed products in Table 3.1, e.g. [6c]/[5c], show linear relationships to [T] whereas the ratio of ring opened products [7c]/[5c] is roughly constant at high [T] but rises rapidly when the trap concentration is reduced below about 20 mM. This behaviour is consistent with Scheme 3.3 and the known rapid rearrangement (vinyl migration) of 1c into 4c\textsuperscript{57,107,132} (Ch.2). That is to say, at high quenching rates (high [T]) the product ratios reflect the kinetics of ring fission and, as might be expected, ring fission to tertiary alkyl radical 3c is substantially favoured over fission to primary alkyl radical 1c. With very low concentrations of T, radicals are quenched much more slowly and 1c has time to rearrange back through 2c to 3c and this is reflected by the increase in [7c]/[5c].

Relative rearrangement rates can be calculated by linear regression or graphical analysis of the data as suggested by kinetic equations 1-3. For example, the slope (b) and abscissa (a) of a plot of [7c]/[5c] against the reciprocal trap concentration [T]\textsuperscript{-1} at 60°C (Figure 3.1) gives: \( k_{c}/k_{T'} = b/a = 0.019 \text{ M} \), and \( k_{3}/k_{1} = a = 6.81 \). Similar treatment of other data in Table 3.2 gives \( k_{1}/k_{T} = 0.26 \text{ M} \) (by eq 1), and \( k_{3}/k_{T} = 1.9 \pm 0.2 \text{ M} \) (eq 2).
Figure 3.1. $7c/5c$ versus $[T]^{-1}$ at 60°C

$7c/5c = 6.81 - 0.13 [T]^{-1}$, $r > 0.999$
### Table 3.2. Hydroxylamine Yields for Rearrangements of 2c, 2d<sup>cis</sup> and 2d<sup>trans</sup>,a

<table>
<thead>
<tr>
<th>rearrangement&lt;sup&gt;b&lt;/sup&gt;</th>
<th>temp, °C&lt;sup&gt;c&lt;/sup&gt;</th>
<th>[T], mM&lt;sup&gt;d&lt;/sup&gt;</th>
<th>6, %&lt;sup&gt;e&lt;/sup&gt;</th>
<th>5, %&lt;sup&gt;e&lt;/sup&gt;</th>
<th>7, %&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c →</td>
<td>60</td>
<td>271</td>
<td>0.48</td>
<td>0.48</td>
<td>3.45</td>
</tr>
<tr>
<td>1c + 3c</td>
<td>60</td>
<td>270</td>
<td>0.54</td>
<td>0.50</td>
<td>3.54</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>144</td>
<td>0.24</td>
<td>0.48</td>
<td>3.47</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>72</td>
<td>0.16</td>
<td>0.48</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>18</td>
<td>–</td>
<td>0.32</td>
<td>4.19</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>4.5</td>
<td>–</td>
<td>0.12</td>
<td>4.31</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>256</td>
<td>0.30</td>
<td>0.98</td>
<td>5.70</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>137</td>
<td>0.15</td>
<td>0.94</td>
<td>6.01</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>68</td>
<td>–</td>
<td>0.58</td>
<td>5.27</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>18</td>
<td>–</td>
<td>0.18</td>
<td>5.31</td>
</tr>
<tr>
<td>2d&lt;sup&gt;cis&lt;/sup&gt; →</td>
<td>59</td>
<td>273</td>
<td>1.69</td>
<td>1.23</td>
<td>5.19</td>
</tr>
<tr>
<td>1d + 3d</td>
<td>59</td>
<td>145</td>
<td>0.82</td>
<td>1.02</td>
<td>4.32</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>71</td>
<td>0.35</td>
<td>1.04</td>
<td>4.68</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>9.0</td>
<td>–</td>
<td>1.11</td>
<td>5.01</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>4.5</td>
<td>–</td>
<td>0.86</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>0.90</td>
<td>–</td>
<td>0.51</td>
<td>2.86</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>256</td>
<td>0.67</td>
<td>1.35</td>
<td>4.93</td>
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<tr>
<td></td>
<td>100</td>
<td>138</td>
<td>0.32</td>
<td>1.21</td>
<td>4.41</td>
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<td></td>
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<td>4.5</td>
<td>–</td>
<td>0.78</td>
<td>3.52</td>
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<tr>
<td></td>
<td>100</td>
<td>0.85</td>
<td>–</td>
<td>0.45</td>
<td>3.61</td>
</tr>
<tr>
<td>2d&lt;sup&gt;trans&lt;/sup&gt; →</td>
<td>59</td>
<td>271</td>
<td>3.94</td>
<td>4.67</td>
<td>5.39</td>
</tr>
<tr>
<td>1d + 3d</td>
<td>59</td>
<td>143</td>
<td>1.82</td>
<td>4.52</td>
<td>4.71</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>72</td>
<td>1.21</td>
<td>5.42</td>
<td>6.01</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>9.0</td>
<td>–</td>
<td>4.54</td>
<td>5.18</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>4.6</td>
<td>–</td>
<td>4.30</td>
<td>5.24</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>0.90</td>
<td>–</td>
<td>0.51</td>
<td>3.07</td>
</tr>
<tr>
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<td>100</td>
<td>255</td>
<td>0.86</td>
<td>3.45</td>
<td>4.79</td>
</tr>
<tr>
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<td>100</td>
<td>139</td>
<td>0.42</td>
<td>3.04</td>
<td>4.31</td>
</tr>
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<td>100</td>
<td>67</td>
<td>0.20</td>
<td>2.87</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>8.4</td>
<td>–</td>
<td>2.62</td>
<td>4.02</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>4.2</td>
<td>–</td>
<td>1.91</td>
<td>3.41</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.84</td>
<td>–</td>
<td>0.72</td>
<td>2.18</td>
</tr>
</tbody>
</table>

<sup>a</sup> In cyclohexane solvent.  <sup>b</sup> Radical N couples with T to give hydroxylamine N + 4.  <sup>c</sup> ±0.3°C  <sup>d</sup> Corrected for thermal expansion and for consumption of the nitroxide.  <sup>e</sup> Percentages of the total HPLC area; actual yields were in the range 20-45% based on two radicals per peroxide molecule.
### Table 3.3 Kinetic Data\(^a\) for Rearrangements of Radicals 2a-2c, 2d\(^{cis}\) and 2d\(^{trans}\)

<table>
<thead>
<tr>
<th>Rearrangement</th>
<th>log (A/s(^{-1})) (^e)</th>
<th>E (kcal/mol) (^e)</th>
<th>(k^{80\circ} (10^6 s^{-1})) (^f)</th>
<th>(k^{25\circ} (10^6 s^{-1})) (^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a→1a (^b)</td>
<td>13.3</td>
<td>7.4</td>
<td>520</td>
<td>75</td>
</tr>
<tr>
<td>1b→2b (^c)</td>
<td>10.2</td>
<td>8.8</td>
<td>0.06</td>
<td>0.006</td>
</tr>
<tr>
<td>2c→1c</td>
<td>13.3</td>
<td>7.2</td>
<td>690</td>
<td>105</td>
</tr>
<tr>
<td>2c→3c</td>
<td>13.5</td>
<td>6.3</td>
<td>4000</td>
<td>760</td>
</tr>
<tr>
<td>1c→2c (^d)</td>
<td>11.6</td>
<td>6.5</td>
<td>36</td>
<td>6.8</td>
</tr>
<tr>
<td>1c→3c (^d)</td>
<td>11.7</td>
<td>6.5</td>
<td>41</td>
<td>7.9</td>
</tr>
<tr>
<td>2d(^{cis})→1d</td>
<td>12.7</td>
<td>6.5</td>
<td>470</td>
<td>85</td>
</tr>
<tr>
<td>2d(^{cis})→3d</td>
<td>13.0</td>
<td>6.1</td>
<td>1700</td>
<td>330</td>
</tr>
<tr>
<td>2d(^{trans})→1d</td>
<td>13.5</td>
<td>7.5</td>
<td>720</td>
<td>100</td>
</tr>
<tr>
<td>2d(^{trans})→3d</td>
<td>14.1</td>
<td>8.3</td>
<td>910</td>
<td>103</td>
</tr>
<tr>
<td>1d→3d (^e)</td>
<td>10.3</td>
<td>7.7</td>
<td>0.34</td>
<td>0.045</td>
</tr>
<tr>
<td>1d→2d(^{trans}) (^f)</td>
<td>10.6</td>
<td>7.7</td>
<td>0.68</td>
<td>0.09</td>
</tr>
</tbody>
</table>

\(^a\) Calculated from relative yield data of Table 3.2 with log \(k_T = 9.7 - 0.9/\theta\) except; \(^b\) see Ch 2, \(^c\) ESR data of Effio \textit{et al} (ref 133), and \(^d\) calculated from data in Sup. Table 2.7 with log \(k_T^{1c} = 9.6 - 0.9/\theta\) (see text and ref 41). \(^e\) Data from Table 3.2 yields approximate Arrhenius coefficients only and may only be accurate within the range 60\(-\)100°C. \(^f\) Calculated from the temperature variation equations. \(^g\) 2d\(^{trans}\) is assumed to be the major pathway between 1d and 3d (see text).
Laser flash photolysis \textsuperscript{41} and radical clock \textsuperscript{57} calibrations have shown that \( k_T \) is not very sensitive to radical stability or geometry at least to the benzyl or tertiary alkyl radical level so that the assumption that \( k_T (2e) = k_T (\text{hex-5-enyl}) \textsuperscript{57} = 1.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} \) at 60°C is unlikely to incur serious error.\textsuperscript{133-137} However, a small correction to \( k_T' (1c) \) for steric factors does appear to be justified by the laser flash photolysis results, i.e. \( k_T (\text{nonyl}) = 1.28 (\pm 0.16) k_T (\text{neopentyl}) \) for trapping with TEMPO at 20°C in isooctane. On these grounds, I have chosen \( k_T (2e) = 1.3 k_T' (1c) \) with a temperature variation represented by \( \log k_T (2e) = 9.7 - 0.9/\theta (\theta = 2.3 \text{ RT kcal/mol}) \textsuperscript{57} \) to derive the absolute rate constants for rearrangements of 2e (and 1c), viz.: \( k_1 = 3.5 \times 10^8 \text{ s}^{-1} \), \( k_3 = 2.4 \times 10^9 \text{ s}^{-1} \), \( k_c = 2.2 \times 10^7 \text{ s}^{-1} \), and \( k_T = 1.9 \times 10^7 \text{ s}^{-1} \) at 60°C.

In the kinetic scheme above \( k_r \) was deduced indirectly, i.e. from a slope to intercept ratio, and thus the value is liable to compounded random and systematic errors. A more precise value for \( k_r \) was established by calibration of the 'authentic' vinyl migration \( 1c \rightarrow 3c \) (Scheme 3.2) by the radical-trapping method (cf. Chapter Two). Product ratios and kinetic data obtained by thermolysis of bis-(3,3-dimethylpent-4-enoyl) peroxide [(1c-CO\textsubscript{2})\textsubscript{2}] with excess T over a range of temperatures are given in Sup. Table 2.7.\textsuperscript{138} At 60°C, this calibration gives \( k_r = 2.3 \times 10^7 \text{ s}^{-1} \) which is in good agreement with the indirect value deduced above and thus engenders confidence in the more direct kinetic data for the ring fission rate constants \( k_1 \) and \( k_3 \). Similar treatment of data obtained at 106°C for 2c affords the approximate Arrhenius parameters given in Table 3.3; the cyclization rate constants were derived by adjustment of the vinyl migration data in Sup. Table 2.7 with eq 4, i.e. \( k_c = 1.15 k_r \) in this temperature range.

The equilibrium constant between 1c and 2c can be calculated from the reaction rates in forward and reverse directions e.g. \( K_{12} = k_c/k_1 = 0.07 \) at 60°C. The Arrhenius expression for \( K_{12} \), i.e. \( \log K_{12} = -1.6 + 0.7/\theta \), indicates that the ring closure reaction (1c \( \rightarrow \) 2c) is slightly exothermic (\( \Delta H^\circ = -0.7 \text{ kcal/mol} \)) but is, in fact, unfavourable owing to the relatively low entropy of the ring closed form (\( \Delta G^\circ = +1.5 \text{ kcal/mol}, \Delta S^\circ = -7.3 \text{ eu} \)). This contrasts with the estimated thermodynamics for ring closure of but-3-enyl (Table 3.4) which is estimated to be endothermic by \( ca. 1.7 \text{ kcal/mol} \) (with \( \Delta G^\circ = +5.8 \text{ kcal/mol}, \Delta S^\circ = -11.8 \text{ eu} \)).\textsuperscript{139} Features of this reaction are further examined below.
In addition to being the thermodynamically favoured reaction, ring fission to 3c should be favoured by the relief of steric repulsion between the radical centre and the cis methyl group and perhaps further enhanced by stereoelectronic factors, i.e. non-bonded interactions between the radical methylene group and the cis methyl group are probably larger in the transition state leading to 1c.

The sum of these factors might be expected to give rise to a larger selectivity for the ring opening than is suggested by the radical-trapping data (5:1). To this extent, the kinetic data for 2c may be seen to reflect the more obvious anomaly in the ring fission of 2d\textsuperscript{trans} and perhaps may be rationalized on the same basis (vide infra).

### 3.4 Cis and Trans 2-Methylcyclopropylmethyl Radicals (2d\textsuperscript{cis} and 2d\textsuperscript{trans})

Castaing et al\textsuperscript{134} made the interesting disclosure that whereas 2d\textsuperscript{cis} gives mostly the thermodynamically expected secondary alkyl radical 3d at -125\degree C and -70\degree C (1d:3d = 0.20 and 0.25 respectively by ESR signal integration), the trans radical (2d\textsuperscript{trans}) rearranged mainly to the primary radical (1d) at -115\degree C (1d:3d = 4.0 by ESR). Further investigation of 2d\textsuperscript{trans} by tributylstannane reduction\textsuperscript{134} of the appropriate halide revealed that the β-fission rates were about equal (k\textsubscript{1} = k\textsubscript{3}) at 25\degree C to 45\degree C. In the same experiments the use of a low stannane concentration (0.01 M mean) showed that under conditions of slow radical quenching, the products consisted almost entirely of reduced 3d (i.e. [3d-H]/[1d-H] = 15); this confirms that 3d is the thermodynamically favoured species and that ring opening to this radical is practically irreversible (an assumption made in the derivation the kinetic equations).

Rearrangements of 2d\textsuperscript{cis} and trans were studied by the experimental and kinetic analysis methods described for radical 2c. The kinetic data summarized in Tables 3.3 and 3.4...
are consistent with Castaing et al's data. Combination of the low temperature ESR data with the radical-trapping data gives eq 3.7 and eq 3.8 \((\theta = 2.3 \, RT \text{ kcal/mol})\).

for \(2d_{cis}\)

\[
\log \left( \frac{k_1}{k_3} \right) = -0.4 - 0.2/\theta
\]  

(3.7)

for \(2d_{trans}\)

\[
\log \left( \frac{k_1}{k_3} \right) = -0.6 + 0.9/\theta.
\]  

(3.8)

Eq 3.8 implies an isokinetic temperature at about 60°C for fission of the trans radical, i.e. above 60°C it opens mostly to the secondary radical \(3d\) but below 60°C ring fission affords mainly \(1d\). Thus if the rearrangement had been studied only at ordinary temperatures, the unusual selectivity manifested at low temperatures may not have been suspected.

Eq 3.7 and eq 3.8, which are derived from a wide temperature range, suggest a slight entropic preference for fission to the secondary radical \((3d)\) in both cases; i.e. \(\Delta S^\ddagger(3d-1d)\) = \(\Delta S^\ddagger(2d\rightarrow 3d) - \Delta S^\ddagger(2d\rightarrow 1d)\) = 2-3 eu. This is surprising in view of the calculated relative product radical entropies (viz. \(\Delta S^\ddagger(3d) - \Delta S^\ddagger(1d)\) = -1 eu)\(^2\) and the expectation of an earlier (= tighter) transition state for fission to \(3d\) (because this fission is the more exothermic).

The different selectivities for ring-fission of the cis and the trans species are probably the result non-bonded interactions between the eclipsed exocyclic groups in \(2d_{cis}\); the difference between eq 3.8 from eq 3.7 is a measure of the amount of strain energy caused by this interaction, viz. 1.1 kcal/mol.

The reason that \(2d_{trans}\) opens preferentially to the primary radical \(1d\) under kinetic control is not immediately obvious; there are several documented cases of \(\beta\)-fission to primary rather than secondary radicals in bicyclic systems\(^{140,141}\) but in those cases clear-cut explanations could often be given on orbital overlap grounds.\(^{141}\) Clearly such arguments are not applicable to \(2d_{trans}\) where the substituent is very unlikely to engender the stereoelectronic biases found in bicyclic systems (or in \(2d_{cis}\)).
Enhancement of $k_1$ in $2d_{\text{trans}}$ might be attributed either to a weakening of the 2,4-bond caused by the methyl substituent (i.e. a ring strain effect) or to electronic stabilization of the transition state or both. The former is corroborated to some extent by electron density calculations on substituted cyclopropanes; these indicate some lengthening of the bond opposite electron donor substituents and an increase in the overall ring strain upon substitution and this is supported by experimental evidence. However, enhancement of both cyclization of 1d and $\beta$-fission of 2d implies a reduction of the intrinsic energy barrier to reaction which is independent of the stability of one or other ground state.

The mechanism of this effect, which is not found in the cyclobutylmethyl system, probably involves the exceptional features of cyclopropane ring bonding, i.e. its considerable $\pi$-character, and a large degree of configuration interaction (involvement of vacant carbon orbitals). These make CPM radicals very polarizeable and greatly improve the homolytic overlap between the radical and ring bonding orbitals as is evidenced by the $10^4$ rate increase for fission of 2a over cyclobutylmethyl which is estimated to have a similar ring strain. A polar transition state (illustrated below) has been proposed to rationalize this and similar ring fission anomalies.

In terms of the configuration mixing model of reactivity, the proposed polarity of the transition state might be caused by a combination of the low ionization energies of CPM radicals and low lying acceptor orbitals on the ring. Thus, in this model, the barrier to $\beta$-fission is reduced by substituents which stabilize the 'natural' polarity of the reaction and vice versa; enhancement of the fission rate may result from either electron donor stabilization of the cationic element of the transition structure or by electron withdrawal at the incipient...
radical centre (e.g. 2e).

The anomalous ring fission of \(2d^{\text{trans}}\) shows that the proposed perturbation effect can outweigh small thermodynamic counter-tendencies and it may play a significant role, in addition to thermodynamic and stereoelectronic factors, in determining the outcome of homoallylic rearrangements of more complex species.

As mentioned above, the cyclization of \(1d\) is faster than that of \(1a\). However, the kinetics of the vinyl migration \(1d \rightarrow 3d\), which occurs subsequent to \(\beta\)-fission of \(2d\) in Scheme 3.3, is complicated by the fact that there are two possible pathways, viz. via \(2d^{\text{cis}}\) or via \(2d^{\text{trans}}\). The relative importance of these pathways cannot be assessed from these experiments because the intermediate radicals are not trapped in sufficient amounts to be quantified under conditions in which the vinyl migration takes place (viz. very low \([T]\) - see Table 3.2). On the other hand, although the rate constants for cyclization through the \(\text{cis}\) and \(\text{trans}\) forms of \(2d\) can not be independently determined, it seems reasonable to assume that most migration occurs via the lower energy \(\text{trans}\) species and thus to calculate the \(k_c\) and \(k_r\) of \(1d\) from the product ratio data for \(2d^{\text{trans}}\) (as described for \(2c \rightarrow 1c \rightarrow 3c\) – see Figure 3.1).

By this method, \(k_c = 3.5 \times 10^5\) and \(12 \times 10^5\ \text{s}^{-1}\) at 60\(^\circ\) and 100\(^\circ\)C respectively and with \(k_r = 0.5\ k_c\) (eq 4) these afford the approximate Arrhenius coefficients of Table 3.3.

The radical-trapping expression for \(k_r\) and the assumptions made to derive it are in good agreement with data from tributylstannane reduction of 4-bromo-3-methyl-1-butene;\(^{134}\) i.e. the latter give\(^{151}\) \(k_r = 0.8-1.3 \times 10^5\ \text{s}^{-1}\) at 45\(^\circ\)C whereas the radical-trapping data indicate ca. \(0.9 \times 10^5\ \text{s}^{-1}\) at this temperature.

3.5 2-Ethoxycarbonylcyclopropylmethyl (2e). Thermolysis of diacyl peroxide \(4e\) in concentrated solutions of \(T\) in benzene (0.5-1.0 M) gave just one identifiable alkoxyamine product \(7e\) at 60\(^\circ\) and 100\(^\circ\)C. Thus, with a trapping rate constant of \(1 \times 10^9\ \text{M}^{-1}\ \text{s}^{-1}\) and a 2\% limit of detection (relative to \(7e\)), this implies a \(\beta\)-fission rate constant greater than \(5 \times 10^{10}\ \text{s}^{-1}\) and selectivity for 2,3-bond fission greater than 50.
Although the resonance stabilization afforded to the product radical 3e (ca 6-7 kcal/mol)\textsuperscript{152-154} could explain the increased selectivity, the fact that CPM is predicted to have an early transition state (that of 2e would be earlier) implies that the magnitude of the change lends some support to the CPM transition state polarity suggested above (i.e. the $\delta^-$ charge would be adjacent to the $CO_2Et$ group for 2,3-fission).

3.6 Thermodynamics and Kinetics of CPM Ring Fissions. The data in Table 4.3 can be summarized by the free energy level diagrams in Figure 3.2 (over). Enthalpy and entropy values (shown in brackets) can also be readily deduced from the data but the limited data bases and assumptions made about $kT$ suggest that detailed comparisons of these parameters are not justified except to consider large effects or unless supplemented by low temperature data (e.g. $k_1/k_3$ for 2de\textsubscript{cis} and 2d\textsubscript{trans}). Relative free energy levels are given for 2d\textsubscript{trans} have been calculated on the basis of the assumptions regarding $k_c(1d)$ made above.
Relative to 1a, one and two methyl groups (at position 2) enhance the cyclization rate by factors of 15 and 1500, i.e. $\Delta G^\ddagger = 1.6$ and 4.4 kcal/mol, respectively. This is a much more dramatic effect than found in the 5-hexenyl system where $\Delta G^\ddagger = 1.4$ kcal/mol for a gem dimethyl group at the $\beta$ or $\gamma$ positions.\(^{36}\)

A major driving force for cyclization of 1c is the relief of steric compression when it rearranges to 2c, i.e. this is the cause of the Thorpe-Ingold effect in cyclopropane formation. In addition to raising the enthalpy, non-bonded interactions in 1c also restrict rotations about bonds emanating from the quaternary carbon centre. The reduction of non-bonded interactions during cyclization might therefore contribute to both the low energy barrier and the high frequency factor for cyclization and vinyl migration for 1c.

It can be seen from Figure 3.2 that the gem dimethyl group increases the thermodynamic driving force and reduces the energy barrier to cyclization of 1c. However, contrary to the conventional picture of reactivity (e.g. the Hammond-Leffler Relationship)\(^{37}\), the kinetic effect is just as large as the thermodynamic effect; that is to say, the reduction of the energy barrier is equal to the improvement in the thermodynamic driving force of 1c → 2c. Moreover, the rate of ring fission to the primary radical ($2c \rightarrow 1c$) is actually increased slightly relative to CPM despite the decreased driving force in this direction.

In 2\(d^{trans}\) a lower intrinsic energy barrier\(^{156-7}\) is proposed to result from the polar transition state effect described above. In 2c this effect might be augmented by the conformational flexibility acquired during ring fission; i.e. the exocyclic groups which are rigidly held syn periplanar in 2c can twist away from each other as the 2,4-bond lengthens and the ring carbons rehybridize towards their product (planar) geometries. Thus, for 2c there may be substantially less van der Waals strain energy in the transition state than in either the reactant or product species.

3.7 Conclusions

Previously inaccessible rate constants for $\beta$-fission of ring substituted cyclopropyl-
methyl radicals have been calibrated using a nitroxide radical trap. Rate constants for reverse reactions i.e. for ring closure of \textbf{1c} and \textbf{1d}, can be determined from the $\beta$-fission product data (Scheme 3.3 with eq 3.3-3.5) or more directly by calibration of the vinyl migration rate constant ($k_v$) (Scheme 3.2 with eq 3.6).

The radical-trapping investigations indicate the following substituent effects:

* 2-methyl group(s) cause a general mobilization of the rearrangements; in particular the ring-closure reactions are accelerated.

* $\beta$-fission of \textbf{2d}$^{\text{trans}}$ to the primary radical (\textbf{1d}) is kinetically favoured in the enthalpy term but not in the entropy term i.e. $\log(k_1/k_3) = -0.6 + 0.9/\theta$ which implies an isokinetic temperature near 60°C.

* cyclization and vinyl migration rates are accelerated by substitution with methyl and especially with gem dimethyl groups in the $\beta$-position of the homoallyl radical (\textbf{1a}), (by factors of 15 and 1500 at 25°C respectively).

* combined cyclization - ring fission rate data afford the thermodynamics for homoallylic rearrangements of \textbf{1a-1d} (Figure 3.2): it is apparent from these that the kinetic effects of the substituent(s) are about equal to or greater than the thermodynamic effects.

Each of the above features can, at least qualitatively, be explained by proposing (a) that methyl groups increase the polarizeability of the transition state particularly for fission of the bond opposite the substituent(s) and (b) that the transition structure offers relief of non-bonded interactions that are present in both reactant and product species. In more constrained systems these features might operate in addition to stereoelectronic factors to determine the rates and stereo-selectivity of the homoallylic rearrangements.
Experimental Section

The instrumentation and general methodology were identical to those described in Chapter 2. HPLC conditions and analytical data are listed in Supplementary Tables 3.1 to 3.5.

3.8 Materials. Preparation of T,5 purification of tert-butyl hydroperoxide, and general procedures for hydrolysis and for preparation of acid chlorides, diacyl peroxides and tert-butyl peresters were described in Ch 2.17.

Bis (2,2-dimethylcyclopropane)acetyl Peroxide (4c). (2,2-Dimethylcyclopropane)-acetic acid43 was converted to its acid chloride with oxaly1 chloride (Ch. 2.17 preparative method 2). Pyridine (400 ml, 5 mmol) was added dropwise at -10°C to a mixture of 20 M H₂O₂ (150 ml, 3 mmol) and the acid chloride (380 mg, 2.5 mmol). After 30 min at 0°C the reaction mixture was diluted with pentane and washed successively with ice-cold water, 10% H₂SO₄, sat. NaHCO₃, and brine then dried (MgSO₄) and evaporated to afford 4c (280 mg, 82%), pure by NMR, IR and 90% by iodometric titration.44 1H NMR (60 MHz, CCl₄), δ -0.1-1.1 (m, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 2.04 (d, 2H); IR νmax (CCl₄) 1740, 1785 cm⁻¹ (C=O).

Bis(cis-2-methylcyclopropane)acetyl Peroxide (4dcis). 3-Pentyn-1-ol (Aldrich) was oxidized to 3-pentynoic acid (36%) with Jones' reagent at room temperature.45 The acid was methylated with BF₃ in methanol46 and the methyl ester was hydrogenated in pyridine over Pd on BaSO₄ catalyst47 at 10 psi for 2 hr. Work up gave pure methyl cis-3-pentenoate (GC 98% cis) in 30% overall yield. The ester was heated to reflux with two molar equivalents of Simmons-Smith reagent48 in ether for 22 hrs to afford, on work-up, methyl (cis-2-methylcyclopropane)acetate (71%) bp 85-87°C (100 mm) (lit.49 bp 84°C at 60 mm), 98% cis by GC; IR50 and NMR49 were consistent with previous reports. Hydrolysis of the ester (Ch. 2.17 method I) and conversion as for 4c gave 4dcis (52% from the ester), pure by NMR, IR, and 93% by iodometric titration.20 1H NMR (60 MHz, CCl₄); δ -0.2 (m, 2H), 0.2-1.5 (m, 12H), 2.15 (d, 4H); IR νmax (CCl₄), 1750, 1788 cm⁻¹ (C=O).
Bis-(2-Ethoxycarbonylcyclopropane)acetyl Peroxide (4e). tert-Butyl vinylacetate was made by a standard procedure from vinylacetetyl chloride. Ethyl diazoacetate (ca. 2 mol. equiv.) was added dropwise to a suspension of anhydrous CuSO₄ (4% molar) in the above ester at 50°C (monitored by GC). The reaction mixture was washed successively with water, dilute aq-NH₃ (twice), and brine; the resulting brown oil was selectively hydrolyzed by treatment with 90% aq-formic acid (2 volumes) for 4 hr at ca. 50°C. The usual isolation of the acidic component (Ch. 2.17) followed by distillation gave (2-ethoxycarbonylcyclopropane)-acetic acid (21% from the ester), bp 140-145°C (0.4 mm), cis:trans = 35:65 by ¹H NMR (cis methylene at δ 2.68, trans at δ 2.36). Treatment of the acid with oxalyl chloride then Na₂O₂ with wet ether (Ch. 2.17 method 3) at <10°C gave 4e (70%), pure by NMR, and 89% by iodometric titration. ¹H NMR (200 MHz, CHCl₃); δ 0.6-1.3 (m, 2H), 1.28 (t, 3H, 7.1 Hz), 1.4 (m, 1H), 1.55 (m, 1H), 2.43 + 2.76 (m + m, 1:1:8, 2H), 4.18 (q, 2H, 7.1 Hz, cis downfield 0.8 Hz). IR νₘₐₓ (CCl₄) 1743, 1755, 1785 cm⁻¹ (C=O).

3.9 Alkoxyamine Products. Products mixtures were prepared by adding peroxides to concentrated refluxing solutions of T in benzene. The mixtures were resolved by flash chromatography on silica (see Ch. 2.18) followed by preparative RP-HPLC of the alkoxyamine fractions (this procedure achieved some separations not practical by HPLC alone and allowed the identification of non-UV active components). General UV and NMR spectral features of N-alkoxy-1,1,3,3-tetramethylisoindolines have been described as have the spectra of 5c and 7c (cf. Ch. 2.18).

2-(2,2-Dimethylcyclopropanemethoxy)-1,1,3,3-tetramethylisoindoline (6c).
NMR (200 MHz, CHCl₃); δ 0.2 (m, 1H), 0.6-1.1 (m, 2H), 1.04 (s, 3H), 1.09 (s, 3H), 1.42 (br s, 12H), 3.72 (m 2H), 7.01 (m, 2H), 7.15 (m, 2H). Anal. Calcd for C₁₇H₂₇NO: C, 79.07, H, 9.95; Found: C, 79.01, H, 9.64.

2-(cis 2-Methylcyclopropanemethoxy)-1,1,3,3-tetramethylisoindoline (6dcis).
¹H NMR (200 MHz, CHCl₃); δ 0.3-1.0 (m, 4H), 1.02 (m, 3H), 1.44 (br s, 12H), 3.74 (m, 2H), 7.01 (m, 2H), 7.14 (m, 2H). Anal. Calcd for C₁₇H₂₅NO: C, 78.72, H, 9.71; Found:
2-(trans 2-Methylcyclopropanemethoxy)-1,1,3,3-tetramethylisoindoline (6dtrans)

$^1$H NMR (200 MHz, CHCl$_3$); $\delta$ -0.33 (m, 1H), 0.10 (m, 1H), 0.64 (m, 1H), 0.86 (m, 1H), 0.97 (d, 3H, 6 Hz), 1.4 (br s, 12H), 3.70 (d, 2H, 6.8 Hz), 7.02 (m, 2H), 7.16 (m, 2H). Anal. Calcd for C$_{17}$H$_{25}$NO: C, 78.72, H, 9.71; Found: C, 78.61, H, 9.79.

2-(2-Methyl-3-buten-1-oxy)-1,1,3,3-tetramethylisoindoline (6d).

$^1$H NMR (200 MHz, CHCl$_3$); $\delta$ 1.10 (d, 3H, 7.2 Hz), 1.4 (v br d, 12H), 2.22 (m, 1H), 3.76 (d, 2H, 7 Hz), 5.02 (m, 2H), 5.82 (m, 1H), 7.00 (m, 2H), 7.11 (m, 2H). Anal. Calcd for C$_{17}$H$_{25}$NO: C, 78.72, H, 9.71; Found: C, 78.76, H, 9.53.

2-(4-Penten-2-oxy)-1,1,3,3-tetramethylisoindoline (7d):

$^1$H NMR (200 MHz, CHCl$_3$); $\delta$ 1.22 (d, 3H, 7 Hz), 1.3-1.5 (m, 12H), 2.19 (m, 2H), 3.92 (s, 1H), 5.01 (m, 2H), 5.81 (m, 1H), 7.00 (m, 2H), 7.11 (m, 2H). Anal. Calcd for C$_{17}$H$_{25}$NO: C, 78.72, H, 9.71; Found: C, 79.01, H, 9.97.

2-(1-Ethoxycarbonyl-3-buten-1-oxy)-1,1,3,3-tetramethylisoindoline (7e):

$^1$H NMR (200 MHz, CHCl$_3$); $\delta$ 1.28 (t, 3H, 7 Hz), 1.2-1.5 (m, 12H), 2.55 (m, 2H), 4.17 (q, 2H, 7Hz), 4.40 (t, 1H), 5.05 (m, 2H), 5.75 (m, 1H), 7.04 (m, 2H), 7.19 (m, 2H). Anal. Calcd for C$_{19}$H$_{27}$NO$_3$: C, 71.89, H, 8.57; Found: C, 71.80, H, 8.45.
CHAPTER FOUR
Alkoxycarbonyl Fragmentations and $\alpha$-Substituted Cyclopropylcarbiny1 Radical Rearrangements

4.1 Introduction

In Chapter Two direct competition between the $\beta$-fission of alkoxycarbonyl radicals $3a^{103}$ and their radical-trapping reaction with $T$ was used to calibrate the radical-trapping rate constant for this type of radical, viz. $k_T = 1.9 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ at 25°C.

Good yields of radical products were obtained under mild conditions (see below) and this, combined with the ease with which tert-butyl monoperoxalic esters can be prepared, suggested that the reaction sequence of Scheme 4.1 might provide an entré to certain alkyl radical isomerizations ($R' \rightarrow R''$) starting from the corresponding alcohols ($R$-OH). It is clear, however, that Scheme 4.1 can only be an efficient source of alkyl radicals if the intervening alkoxycarbonyl radicals (ROC'O) decarboxylate more rapidly than they are trapped by $T$.

Scheme 4.1
Scheme 4.2 Reactions of Alkoxycarbonyl Radicals in the Presence of Nitroxide T
Similar problems confront synthetic versions of this scheme (e.g. CCl₄ in place of T gives alkyl chlorides¹⁶¹) and so it is of practical as well as theoretical interest to discover how the decarboxylation rate constant $k_D$ is affected by the stability and structure of the $R$ group. In this report radical-trapping is used to gauge these effects in the series 3a-3g.

Monoperoxalic esters¹²⁵a,b 2d-2g were found to be fruitful precursors for the cyclopropylcarbinyl radicals 4d-4g even under the conditions of high trapping rate (i.e. high [T]) required for the investigation of the rearrangements 4→4' (Scheme 4.2). For these reactions, it was possible simultaneously to determine the kinetics both of the fragmentation of 3 and of the subsequent rearrangement of the alkyl radical 4.

With the aid of direct calibration data for the $k_T$ of stabilized radicals, the scope of nitroxide radical-trapping as a kinetic technique is further demonstrated by the evaluation of the complete kinetic and thermodynamic parameters of rearrangements between the radical isomers 4h, 4' h cis and 4' h trans.

![Scheme 4.3](image)

Results and Discussion

4.2 Methods. **OO-tert-Butyl** monoperoxalic esters 2a-2g were prepared from
the appropriate alcohols (1a-1g) by treatment with tert-butylperoxyal chloride\textsuperscript{125a} in the presence of pyridine as described by Bartlett \textit{et al.}\textsuperscript{125a,b} Some of these compounds were explosively unstable in the pure state but they could be prepared, stored (-20°C) and safely handled in hydrocarbon solvents.

Mixtures of the precursor with a ten fold excess of T in cyclohexane were degassed then heated in the sealed ampoules in the usual way (Ch 2.16) except that for reaction mixtures containing the tert-butyl peroxalic esters (which were more heat sensitive than the diacyl peroxides)\textsuperscript{75,125b} the temperature was maintained below 10°C up to the heating stage. Evaporation and HPLC analysis of the various product mixtures revealed alkoxyamines in the molar ratios listed in Table 4.1.

\textbf{4.3 Kinetic Equations.} Kinetic analysis of reaction Schemes 4.2 and 4.3, using the steady-state and pseudo-first-order approximations, yields kinetic equations (4.1), (4.2) and (4.3) (cf. Appendix A) in which $k_\text{T}N$ is the trapping rate constant for radical N and where $[\text{N+2}]$ is the molar concentration of the corresponding alkoxyamine (i.e. trapped radical). The suffixes a-h are implicit.

for decarboxylations ($3 \rightarrow 4$)

$$k_D/k_\text{T}^3 = [\text{T}] [6' + 6]/[5] \quad (4.1)$$

for irreversible rearrangements ($4 \rightarrow 4'$)

$$k_r/k_\text{T}^4 = [\text{T}] [6']/[6] \quad (4.2)$$

for reversible rearrangements ($4 \leftrightarrow 4'$)

$$\frac{[6]}{[6']} = \frac{k_\text{T}^4}{k_r} \left[ \frac{k_r}{k_\text{T}^4} + [\text{T}] \right] \quad (4.3)$$

Kinetic data for each of the decarboxylations and for the rearrangements of radicals.
4d-4f were consistent with eq 4.1 and eq 4.2 respectively to within experimental uncertainties. Kinetic data for these reactions are given in Table 4.1.

Rearrangements of 4g and 4h were found to be appreciably reversible. That is to say, plots of the molar product ratios [6]/[6'] versus nitroxide concentration [T] were found to be linear (slope b) but with a significant [T] = 0 intercept a (for irreversible reactions a = 0). Comparison of the linear equation (eq 4.4) with eq 4.3 gives relationships eq 4.5 and eq 4.6.

\[
\frac{[6]}{[6']} = a + b [T] \quad (4.4)
\]

\[
b^{-1} = \frac{k_r}{k_T^4} \quad (4.5)
\]

and

\[
a/b = \frac{k_r}{k_T^4} \quad (4.6)
\]

Thus by graphical or by linear regression analysis of the data, rate constants for forward and reverse reactions could be obtained relative to the trapping rate constant of the respective initial species. The procedure is further specified for radical 4h in Table 4.4.

4.4 Decarboxylations. Thermolysis of tert-butyl monoperoxal esters 2a-2g in the presence of excess T proceeded at practical rates in the range 25-80°C.125b Product distributions were consistent with Scheme 4.2 (without α-fission - see below); that is, 50% of the total alkoxyamine yield was trapped cyclohexyl (from the reaction of tert-butoxyl radicals with the solvent) and the ratio of the total alkyl product (6 + 6') to the alkoxy carbonyl product 6 was inversely proportional to the nitroxide concentration (eq 4.1).

Based on the assumption that all simple alkoxy carbonyl radicals are trapped with approximately the same rate constant, the radical clock calibration of \(k_T^{3a}\) (eq 4.7 and Intro.) may be combined with the relative kinetic data \((k_f/k_T^3)\) in Table 4.1 to afford absolute rate constants for decarboxylation of radicals 3c-3g. These are listed in Table 4.2.

\[
\log \left( \frac{k_T^{3a}}{M^{-1}s^{-1}} \right) = 9.5 - 0.3/\theta, \quad (\theta = 2.3 \, RT \, \text{kcal/mol}) \quad (4.7)
\]

The data in Table 4.2 show that the fragmentation of alkoxy carbonyl radicals is sensitive to the nature of the product radical (R•). Other product studies have indicated effects
### Table 4.1. Alkoxylamine Product Ratios and Kinetic Data for Reactions of 3c-g<sup>a</sup>

<table>
<thead>
<tr>
<th>Radical</th>
<th>temp, °C&lt;sup&gt;b&lt;/sup&gt;</th>
<th>[T] , mM</th>
<th>[6+6']/[5]</th>
<th>(k_D/k_T), M</th>
<th>[6']/[6]</th>
<th>(k_r/k_T), M</th>
</tr>
</thead>
<tbody>
<tr>
<td>3c&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42</td>
<td>19</td>
<td>2.02</td>
<td>0.038</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>47</td>
<td>0.78</td>
<td>0.037</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>17.2</td>
<td>3.71</td>
<td>0.063</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>16.1</td>
<td>6.92</td>
<td>0.11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>43</td>
<td>2.38</td>
<td>0.10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>85</td>
<td>1.32</td>
<td>0.11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3d</td>
<td>25(±1)</td>
<td>10.0</td>
<td>0.90</td>
<td>0.0090</td>
<td>3.10</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>9.1</td>
<td>2.12</td>
<td>0.019</td>
<td>8.93</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>59.5</td>
<td>24</td>
<td>1.70</td>
<td>0.041</td>
<td>5.71</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>59.5</td>
<td>45</td>
<td>0.81</td>
<td>0.036</td>
<td>2.57</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>21</td>
<td>2.82</td>
<td>0.059</td>
<td>10.5</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>44</td>
<td>1.50</td>
<td>0.066</td>
<td>5.91</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>72</td>
<td>0.81</td>
<td>0.058</td>
<td>3.23</td>
<td>0.23</td>
</tr>
<tr>
<td>3e</td>
<td>60</td>
<td>18.0</td>
<td>0.81</td>
<td>0.013</td>
<td>10.1</td>
<td>0.19&lt;sup&gt;(2)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>8.4</td>
<td>3.0</td>
<td>0.025</td>
<td>(&gt;30)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>17.3</td>
<td>1.8</td>
<td>0.031</td>
<td>18.8</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>73</td>
<td>0.50</td>
<td>0.036</td>
<td>5.1</td>
<td>0.37</td>
</tr>
<tr>
<td>3f</td>
<td>60</td>
<td>17.8</td>
<td>0.76</td>
<td>0.0028</td>
<td>3.9</td>
<td>0.07&lt;sup&gt;(1)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>8.4</td>
<td>0.62</td>
<td>0.005</td>
<td>16.1</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>17.2</td>
<td>0.28</td>
<td>0.005</td>
<td>7.2</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>72</td>
<td>0.08</td>
<td>0.006</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3g&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42</td>
<td>4.8</td>
<td>-</td>
<td>-</td>
<td>0.167&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reversible</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>18.0</td>
<td>-</td>
<td>-</td>
<td>0.078</td>
<td>-See Table</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>91</td>
<td>12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.019</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>4.5</td>
<td>-</td>
<td>-</td>
<td>0.32</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>17.3</td>
<td>-</td>
<td>-</td>
<td>0.169</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>88</td>
<td>18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.052</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>44</td>
<td>-</td>
<td>-</td>
<td>0.62</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>17.5</td>
<td>-</td>
<td>-</td>
<td>0.41</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>85</td>
<td>29&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.142</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions in cyclohexane; trapped cyclohexyl was present in amounts consistent with Scheme 4.2 without significant α-fission.  
<sup>b</sup> ±0.5°C.  
<sup>c</sup> Corrected for thermal expansion and for the estimated consumption of nitroxide.  
<sup>d</sup> Rates corrected for spectral differences between the products.  
<sup>e</sup> 3g overlapped various non-trapped aromatic products from the decay of 2g, thus these data are approximate only.
Table 4.2. Kinetic Data for Decarboxylations of 3a-3g<sup>a</sup>

<table>
<thead>
<tr>
<th>Radical</th>
<th>( k_D^{80^\circ C}, 10^6 \text{s}^{-1} )</th>
<th>( \log A, \text{s}^{-1} )</th>
<th>( E, \text{kcal/mol} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a&lt;sup&gt;5&lt;/sup&gt;</td>
<td>3.6</td>
<td>13.8</td>
<td>11.7</td>
</tr>
<tr>
<td>3b&lt;sup&gt;1&lt;/sup&gt;</td>
<td>13.6</td>
<td>13.2</td>
<td>9.8</td>
</tr>
<tr>
<td>3c</td>
<td>24.0</td>
<td>12.4</td>
<td>6.5</td>
</tr>
<tr>
<td>3d</td>
<td>12.0</td>
<td>12.9</td>
<td>7.8</td>
</tr>
<tr>
<td>3e</td>
<td>6.7±1.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3f</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3g&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1000</td>
<td>14.1</td>
<td>6.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Derived from relative kinetic data with the radical clock data from 3a (= 12 in Ch 2), viz. \( \log k_T \cdot M^{-1} \text{s}^{-1} = 9.5 - 0.3/\theta, (\theta = 2.3 \text{ RT kcal/mol}) \); <sup>b</sup> 3b (= 13 in Ch 2); <sup>c</sup> Approximate figures only.

of similar magnitude and have established that decarboxylation rates increase in the order: \( R = \) aryl, primary, secondary, tertiary, and benzylic. This order is based upon Bartlett and Pincock's pioneering studies<sup>125a,b</sup> of the thermal decay of monoperoxalate esters (with \( R = \text{Et, t-Bu, Bz and para-substituted Bz} \)) and on the data Pfenninger et al<sup>161</sup> obtained for the tributylstannane reduction of phenylselenocarbonates. The latter reaction is proposed to proceed via alkoxycarbonyl radical (ROC=O) intermediates; the yields of formate ester (ROCHO) and hydrocarbon (R-H) products are consistent with relative decarboxylation rate constants for \( R = \) primary, secondary, and tertiary alkyl of 1:4:19 (at 80°C in benzene).

Pffeninger et al<sup>5</sup> also reported that \( \alpha \)-fission or decarbonylation accounted for about 50 and 100% of the total fragmentation products when \( R = \) primary and aryl respectively. In our experiments \( \alpha \)-fission would be indicated by a larger than usual amount of trapped cyclohexyl, i.e. in excess of 50% of the total alkoxyamine yield (see above and the upper section of Scheme 4.2). The HPLC data indicated less than 10% \( \alpha \)-fission for 3a-g.

The fragmentation of the tertiary alkoxycarbonyl radicals (3a-d) is remarkably sensitive towards substitution in the \( R \) group - replacement of a methyl with a cyclobutyl or cyclopropyl group increases \( k_D \) by 5 or 80 respectively at 80°C. However, the effect of a
cyclopropyl group is smaller when \( R \) is secondary i.e. \( k_D (3e) = 5 k_D (3f) \). By analogy with substitution effects in \( S_N 1 \) type reactions, the relatively large effect for a tertiary \( R \) group is proposed to arise, in part, by what Brown has termed the \( B\)-strain effect.\(^3\)\(^\text{9} \) That is to say, the relatively large degree of strain energy in the "Back" of sterically crowded species such as \( 3b \) and \( 3c \) promotes the reaction because \( \beta \)-fission allows the \( R \) group to become planar.

Repulsion between the \( R \) and carboxyl groups is likely to assist the fragmentation for the obvious reason but also because of a stereoelectronic effect, viz. that repulsion between the \( R \) and \( C=O \) groups favours the conformation in which the initial radical orbital (SOMO) most effectively overlaps the \( R-O \) bond (i.e. \( R-OC=O \) co-planar) thereby effectively lowering the energy barrier of the fission.

It is clear from the radical-trapping data for \( 3c \) and \( 3g \) and from the other studies that stabilization in the product radical promotes the decarboxylation but not to the full extent of the radical stabilization energy. For instance, if benzyl radical stabilization (10 kcal/mol) were fully manifested in the \( \beta \)-fission reaction a \( 10^6 \)-fold increase of rate would result (!); this is a much larger figure than that suggested by the data of Table 4.2 combined with those of Pffeninger et al (i.e. \( k_D ^{R=benzyl} = 120 k_D ^{R=primary} \)). This implies that there is only a small product character in the transition state (say 30%). On theoretical grounds also, the fission is predicted to have an early transition state; i.e.thermochemical data suggest that fission of \( 3a \) is quite favourable (\( \Delta H^\infty = -3 \) kcal/mol and \( \Delta G^\circ = -10 \) kcal/mol\(^1\)\(^6\)\(^2\)\(^5\)) and thus the Hammond-Leffler relation (cf. ref 178) suggests that the transition state is more reactant-like than product-like.

In addition, the progressively lower frequency factors in the series \( 3a, 3b, \) and \( 3d \) may reflect a 'tightening' of the transition state as the \( \beta \)-fission becomes more exothermic. The
Chapter 4: Alkoxycarbonyl and Cyclopropylcarbinyl Radicals

trend may be a manifestation of rotational restrictions in the transition structure; that is, restricted rotation of the carboxy group and, where $R$ is resonance stabilized, within the incipient radical. For example, the phenyl rotor in 3c may be partially frozen by delocalization of the SOMO into the phenyl ring at the transition state.

4.5 Rearrangements of 4d-4f. Once liberated from 3d-f, cyclopropylcarbinyl radicals 4d-f ring open very rapidly to afford homoallylic radicals 4’d-4’f. Reactions using low nitroxide concentrations established that the reversibility of ring opening was less than 5% in each case; this implied free energy differences ($\Delta G^\circ$) between the ring-opened and closed forms of greater than 2 kcal/mol.

Cis and trans isomers of 6’e-6’f could not be separated by HPLC but for 6’f NMR analysis of a prepared isomer mixture indicated $\text{trans: cis} = 1.5$. The selectivity of trans ring opening of 4f (which is higher at 0°C$^\circ$) has been explained$^86$ as an orbital overlap or stereo-electronic effect (see 4h below).$^86$

Evaluation of absolute $\beta$-fission rates from the data in Table 4.1 requires estimates for the trapping rate constants of the initial alkyl radicals i.e. $k_T^4$ in eq 4.2. It is apparent from laser flash photolysis calibrations$^41$ that $k_T$ is not very sensitive towards radical stabilization at least to the benzyl radical level where $k_T^\text{benzyl} = 0.5k_T^\text{nonyl}$; a cyclopropyl group is much less stabilizing than a phenyl group ($E_{\text{stab}} = 0.7 - 2.5$ versus 10.1 kcal/mol respectively$^{136-139,163,164}$), so that use of $k_T$ values derived for ordinary secondary and tertiary alkyl radicals should not lead to serious error. Accordingly, the relative radical-trapping rate constants of eq 4.8 were adopted for these species and the temperature variation was assumed to be the same as that for the primary radical, viz. eq 4.9 ($\theta = 2.3$ RT kcal/mol),$^{41,57}$

\begin{align}
  k_T^{4d} &= 0.8 \ k_T^{4e} = 0.6 \ k_T^{\text{primary}} \\
  \log (k_T^{\text{primary}}/\text{M}^{-1}\text{s}^{-1}) &= 9.7 - 0.9/\theta.
\end{align}

i.e., $k_T^{\text{primary}} = 1.4 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ at 80°C or $1.0 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ at 25°C.
Rate constants derived for ring fission of $\text{4d-4f}$ and of cyclopropylmethyl radical$^{57}$ (Ch 2.4) are presented in Table 4.3 together with the muon spin decay kinetic data of Fischer et al.$^{85,165}$ for $\text{4d}$ and $\text{4f}$. Agreement between these calibration data is fair considering the extrapolation between temperature ranges and in view of the rather improbable log $A$ suggested for $\text{4f}$ by the latter method (it implies $\Delta S^\circ = -10$ eu for a ring fission). A calibration$^{82}$ using triphenylstannane afforded a value of $k_r = 7 \times 10^6 \text{ s}^{-1}$ at 0°C which extrapolates to $1.7 \times 10^8 \text{ s}^{-1}$ at 80°C if a 'normal'$^{24}$ pre-exponential of $10^{13} \text{ s}^{-1}$ is assumed [log ($k_r, \text{s}^{-1}$) = 13.0 - 7.7/$\theta$].

Table 4.3. Kinetic Data for Ring Fissions of Cyclopropylcarbinyl Radicals $\text{4d-4f}^a$

<table>
<thead>
<tr>
<th>radical</th>
<th>$k_T, 10^6 \text{ s}^{-1}$</th>
<th>log $A, \text{ s}^{-1}$</th>
<th>$E, \text{ kcal/mol}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{c-C}_3\text{H}_5\text{CH}_2^* \text{c}$</td>
<td>520</td>
<td>13.3</td>
<td>7.4</td>
</tr>
<tr>
<td>$\text{4d}$</td>
<td>$175 \pm 20$</td>
<td>$13.7 \pm 0.6$</td>
<td>$8.8 \pm 0.9$</td>
</tr>
<tr>
<td></td>
<td>(115)$^b$</td>
<td>(14.5 ± 0.8)</td>
<td>(10.4 ± 1.3)</td>
</tr>
<tr>
<td>$\text{4e}$</td>
<td>$160 \pm 40$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\text{4f}$</td>
<td>$140 \pm 40$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(52)$^b$</td>
<td>(11.0 ± 1.2)</td>
<td>(5.3 ± 1.4)</td>
</tr>
</tbody>
</table>

$^a$ All reactions in cyclohexane. $^b$ From muon spin decay data (ref 85, 165).

The trend in Table 4.3 is not completely consistent with 'first-sight' thermodynamic expectations. Ring fissions of $\text{4d-4f}$ directly convert $\alpha$-substituted radicals into primary radicals so that it might be predicted that ring fission rate constants would reflect the 'stability' of the initial radical; since tertiary and secondary radicals are respectively about 5 and 3 kcal/mol$^{25}$ more stable than primary radicals, the expected order would be $\text{CPM > 4f > 4d}$ (with incremental factors of $ca$ five being predicted on thermodynamic grounds$^{166}$). However, this is a gross oversimplification because much of the 'stability' associated with a radical being secondary or tertiary probably arises from steric repulsions in the $sp^3$ hybridized parent compounds; during the course of CPC radical ring fission the radical centre remains $sp^2$ hybridized and thus smaller than expected radical stabilization effects may ensue. Indeed, a thermochemical calculation,$^{146,167}$ which implicitly includes such factors as the high relative stability of the isobutylene element in product species $\text{4d}$, correctly predicts the experimental
order i.e. $k_r$ for CPM $> 4d > 4f$ with relative free energies of reaction ($\Delta \Delta G^\circ$) of 0, -1.1, and -1.3 kcal/mol respectively.

The rapid ring opening of $4e$ may be seen to support other indications\textsuperscript{136} that $\alpha$-cyclopropyl groups afford only a small amount (0.4 - 2.6 kcal/mol) of extra stabilization to the radical centre\textsuperscript{152-154} but, as above, this interpretation may need to be modified by a more detailed examination of the reaction's stereoelectronic parameters and, in particular, of the effect of the putative polar transition state (cf. Ch 3.4).\textsuperscript{170}

### 4.6 $\alpha$-Phenylcyclopropylcarbinyl Radical (4g).

Linear regression analysis of the kinetic data, i.e. by least-squares fitting $[6g]/[6'g]$ versus $[T]$ to eq 4.3, afforded the relative rates for rearrangements of $4g$ and $4'g$ (see 4h). Over the range 25° to 80°C, the data are consistent with the temperature variation expressions of eq 4.10 and eq 4.11.

\[
\log \left( \frac{k_r}{k_T} \right) = 5.4 - 11.9 / \theta \quad (4.10)
\]

\[
\log \left( \frac{k_r}{k_T} \right) = 2.1 - 6.2 / \theta \quad (4.11)
\]

The trapping rate of $\alpha$-methylbenzyl radicals by TEMPO has been calibrated by Chateauneuf et al\textsuperscript{41} and it seems reasonable that the trapping rate of ' $\alpha$-cyclopropylbenzyl' (4g) would have a similar value.\textsuperscript{168,41} Accordingly, I have used $k_T^{4g} = 0.125 \times 10^8$ M$^{-1}$s$^{-1}$ at 80°C with the usual temperature variation, viz. $E_T = 0.9$ kcal/mol, to derive the absolute rate expressions eq 4.12 and eq 4.13;

for ring-opening ($4g \rightarrow 4g'$)

\[
\log (k_r / s^{-1}) = 14.3 \pm 0.9 - (12.8 \pm 1.2) / \theta, \quad k_T^{80\circ} = 2.4 \times 10^6 \text{ s}^{-1} \quad (4.12)
\]

for ring-closure ($4'g \rightarrow 4g$)

\[
\log (k_r / s^{-1}) = 11.7 \pm 1.2 - (7.0 \pm 1.5) / \theta, \quad k_T^{80\circ} = 2.4 \times 10^7 \text{ s}^{-1} \quad (4.13)
\]

and, therefore, for equilibrium ($4g \leftrightarrow 4'g$) ($K = k_r/k_r$)

\[
\log K = 2.6 \pm 1.5 - (5.8 \pm 1.9) / \theta, \quad K^{80\circ} = 0.10 \quad (4.14)
\]
Equilibrium is rapidly established between $4g$ and $4'g$ with the true equilibrium lying decidedly on the ring-closed side of the equation, i.e. the data indicate that ring-closure is exergonic by 2.3 kcal/mol at 25°C. By contrast, several product studies of this and other $\alpha$-benzylic-cyclopropylcarbinyl species$^{169,170}$ have found that it is generally the ring-opened products which predominate. However, the discrepancy is only apparent and it may readily be explained by the large differences between the reactivity of benzylic (ring-closed) and that of alkyl (ring-opened) radicals towards reagents such as stannanes,$^72$ CC1$_4$ and cyclohexane. In such systems ring-opening may be thermodynamically unfavourable but ring-opened products may nevertheless predominate because they arise from the most rapidly quenched species in the reaction. This hypothesis is supported by data from reactions involving similar radical species under conditions of 'allylic bromination' (Wohl-Ziegler) (viz. N-bromosuccinamide plus radical initiator in refluxing CC1$_4$) in which the ring-closed bromides were the major products.$^{131}$ Here the radical trapping agent, viz. a very low concentration of bromine,$^170a$ is relatively non-selective so that thermodynamic radical concentrations are more truly reflected in the product distribution.

4.7 $\alpha$-(tert-Butoxy carbonyl)cyclopropylcarbinyl Radical ($4h$). $4h$ was generated by thermal decomposition of the tert-butyl perester 7. The alkoxyamine products were formed in relative yields (Table 4.4 - over) which were consistent with reversible reaction kinetics, i.e. the relative yield of the 'unrearranged' radical product tended to an 'equilibrium' value, rather than zero, as the concentration of the radical trap, [T], was reduced. Unlike $4g$, the $cis$ and $trans$ alkoxyamine products, $6'h^{cis}$ and $6'h^{trans}$, were readily resolved and quantitated by RP-HPLC. Thus linear regression of the data to eq 4.3 (Table 4.5) gave estimates for $\beta$-fission and ring-closure rates for both the $cis$ and $trans$ reactions relative to the appropriate $k_T$ value (Scheme 4.3).

The $k_T$ for the ring-opened forms, $4'h^{cis}$ or $4'h^{trans}$, can reasonably be assumed to be the same as that for hex-5-enyl so that absolute ring-closure rate constants, $k_T^{cis}$ and $k_T^{trans}$, can be derived from the product data using eq 4.3.$^{57}$ On the other hand, there are no reliable calibrations available for the $k_T$ of species similar to $4h$, i.e. $\alpha$-alkoxycarbonyl-alkyl radicals.
Chapter 4: Alkoxycarbonyl and Cyclopropylcarbinyl Radicals

Table 4.4. Relative Alkoxylamine Yields for 4h

<table>
<thead>
<tr>
<th>temp, °C</th>
<th>[T], mM</th>
<th>6h/[6'h]&lt;sup&gt;trans&lt;/sup&gt;</th>
<th>6h/[6'h]&lt;sup&gt;cis&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>4.5</td>
<td>0.28</td>
<td>4.33</td>
</tr>
<tr>
<td></td>
<td>18.0</td>
<td>0.69</td>
<td>6.47</td>
</tr>
<tr>
<td></td>
<td>72.6</td>
<td>2.35</td>
<td>15.1</td>
</tr>
<tr>
<td>83</td>
<td>4.2</td>
<td>0.181</td>
<td>2.85</td>
</tr>
<tr>
<td></td>
<td>16.8</td>
<td>0.332</td>
<td>3.62</td>
</tr>
<tr>
<td></td>
<td>41.6</td>
<td>0.682</td>
<td>4.83</td>
</tr>
<tr>
<td></td>
<td>76.2</td>
<td>1.10</td>
<td>6.93</td>
</tr>
<tr>
<td>100</td>
<td>4.0</td>
<td>0.137</td>
<td>1.99</td>
</tr>
<tr>
<td></td>
<td>15.4</td>
<td>0.209</td>
<td>2.24</td>
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<td></td>
<td>69.5</td>
<td>0.532</td>
<td>3.58</td>
</tr>
<tr>
<td>121</td>
<td>3.8</td>
<td>0.088</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>40.9</td>
<td>0.200</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>65.9</td>
<td>0.274</td>
<td>1.898</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cyclohexane solvent; the implicit product is trapped cyclohexyl C with %C = %([6h] + [6'hcis] + [6'h]<sup>trans</sup>) (±10%) by HPLC integration. <sup>b</sup> ± 0.5 °C. <sup>c</sup> Corrected for thermal expansion and for the estimated consumption of nitroxide. <sup>d</sup> Alkoxylamine yields were in the range 75-83%.

Table 4.5. Linear Regression Data for 4h. (Scheme 4.3)<sup>a</sup>

<table>
<thead>
<tr>
<th>temp, °C</th>
<th>trans fission</th>
<th>cis fission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b, M&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>59</td>
<td>1.43</td>
<td>30.4</td>
</tr>
<tr>
<td>83</td>
<td>0.124</td>
<td>12.9</td>
</tr>
<tr>
<td>100</td>
<td>0.113</td>
<td>6.02</td>
</tr>
<tr>
<td>121</td>
<td>0.077</td>
<td>3.00</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data in Table 4.5 fitted to 6h/6'hcis = a + b[T], etc. for trans, where b<sup>-1</sup> = k<sub>r</sub> / k<sub>T</sub> (4h), and a/b = k<sub>r</sub>/k<sub>T</sub> (4'h) by eq 4.3.
Figure 4.1. \( \frac{[6h]}{[6'h_{\text{trans}}]} \) versus \([T]\) at 83°C in Cyclohexane
•CR₂CO₂R. In order to make a reasonable estimate of $k₄₄^{th}$ the resonance stabilization of 4₄ needs to be considered. Radical stabilization is usually equated to reduction of the corresponding C-H bond dissociation energy, D(C-H), relative to a reference species. However, the thermodynamic data available for bond strengths in esters (and ketones) appear not to be reliable.²⁵,¹⁵²,¹⁵³ A more accurate estimate can probably be obtained through Nonhebel and Walton’s empirical relationship between D(C-H) and the rotational barrier in the corresponding radical; this relationship when combined with Lung-Min and Fischer’s ESR data for •CH₂CO₂R species affords a stabilization energy of $E_{stab} = 8±1$ kcal/mol.¹⁵² This figure has been corroborated by recent theoretical and experimental data.¹⁵⁴ Thus, based on the assumption that it is principally radical stability and spacial factors which dictate the radical coupling rate (for further discussion see Ch 5.5), it appears likely that $k₄₄^{th}$ would lie between the known value for a secondary radical and that for α-methylbenzyl (vide supra). Moreover, to be consistent with the linear relationship between the logarithm of rate constants and free energies, $\log k₄₄^{th}$ a has been linearly interpolated between the values for α-methylbenzyl and sec-alkyl¹¹ using stabilization energies of 10 kcal/mol for benzylic and 8 kcal/mol for α-ester groups as guides (cf. Ch 5.5). This procedure gives $k₄₄^{th} = 2.8 \times 10^8$ M⁻¹s⁻¹ at 80°C and thus, assuming the temperature dependence is similar to that for primary radicals, we obtain the Arrhenius expression: $\log (k₄₄^{th}/$M⁻¹s⁻¹) = 9.0-0.9/°. Substitution of this expression into the relative kinetic data of Table 4.4-5 affords estimates of the absolute rate constants (Table 4.6).

Table 4.6. Arrhenius Coefficients and Rate Constants for Rearrangements at 4₄.²

<table>
<thead>
<tr>
<th>rearrangement</th>
<th>log A, s⁻¹</th>
<th>E, kcal/mol</th>
<th>$k^{25°}, 10^6$ s⁻¹</th>
<th>$k^{80°}, 10^6$ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{trans}$</td>
<td>14.0</td>
<td>10.8</td>
<td>1.5</td>
<td>26</td>
</tr>
<tr>
<td>$k_{cis}$</td>
<td>14.4</td>
<td>12.6</td>
<td>0.18</td>
<td>5.0</td>
</tr>
<tr>
<td>$k_{trans}$</td>
<td>12.3</td>
<td>7.5</td>
<td>6.3</td>
<td>45</td>
</tr>
<tr>
<td>$k_{cis}$</td>
<td>12.7</td>
<td>8.0</td>
<td>6.8</td>
<td>56</td>
</tr>
<tr>
<td>$k_{trans}$</td>
<td>11.5</td>
<td>7.5</td>
<td>1.0</td>
<td>7.2</td>
</tr>
<tr>
<td>$k_{cis}$</td>
<td>12.6</td>
<td>8.0</td>
<td>5.4</td>
<td>44</td>
</tr>
</tbody>
</table>

² In cyclohexane trapping rate constants in eq 4.3 were assumed to be: $k₄₄(4'₄) = 5 k₄₄(4₄)$, with log $k₄₄(4'₄) = 9.7 - 0.9/°$. Rate constants at 25° and 80°C were calculated from the Arrhenius coefficients.
Data in Table 4.6 show that, relative to but-3-enyl for instance, the ring-closure of \(4'h\) is strongly promoted by the ester group; a rough analogy may be made with intermolecular radical addition reactions of acrylic esters versus unactivated olefins (see below, however). On the other hand, rate constants for the cis and trans \(\beta\)-fission reactions of \(4h\) \((k_{t}^{\text{trans}} \text{ and } k_{t}^{\text{cis}})\) are 50 and 10 times lower at 80°C, respectively, than the ring-opening rate constant of the CPM radical (per bond). The foregoing implies that, as for \(4g\), a large (nett) resonance energy is associated with the ring-closed form; a novel method for deducing this resonance energy from the kinetic data is suggested in the 'Thermodynamics' section below.

The ring-fission of \(4h\) is more selective than that of \(4f\) under conditions of kinetic control. This is probably a reflection of the relative degree of non-bonded interactions between the \(\alpha\)-substituents and the ring methylene groups in the transition states (illustrated for \(4h\) over). Selectivity for the \(\text{trans}\) product is greater at lower temperatures, e.g. \(k_{t}^{\text{trans}} / k_{t}^{\text{cis}} = 5.4\) at 80°C but 8.3 at 25°C, which indicates that the stereoselectivity arises from differences in the activation energy.

**Stereoelectronic Parameters for Cisoid and Transoid Fission of \(4h\)**

The rate at which one ring-opened isomer rearranges to the other can be calculated by a kinetic analysis of Scheme 4.3:

for \(\text{cis}\) to \(\text{trans}\) isomerization,

\[
k_{c \rightarrow t} = (1 + k_{t}^{\text{trans}} / k_{t}^{\text{cis}})^{-1} k_{t}^{\text{cis}}
\]

and for \(\text{trans}\) to \(\text{cis}\) isomerization,

\[
k_{t \rightarrow c} = (1 + k_{t}^{\text{trans}} / k_{t}^{\text{cis}})^{-1} k_{t}^{\text{trans}}
\]
The isomerization rate constants in Table 4.7 indicate that at equilibrium $K_{c\rightarrow t} = k_{c\rightarrow t}/k_{t\rightarrow c} = 6$ at 80°C; thus, in this instance, the thermodynamic and the kinetic stereoselectivities are virtually the same, i.e. 6:1 versus 5:1, respectively, at 80°C. More specifically, the free energy difference between the cis and trans isomers of $4'h$ is calculated to be $\Delta\Delta G^\circ = 1.3$ kcal/mol whereas the analogous quantity for the cisoid and transoid transition states is just slightly lower, viz. $\Delta\Delta G^\# = 1.1$ kcal/mol. This implies that energetic discrimination in the ground state is very similar to that in the transition state; which further suggests, but does not necessarily prove, reactant-like transition states for the ring-closures.

4.7 Kinetic Parameters for Rearrangements of $4g$ and $4h$. At the outset, it must be admitted that there is a degree of uncertainty in the absolute kinetic data of eq 4.13 and Table 4.7 arising both from the experimental errors and from the assumptions made about the $k_T$ of the respective species. In view of this, detailed interpretation of the data in terms of the 'entropic' and 'enthalpic' parameters of the reactions is probably not warranted. Nevertheless, since the true Arrhenius coefficients for the radical-trapping reactions of $4g$ and $4h$ are hardly likely to be much lower than the assumed values ($E_T$ cannot be negative!), there remains the suggestion that the log $A$ and $E$ terms for the ring-fission of these species are considerably higher than those for ordinary cyclopropylcarbinyl ring-fission reactions.

High log $A$ and $E$ terms relative to the unsubstituted radical (CPM) might be rationalized from the thermodynamic data. That is to say, the ring-opening is substantially endothermic in $4g$ (cf. eq 4.13) and this may (a) increase the kinetic energy barrier and (b) make the fission reaction more product-like than for the CPM radical (by the *Hammond Postulate* q.v.177). Ring-opening is entropically favourable ($\Delta S^\circ = 8$ eu for a 3-membered ring opening, cf. ref 146) so that the more product-like transition state in $4g$ may also lead to an increase in the entropy of activation, i.e. to a higher log $A$ term. More specifically, the entropy effect may operate through the rotation of the phenyl group; i.e. the restriction placed upon the rotation of the phenyl group by radical delocalization in the ground state of $4g$ ($E_{rot.4g} = 14$ kcal/mol) may be substantially reduced in the transition state and this leads to a higher entropy of activation. A similar argument can be applied to rationalize the data for $4h$. 
The enhanced ring-closure rate constants of $4'g$ and $4'h$ relative to but-3-enyl parallels the high reactivity of styryl or acrylic groups compared with ordinary vinyl groups in intermolecular free radical addition (IMFRA) reactions, e.g. polymerization. However, the fact that acrylic groups are generally much more reactive than styryl groups towards IMFRA shows that the analogy is not accurate; $4'g$ cyclizes faster than $4'h$. The obvious difference between IMFRA and 1,3-cyclizations is the 27 kcal/mol ring strain factor; that is to say, IMFRA reactions are some 27 kcal/mol more exothermic than (otherwise) comparable 1,3-cyclizations. Thus, though IMFRA reactions are considered to be controlled primarily by various frontier reactivity terms, viz. frontier-orbital, polar, and steric factors, this may not be the case for the more thermoneutral 1,3-ring closures where the thermodynamics of reaction must play a larger or even dominant role. The foregoing reaction profile argument is illustrated below with approximate kinetic parameters given for $X = \text{phenyl}$.

**Approximate Relative Energetic Parameters of IMFRA and 1,3-Cyclization**

![Reaction Profile]

**4.8 Thermodynamics.** Rate constants and Arrhenius coefficients for both forward and reverse reactions have been determined so that, in principal, the full thermodynamic parameters for rearrangements of $4g$ and $4h$ can be deduced. However, as noted above, much hinges on the accuracy of assumptions concerning the $k_T$ of stabilized species and, in addition, experimental uncertainties may be compounded in the data analysis; for example, error incurred from both the slope and abscissa estimates of the regression analysis may be compounded in $k_r$ – see eq 4.6.

The thermodynamic and kinetic parameters of CPM, $4g$, and $4h$ are summarized in
Figure 4.2. The reference in each case is the cyclic species ($\Delta G^0$, $\Delta H^0$, $\Delta S^0 = 0$). The y-axis gauges the free energy levels; enthalpy and entropy changes are bracketed to emphasize that they are likely to be less accurate than the $\Delta G^0$ values.

Figure 4.2. Free Energy (Enthalpy, Entropy) Levels at 298 K from Radical-Trapping Data.

Cyclopropylcarbinyl ring-openings might generally be expected to be exothermic due to relief of the large ring strain (28 kcal/mol). However 'cycloethane' is also very strained and the trade-off of three strained $\sigma$-bonds (in CPM) for a two $\sigma$- plus one $\pi$-bond (in homoallyl) leaves the reaction just slightly exothermic (but some-what more exergonic due to the favourable entropy change of a ring opening).

Thermochemical calculation gives $\Delta H^0 = -4.7$ kcal/mol, $\Delta S^0 = 7.6$ e.u. and $\Delta G^0 = -7.0$ kcal/mol for cyclopropylmethylyl ring-fission; the agreement with our kinetic estimate is good considering the disparate sources for $k_r$ and $k_t$, and the neglect of ring strain perturbations in the calculation.

Ring fission becomes less favourable upon substitution of a stabilizing group at the
radical centre. Furthermore, the degree of radical stabilization can be estimated by comparison of the calculated thermodynamic parameters with those of CPM. For example, the 'nett' stabilization energy for 4g may be calculated by subtracting the free energy of reaction for CPM from that of the substituted radical, i.e. \( \Delta G^\circ = 5.6 - (-1.7) = 7.3 \text{ kcal/mol} \) (see Fig. 4.2). Neglecting non-bonded interactions, the radical stabilization energy \( (\Delta E_{\text{stab}}) \) afforded by the substituent is larger than the 'nett' figure by the amount of delocalization energy in the acyclic form, e.g. for 4'g ca.1.7 kcal/mol resonance energy is calculated for styrenes so that \( \Delta E_{\text{stab}} = 9.0 \text{ kcal/mol} \). A similar calculation for 4h (trans) gives \( \Delta E_{\text{stab}} = 7.3 \text{ kcal/mol} \) for an \( \alpha \)-alkoxycarbonyl group.

Both of the above estimates are in good agreement with the resonance energies which have been calculated for \( \text{PhCH}_2\cdot \) and \( \text{ROCOCH}_2\cdot \) species. The presence of non-bonded interactions would mean that \( \Delta E_{\text{stab}} \) is underestimated by the above method if the degree of these interactions is greater in the cyclic species or vice versa. The effect is clearly illustrated in 4h where the calculation affords \( \Delta E_{\text{stab}} = 7.3 \text{ kcal/mol} \) from the trans fission but 8.9 kcal/mol from the cis fission; the former is probably more accurate because, in spacial terms, \( 4h^{\text{trans}} \) is closer to the ground state conformation of 4h than is \( 4h^{\text{cis}} \).

The correlation of equilibrium with \( \Delta E_{\text{stab}} \) might be used in the converse sense; that is, to predict the effect of \( \alpha \)-substituents on the partitioning between ring-opened and ring-closed forms in more complex homoallylic radical systems.

Conclusions

Alkoxycarbonyl radicals 3a-3g were readily generated by thermolysis of tert-butyl monoperoxalyl esters 2a-2g. Rate constants for the decarboxylation of 3a-3g have been calibrated by the radical-trapping method. Results (Table 4.2) indicate that product radical (R•) stability is an important factor but that strain may be the dominant factor in the tertiary species.

\( \alpha \)-Substituted CPC radicals, some of which were accessible via appropriate tert-butyl monoperoxalyl esters (2d-2g), ring open at rates determined by the thermodynamic
stabilization of the radical centre and by the degree of steric repulsion between the ring and the substituent(s). As might be expected, the kinetic stereoselectivity of ring fission was increased by the steric bulk of the substituent, e.g. $k_{\text{trans}}/k_{\text{cis}} = 2$ for a methyl group (4f) versus 5 for the tert-butoxycarbonyl group (4h).

Radicals 4g and 4h rapidly attain equilibrium with their isomeric forms (Schemes 4.2 and 4.3). The kinetics of both the forward and reverse reactions have been deduced from the response of the radical-trapping kinetic data. Equilibrium constants for these radicals show that ring-closed forms are thermodynamically favoured in both cases presumably because of radical delocalization in these species. The rates at which the cis and trans isomers of 4'h interconvert could also be deduced and so yielded their relative ground energies.

Finally, comparison of relative energy levels of the isomers of 4g and 4h with those of the CPM radical indicates that the radical stabilization afforded by α-phenyl and alkoxy carbonyl groups is 9.2 and 7.2 k cal/mol respectively.

Experimental Section
Details of the instrumentation and reaction/analysis procedures have previously been described (Ch 2). However, because the monoperoxalic esters (2a-2g) decomposed at lower temperatures than the acyl peroxides (e.g. 9), reaction mixtures containing the former were maintained below 10°C before immersion in the thermostatted oil baths. Experimentally useful temperature ranges were 25-80°C for the monoperoxyoxalates and 60-125°C for the acyl peroxides. The alkoxyamine product ratios were reproducible and stable under the respective reaction/analysis conditions (cf. Ch 2).

4.9 Starting Materials. 2-Cyclopropyl-2-propanol (1d) was prepared by treatment of acetyl cyclopropane with excess MeMgI in ether at reflux. Dicyclopentylmethanol (1e), 1-cyclopropylethanol (1f), and cyclopropylphenylmethanol (1g) were prepared by LiAlH₄ reduction of the corresponding ketones (Aldrich). Properties and spectral data
agreed with that in the cited publications. Preparation and properties of monoperoxalic esters 2a, 2b, and 2c have previously been described. Monoperoxalic esters (2d-2g) were formed in pentane by the same procedure but were not isolated due to explosive decomposition of one at least (2d) when pure; instead the pentane was removed by evaporative displacement with cyclo-hexane (10 mm Hg, <10°C), after which the peroxide solution was made up to volume with cyclohexane and standardized by iodometric titration.116

Di-tert-butyl Cyclopropanemonoperoxymalonate (9). Cyclopropane-acetyl chloride (Aldrich) was converted into its tert-butyl ester by a standard procedure (Vogel172e) (65%). The ester (4.04 g) in THF (25 ml) was added to LDA (1.0 mol. equiv.) in THF/hexane at -30°C then a fast stream of dry CO₂ was passed for 10 min after which the reaction mixture was diluted with water and extracted with chloroform. Base extraction (aq-NaHCO₃), careful acidification (HCl), isolation with chloroform, and recrystallization from cyclohexane afforded tert-butyl hydrogen cyclopropanemalonate (2.8 g, 48%) as colourless plates mp 70°C: ¹H NMR (100 MHz, CDCl₃); δ 0.4 (m, 2H), 0.55 (m, 2H), 1.1 (m, 1H), 1.30 (s, 9H), 2.55 (d, 1H, 8 Hz), 10.8 (s, 1H); IR ν_max 1730, 1773 (C=O) cm⁻¹. Anal. Calcd for C₁₀H₁₆O₄: C, 59.99 H, 8.05; Found: C, 60.23 H, 8.32. The hydrogen malonate ester was converted into the acid chloride then treated with tert-butyl hydroperoxide/pyridine (general procedures (2) and (4) of Ch 2.17) to afford the title perester (63%) of 96% iodometric purity: ¹H NMR (100 MHz, CDCl₃); δ 0.4 (m, 2H), 0.6 (m, 2H), 1.05 (m, 1H), 1.38 (s, 9H), 1.53 (s, 9H), 2.62 (d, 1H, 8 Hz); IR ν_max 1736, 1773 (C=O) cm⁻¹.

4.10 Alkoxymine Products. The methods used for the preparation and identification of the alkoxamines have previously been described as have their characteristic NMR and UV spectral features (cf. Ch 2.18). All alkoxamines were colourless viscous oils unless otherwise specified.

2-Cyclopropyl-2-propyl 1,1,3,3-Tetramethylisoindolin-2-yl Carbonate (5d). ¹H NMR (CDCl₃, 200 MHz); δ 0.50 (m, 4H), 0.9 (m, 1H), 1.38 (s, 6H), 1.40 (s, 6H), 1.43 (s, 6H), 7.09 (m, 2H), 7.21 (m, 2H); IR ν_max (CCl₄) 1774, 1749 (C=O) cm⁻¹.
Chapter 4: Alkoxycarbonyl and Cyclopropylcarbinyl Radicals

2-(2-Cyclopropyl-2-propoxy)-1,1,3,3-tetramethylisoindoline (6d): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.46 (m, 4H), 0.96 (m, 1H), 1.22 (s, 6H), 1.42 (s+d, 6H+6H), 7.02 (m, 2H), 7.16 (m, 2H).

Dicyclopropylmethyl-1,1,3,3-Tetramethylisoindolin-2-yl Carbonate (5e): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.41 (m, 8H), 0.92 (m, 2H), 1.38 (s, 6H), 1.43 (s, 6H), 3.54 (t, 1H, 5 Hz), 7.09 (m, 2H), 7.21 (m, 2H); IR \(\nu_{max}\) (CCl\(_4\)) 1776, 1759 (C=O) cm\(^{-1}\).

2-Dicyclopropylmethoxy-1,1,3,3-tetramethylisoindoline (6e): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.35 (m, 8H), 0.98 (m, 2H), 1.42 (m, 12H), 2.85 (t, 1H, 6Hz), 7.02 (m, 2H), 7.16 (m, 2H).

2-(4-Cyclopropyl-3-buten-1-oxy)-1,1,3,3-tetramethylisoindoline (6'e): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.4-1.0 (m, 4H), 1.38 (br s, 12H), 1.56 (m, 1H), 2.45 (q, 2H), 3.89 (t 2H, 6.3 Hz), 5.32 (m, 2H), 7.02 (m, 2H), 7.16 (m, 2H).

1-Cyclopropyl-1-ethyl 1,1,3,3- Tetramethylisoindolin-2-yl Carbonate (5f): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.4 (m, 4H), 0.99 (m, 1H), 1.25 (d, 3H, 6 Hz), 3.05 (q, 1H, 6Hz), 7.08 (m, 2H), 7.20 (m, 2H); IR \(\nu_{max}\) (CCl\(_4\)) 1772, 1749 (C=O) cm\(^{-1}\).

2-(1-Cyclopropyl-1-ethoxy)-1,1,3,3-tetramethylisoindoline (6f): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.4 (m, 4H), 0.95 (m, 1H), 1.15 (d, 3H, 6 Hz), 3.35 (q, 1H, 6Hz), 7.02 (m, 2H), 7.16 (m, 2H).

2-(3-Penten-1-oxy)-1,1,3,3-tetramethylisoindoline (6'f). \(^1\)H NMR of the isomer mixture was consistent with a 1.6:1 \textit{trans}:\textit{cis} ratio based on the following assignments which were corroborated by those of authentic \textit{cis} and \textit{trans} 3-penten-1-ol\(^{172f}\): 6'\textit{ftrans}; \(\delta\) 1.42 (brs, 12H), 1.68 (dd, 3H, 4 Hz, 1 Hz), 2.17 (m, 2H), 3.85 (t, 2H, 7 Hz), 5.50 (m, 2H), 7.02 (m, 2H), 7.18 (m, 2H), 6'\textit{fcis}; same except: \(\delta\) 1.63 (d, 5H), and 2.30 (q, 2H, 6 Hz).
Cyclopropylphenylmethyl 1,1,3,3-Tetramethylisoindolin-2-yl Carbonate (5g).

$^1$H NMR (CDCl$_3$, 200 MHz), δ 0.3 (m, 1H), 0.5 (m, 2H), 0.98 (m, 1H), 1.48 (brs, 12H), 4.55 (d, 1H, 6 Hz), 7.15 (m, 2H), 7.20 (m, 2H), 7.30 (m, 5H); IR $\nu_{\text{max}}$ (CCl$_4$) 1770, 1743 (C=O) cm$^{-1}$; UV $\lambda_{\text{max}}$ (log ε) (MeOH), 228 (3.21), 257 (2.90), 264 (3.04), 270 (3.04) nm.

2-Cyclopropylphenylmethoxy-1,1,3,3-tetramethylisoindoline (6g). $^1$H NMR (CDCl$_3$, 200 MHz), δ 0.3 (m, 1H), 0.5 (m, 2H), 0.95 (m, 1H), 1.40 (m, 12H), 4.75 (d, 1H, 6 Hz), 7.05 (m, 2H), 7.19 (m, 2H), 7.25 (m, 5H). UV $\lambda_{\text{max}}$ (log ε) (MeOH), 229 (3.19), 255 (2.87), 264 (3.02), 271 (3.02).

2-(4-Phenyl-but-3-enoxy)-1,1,3,3-tetramethylisoindoline (6'g): $^1$H NMR indicated the trans form by comparison with data for authentic trans 4-phenyl-3-buten-1-ol. $^1$H NMR (CDCl$_3$, 200 MHz), δ 1.43 (brs, 1H, 12H), 2.45 (q, 2H, 6 Hz), 3.91 (t, 2H, 7 Hz), 6.10 (dt, 1H, 17 Hz/6 Hz), 6.51-7.02 (m-2H), 7.08 (m, 2H), 7.14-7.35 (m, 7H); UV $\lambda_{\text{max}}$ (log ε) (MeOH), 251 (4.25), 264 sh (3.22), 270 (3.23), 273 (3.02).

tert-Butyl α-(1,1,3,3-Tetramethylisoindolin-2-yl)-cyclopropaneacetate (6h).

$^1$H NMR (CDCl$_3$, 200 MHz), δ 0.4 (m, 1H), 0.6 (m, 2H), 0.98 (m, 1H), 1.15 - 1.50 (m, 21H), 5.05 (d, 1H, 6 Hz), 7.05 (m, 2H), 7.19 (m, 2H). IR $\nu_{\text{max}}$ 1778, 1640 (C=O) cm$^{-1}$.

tert-Butyl cis-5-(1,1,3,3-Tetramethylisoindolin-2-yl)-pent-2-enoate (6'hcis).

$^1$H NMR (CDCl$_3$, 200 MHz), δ 1.32 (s, 9H), 1.45 (br s, 12H), 2.61 (m, 2H), 3.75 (t, 2H, 8.1 Hz), 5.74 (dt, 1H, 11.4 Hz/ 2.2 Hz), 6.32 (dt, 1H, 11.4 Hz/ 7.3 Hz), 7.07 (m, 2H), 7.19 (m, 2H). IR $\nu_{\text{max}}$ 1718 (C=O) cm$^{-1}$.

tert-Butyl trans-5-(1,1,3,3-Tetramethylisoindolin-2-yl)-pent-2-enoate

(6'htrans). $^1$H NMR (CDCl$_3$, 200 MHz), δ 1.34 (s, 9H), 1.45 (br s, 12H), 2.40 (m, 2H), 3.80 (t, 2H, 8.1 Hz), 5.79 (dt, 1H, 14.9 Hz/ 1.8 Hz), 6.98 (dt, 1H, 14.9 Hz/ 6.8 Hz), 7.07 (m, 2H), 7.19 (m, 2H). IR $\nu_{\text{max}}$ 1722 (C=O) cm$^{-1}$.
CHAPTER FIVE

Investigations of Various Alkyl Radical Rearrangements

Abstract

In this chapter radical-trapping investigations of various alkyl radical rearrangements are reported, namely: (I) cyclization of \( \varepsilon \)-alkenyl radicals 16, 17 and 18 and the ring opening of 18', (II) the extremely rapid transannular radical addition of 6-methylenecyclodecyl radical 19, (III) ring opening of cyclobutylmethyl radicals 5 and 19 and (IV) a mechanistically puzzling, rapid isomerization of 1,1-diduterio-2-(9-anthryl)-ethyl radical 20. Also reported are the reappraised kinetics for ring closures of 3, 6 and 9 (see Ch 2.7) and investigations of the reactions of highly stabilized radicals with T (performed apropos of 20).

[NB: Radical numbering follows from Chapter Two with isomeric radicals being denoted unprimed for the initial species or primed for the rearranged species (e.g. 18\( ' \)\( ' \)\( ' \)), radical precursors are denoted by the suffix P (e.g. 18P) and alkoxyamine products by the suffix T (e.g. 18T, 18'T and 18''T)].

(I) \( \omega \)-Alkenyl Radical Ring Closures\(^{173,174} \)

5.1 Introduction. Suitably constituted \( \omega \)-alkenyl radicals undergo intramolecular radical addition. The most common and widely studied of these reactions are the ring closures of 5-hexenyl radicals, i.e.

\[
\begin{align*}
R_1 & \quad \cdots \quad R_2 \quad \cdot \quad R_3 \quad \cdots \quad R_4 \\
R_5 & \quad \cdots \quad R_6
\end{align*}
\]

A thermochemical calculation for the unsubstituted radical using Benson's method shows that the reaction is highly exothermic with formation of the endo radical being substantially favoured over exo, i.e. \( \Delta H^\circ_{\text{endo}} = -23.5 \) and \( \Delta H^\circ_{\text{exo}} = -15.5 \text{ kcal/mol} \). The large
enthallpies of reaction mean that generally these cyclizations are irreversible. Exceptions arise when the open chain radicals are strongly stabilized; for instance when \( R_1 = R_2 = \text{CO}_2\text{Et}^{175} \) or phenyl\(^{176} \) (scheme above) the ring closure is reported to be reversible. Schiesser has studied the cyclization of the mono substituted species 17 (\( R_1 = \text{CO}_2\text{Et}, R_2 = \text{H} \)) using the stannane method;\(^{175} \) he detected signs of reversibility in this reaction but could only report a relative cyclization rate, i.e. \( k_f/k_H \), since there are no calibrations available for the hydrogen atom transfer rate constant \( k_H \) between \( \alpha\)-alkoxy-carbonyl-alkyl radicals and the stannane. It was hoped that the relatively low selectivity of radical-trapping would allow a more definite calibration of \( k_f(17\rightarrow17') \) and thus that the combination of radical-trapping data with the stannane data would provide an estimate for \( k_H(17) \).

Despite the endo radical being thermodynamically favoured by some 8 kcal/mol, evidence from ESR and product studies has demonstrated that in the majority of cases 5-hexenyl radicals cyclize preferentially to the exo species with reported (kinetic) selectivities often exceeding 50:1 in favour of the exo product(s). The discrepancy between the kinetic and thermodynamic data can be partially explained by the strongly exothermic nature of the reaction; i.e. a reactant-like transition structure is predicted (by the Hammond Postulate\(^{177} \)) so that product radical stability is of only minor importance in determining the kinetic energy barrier for the ring closure.

Beckwith\(^{173} \) has proposed that it is the degree of non-bonded interaction in the transition structure which determines the regio- and stereo-selectivity of 5-hexenyl cyclizations. This hypothesis correctly predicts the observed regio-selectivity: the long \( CI \) to \( C5 \) distance in the predicted transition structure\(^{175,119} \) allows a favourable cyclohexane-like "pseudo-chair" conformation (see below) to be adopted for 1,5-exo cyclization, whereas for the 1,6-endo cyclization, attainment of the mandatory transition structure creates a relatively large amount of strain energy. It is only when the 5-position is substituted (e.g. \( R_5 = \text{Me}^{173,85b} \)) that 1,6-cyclization is favoured.

Beckwith and Schiesser have used Molecular Mechanics\(^{187} \) calculations to estimate
Chapter 5: Alkyl Radical Rearrangements

the relative strain of transition structures leading to the exo- and endo-cyclic isomers of various \( \omega \)-alkenyl radicals (the \textit{ab initio}/MINDO3 predicted geometry for hex-5-ynyl is shown below). The authors successfully predicted the regio- and stereo-chemical outcome of a large number of such rearrangements.\textsuperscript{175,119}

\[
\begin{align*}
\mathrm{d}_{15} &= 2.20 \, \text{Å} \\
\mathrm{d}_{96} &= 1.39 \, \text{Å} \\
\angle 156 &= 104^\circ
\end{align*}
\]

One (the only!) case where the method failed to predict the correct stereochemistry was for the cyclization of the 6-methylenecyclodecyl radical (19): investigation by the stannane method indicated a 3:1 predominance of the \textit{cis} cyclized product whereas the MM2 calculation predicted a kinetic preference of about the same magnitude for the \textit{trans} cyclization \((\Delta \Delta H^\# = 1.4 \, \text{kcal/mol})\). The cyclization was extremely rapid and consequently the stannane reduction method could not provide an estimate for the cyclization's rate constant because only the rearranged hydrocarbon products were detected (viz. \textit{cis} and \textit{trans} 9-methyldecalin). It appeared to the present author that since the trapping rate constant \( k_T \) for similar (secondary) radicals is some 400 times higher than \( k_H \),\textsuperscript{72,56} that radical-trapping would be an ideal method with which to perform a follow-up investigation.

Results

5.2 2-Oxo-3-oxa-hex-5-ynyl Radical (16). The precursor for this radical, \( \text{Q-allyl QO-tert-butyl monoperoxymalonate 16P}, \) was prepared by half hydrolysis of diallyl malonate (prepared from malonyl dichloride) followed by treatment with oxalyl chloride and conversion of the resulting acid chloride into 16P with anhydrous tert-butyl hydroperoxide and an excess of pyridine (cf. Ch 2.17). Preparation of the diacyl peroxide was attempted but it was too labile to be isolated.

Mixtures of the perester 16P with 10 mol. equiv. T (0.2, 0.5 and 2.0 mM) in cyclohexane were degassed, heated (80°C, 4hr) and analyzed in the usual manner (Ch 2.3 and 2.15)
HPLC analysis revealed a 1:1 ratio of two products, viz. trapped cyclohexyl (from reaction of tert-butoxyl with the solvent) and 16T. The possibility that 16T and 16'T were co-eluted was precluded by NMR analysis of "16T" (3.5 mg) isolated from a 0.2 mM reaction mixture. Thus, assuming that $k_T = 1.0 \times 10^9 \text{M}^{-1}\text{s}^{-1}$ and that the NMR analysis could detect 10% of 16'T in the sample of 16T, one can estimate that the cyclization rate constant must be less than $2 \times 10^4 \text{s}^{-1}$ at 80°C.

5.3 1-Ethoxycarbonylhex-5-enyl Radical (17). The precursor was prepared by alkylation of diethyl malonate with but-3-enyl bromide followed by half hydrolysis of the resulting diester and conversion into the tert-butyl perester 17P as above.

Thermal decomposition of 17P in cyclohexane solutions of T gave the trapped cyclohexyl radical, 17T and 17'T; the cis and trans isomers of 17'T were not resolved by HPLC but the NMR spectrum of the isolated isomer mixture indicated that it contained approximately equimolar amounts of the cis and trans isomers. The 1,6-cyclized product was not isolated but because there were a number of minor peaks in the HPLC trace, the largest of which was 15% of $17T + 17'T$, it could only be concluded that 1,5-cyclization was at least five times faster than 1,6-cyclization. Schiesser's stannane data$^{175}$ indicated 'exclusive' 1,5-cyclization. With [T] = 1.5, 0.75 and 0.40 mM the molar concentration ratios 17'T:17T obtained were 0.16±0.02, 0.31±0.04, and 0.65±0.08 respectively (three runs each); yields varied from 70% to 80%. Relatively large random errors in these data appeared to be associated with the use of very dilute solutions of T (see Appendices A1.4 and A3.3).
The kinetic data afford the rate ratio $k_c/k_T = 2.4 \pm 0.3 \times 10^{-4}$ M. Direct calibration data for stabilized radicals (see Ch 1.11) suggest a trapping rate constant of $4-6 \times 10^8$ M$^{-1}$s$^{-1}$ for the resonance stabilized radical 17 (cf. Ch 4.7 and below) so that

$$k_c(17 \rightarrow 17') = 1.0-1.5 \times 10^5 \text{ s}^{-1} \text{ at } 80^\circ\text{C.} \quad (5.1)$$

The radical-trapping data appear to agree with eq 2.1 and thus do not indicate reversibility.

At this temperature Schiesser estimated $k_c(17 \rightarrow 17')/k_H(17) = 0.12$ M so that combination of the stannane and radical-trapping data gives, $k_H(17) = (1.0 \pm 0.3) \times 10^5$ s$^{-1}$ at $80^\circ\text{C}$. This value is about a factor of four lower than that derived by Ingold et al for ordinary secondary radicals; presumably because of radical delocalization in 17.

### 5.4 6-Cyclopropyl-2,2-dimethylhex-5-enyl Radical (18).

\textit{trans} 4-Bromo-1-cyclopropyl-1-butene was (fortuitously) prepared by treatment of dicyclopropylmethanol with triphenylphosphine/Br$_2$ in DMF. Conjugate addition of the bromide's Grignard reagent to diethyl isopropylidenemalonate followed by decarbethoxylation with LiCl in refluxing DMSO afforded ethyl 7-cyclopropyl-6-heptenoate which was converted into 18P ($18-CO_2$)$_2$ by standard procedures (cf. Experimental and Ch 2.17 – 3P and 6P).

---

Thermal decomposition of 18P in the presence of 10 mol equiv. of T at $81^\circ\text{C}$ afforded alkoxyamines 18T, 18'T and 18''T in relative amounts given in Table 5.1; yields based on the peroxide were in the range 60-70%.

Kinetic analysis of the reaction scheme gives the following relationships between the relative molar concentrations of products and the rate constants (follows from Appendix A2.2):
Chapter 5: Alkyl Radical Rearrangements

for cyclization

\[ k_c/k_T = [T].(18'T+18''T)/18T \]  \hspace{1cm} (5.2)

for ring opening

\[ k_i/k_T = [T].18''T/18'T \]  \hspace{1cm} (5.3)

Eq 5.2 and eq 5.3 were used to derive the kinetic data in Table 5.1; thus with \( k_T = k_T' = 1.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1} \) (Ch 2) the rate constants at 81°C are

\[ k_c(18T\rightarrow 18'T) = (5.4\pm 0.5) \times 10^7 \text{ s}^{-1} \]  \hspace{1cm} (5.4)

and \[ k_i(18'T\rightarrow 18''T) = (10.7\pm 1.5) \times 10^7 \text{ s}^{-1} \]  \hspace{1cm} (5.5)

The cis and trans isomers of 18''T were not separated by HPLC (column #2) so that eq 5.5 represents the total ring fission rate constant for 18'T. However, NMR analysis of a sample of 18''T was consistent with an isomer ratio of \( \text{ca} \ 3:1 \) with the major isomer presumed to be trans by analogy with the ring fission of \( \alpha \)-methylcyclopropylcarbinyl radical (for which \( k_i \text{trans} : k_i \text{cis} = 2.3 \) at 25°C154, cf. Ch 4.3).

Table 5.1  Kinetic Data for Radical Rearrangement 18\( \rightarrow 18' \rightarrow 18'' \) at 81°C

<table>
<thead>
<tr>
<th>[T]( ^a,b ), mM</th>
<th>[18'+18'']/[18]</th>
<th>( k_c/k_T ), M</th>
<th>[18'']/[18']</th>
<th>( k_i/k_T' ), M</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.6</td>
<td>4.0(3)</td>
<td>0.043</td>
<td>7.8(5)</td>
<td>0.083</td>
</tr>
<tr>
<td>21</td>
<td>2.3</td>
<td>0.048</td>
<td>4.2</td>
<td>0.088</td>
</tr>
<tr>
<td>42</td>
<td>0.95</td>
<td>0.039</td>
<td>2.6</td>
<td>0.11</td>
</tr>
<tr>
<td>85</td>
<td>2.3</td>
<td>0.048</td>
<td>0.91</td>
<td>0.077</td>
</tr>
</tbody>
</table>

\( ^a \) Stock solutions: [T]\( _i \) = 98, 49, 25, and 12 mM in cyclohexane with 0.1 mol equiv 18P. \( ^b \) Corrected for thermal expansion and for the consumption of T by the reaction.

Discussion

5.5 Calibration of 5-Hexenyl Cyclizations. The examples presented above are only a fraction of the total number of 5-hexenyl cyclizations studied in the present work – the remainder have been previously calibrated by other methods and are thus treated as radical
'clocks' in Chapter Two (q.v.). However, at this point perhaps the best way to compare the various rearrangement rate constants is to use the radical-trapping data, in combination with (selected) radical clock and laser flash photolysis (LFP) values for $k_T$, to reassess the cyclization reactions studied so far. In this way, even if the absolute values are not '100%’ accurate, the comparison may at least be based upon a consistent kinetic standard, viz.: that the relative trapping rate constants for non-stabilized primary, neopentyl, secondary and tertiary radicals are 1.0 : 0.8 : 0.85 : 0.65 (all ±5%), respectively, and that the temperature variation of $k_T^{\text{primary}}$ can be represented by the Arrhenius equation, \( \log k_T/M^{-1}s^{-1} = 9.7 - 0.9/\theta \) (i.e. \( k_T = 1.4 \times 10^9 M^{-1}s^{-1} \) at 80°C) in cyclohexane.

For stabilized radicals the kinetics of radical-trapping are less well defined but 'reasonable' estimates of $k_T$ can be deduced from the LFP data; that is, if one assumes that it is principally the combined effect of radical stability and steric factors which dictate the coupling rate constant. For instance; the stabilization energy of primary $\alpha$-alkoxycarbonyl radicals, such as 16, is estimated to be about 7 kcal/mol,154 for the benzyl radical $E_{\text{stab}} = 10$ kcal/mol138 and so it seems reasonable that $k_T^{16}$ would lie somewhere between $k_T^{\text{benzyl}}$ and $k_T^{\text{primary}}$, i.e. between $7 \times 10^8$ and $14 \times 10^8 M^{-1}s^{-1}$ at 80°C. Furthermore, the fact that it is the logarithm of $k_T$ that is proportional to the free energy barrier suggests that the change in log $k_T$ from that of the non-stabilized reference species (\( \delta \log k_T \)) is linearly related to $E_{\text{stab}}$; based upon this idea we have,

\[
\delta \log k_T^{16} / \delta \log k_T^{\text{benzyl}} = E_{\text{stab}}^{16}/E_{\text{stab}}^{\text{benzyl}} = 7/10
\]

which gives $k_T^{16} = 0.75 k_T^{\text{primary}} = 10 \times 10^8 M^{-1}s^{-1}$. Similarly, $k_T^{17}$ can be estimated by interpolation between $k_T^{\text{secondary}}$ and $k_T^{\alpha$-methylbenzyl} (see 5.3). Trapping rate constants deduced by this method are not likely to be seriously in error unless polar factors are quite important; for example, if T were a nucleophilic radical then $k_T$ for electron deficient radicals such as 16 and 17 would be higher than the estimates made above.

In Table 5.2 I have summarised the radical-trapping kinetic data for all hexenyl cyclizations studied in the present work. It appears from the Arrhenius data that, with the possible exception of $2\rightarrow2'$, the frequency factors do not vary significantly from the value for
Table 5.2 Kinetic Data for 5-Hexenyl Cyclizations from Radical-Trapping Data\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Cyclization</th>
<th>$k_C^{80^\circ},10^6s^{-1}$</th>
<th>log $A/M^1s^{-1}$</th>
<th>$E_A$,kcal/mol</th>
<th>$k_C^{25^\circ},10^6s^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$\rightarrow$1'</td>
<td>1.35</td>
<td>10.4</td>
<td>6.85</td>
<td>0.24</td>
</tr>
<tr>
<td>2$\rightarrow$2'</td>
<td>17</td>
<td>9.9</td>
<td>4.4</td>
<td>4.7</td>
</tr>
<tr>
<td>3$\rightarrow$3'</td>
<td>17</td>
<td>10.4</td>
<td>5.1</td>
<td>4.6</td>
</tr>
<tr>
<td>6$\rightarrow$6'</td>
<td>9.5</td>
<td>10.4</td>
<td>5.5</td>
<td>2.3</td>
</tr>
<tr>
<td>8$\rightarrow$8'</td>
<td>11.5</td>
<td>10.1</td>
<td>4.7</td>
<td>3.9</td>
</tr>
<tr>
<td>9$\rightarrow$9'</td>
<td>16</td>
<td>10.2</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>16$\rightarrow$16'</td>
<td>&lt; 0.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CO$_2$Et$\rightarrow$CO$_2$Et</td>
<td>ca 0.12</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18$\rightarrow$18'</td>
<td>54</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All data were obtained in cyclohexane solvent. \textsuperscript{b} Assumptions regarding $k_T$ are given in the text. \textsuperscript{c} Calculated from the Arrhenius coefficients.
hex-5-enyl, i.e. log $A = 10.0-10.5$. Glover and Beckwith's steady-state ESR study also revealed that the frequency factor of $2 \rightarrow 2'$ was significantly lower than that of $1 \rightarrow 1'$, viz. by a factor of three ($\Delta \Delta S^\ddagger = 2.3$ eu). The kinetic data for these reactions suggest a tighter transition state but lower enthalpy barrier for $2 \rightarrow 2'$ compared with $1 \rightarrow 1'$. This might be rationalized on the basis of the smaller bond angle in the 3-position of 'ether' radical 2, i.e. $\angle C-O-C < \angle C-C-C$, which favours a shorter $C1-C5$ distance in the transition structure (illustrated above), or perhaps it is indicative of greater rotational freedom about the $O-C$ bonds in 2 compared with the $C-C$ bonds in 1, i.e. adoption of the transition stucture involves a larger loss of entropy in 2 than in 1 ($\Delta S^\ddagger$ is more negative) and thus cyclization of the former has a lower frequency factor.

The trend in the series 3, 8 and 9 has been previously discussed (Ch 2.7). The relatively high ring closure rate of 9, despite the obvious thermodynamic and steric counter forces, might be seen to support the proposed dipolar transition state with the positive charge on the 1-position.173

The radical-trapping data for 3 and 6 indicate that, contrary to the stannane data, the cyclization of 3 is faster than of 6. This might be explained by the following argument: A gem dimethyl group promotes 5-hexenyl cyclizations principally because gauche non-bonded interactions in the acyclic species are mitigated in the pseudo-cyclic transition state. It can readily be seen that 3 suffers a larger number of unavoidable gauche interactions with the methyl groups than 6 ($2 \times sp^3 + 2 \times sp^2$ versus $2 \times sp^3$, respectively$^{56}$) and so a slightly larger gem dimethyl effect is indicated for the former.

The relatively low ring closure rates for 16 and 17 may be explained by resonance delocalization of the radical orbital onto the carbonyl group, i.e. a reduced frontier-orbital density. At first sight it seems remarkable that 16 cyclizes much more slowly than 17 since presumably the latter is more stabilized (being secondary). However, inspection of the likely transition states reveals that for 16 the radical orbital may only effectively overlap the double bond by twisting out of conjugation with the carbonyl group thus suffering a large increase in enthalpy. For 17 this does not apply. A similar argument has been applied to resolve the
discrepancy between the cyclization rates of $\text{10}^{81,175}$ and $\alpha$-methoxy-hex-5-enyl $\text{5A}$ (see below). Explanations stemming from the relatively large $O-(CO)-C$ bond angle for $\text{16}$ ($\approx 120^\circ$) may also be possible.

Explanations stemming from the relatively large $O-(CO)-C$ bond angle for $\text{16}$ ($\approx 120^\circ$) may also be possible. A relatively large $O-(CO)-C$ bond angle for $\text{16}$ ($\approx 120^\circ$) may also be possible.

Relative to $\text{6}$, the ring closure rate of $\text{18}$ is increased by a factor of 3.2 by the cyclopropyl substituent. This is only slightly larger than the effect of a trans methyl group in the 6-position which is a factor of 1.8. The smallness of the effect supports the hypothesis of a transition state with a $\delta^-$ charge at the 6-position; that is, at least to the extent that it argues against the opposite polarization since a $\delta^+$ charge at this position would be greatly favoured by the cyclopropyl group.\textsuperscript{146} The ring opening of $\text{18'}$ to $\text{18''}$ has a rate constant similar to $\text{4f-4'f}$ of Ch 4.3.
Chapter 5: Alkyl Radical Rearrangements

(II)

9-Methylenecyclodecyl Radical (19)

5.6 Preparation of the Precursor (19P). 6-Hydroxymethyl-cyclodecanone was prepared from decalin in seven steps by a procedure which has been fully described by Becker and Cappuis. The reaction scheme is shown below. The third reaction, the Criegee rearrangement, appears similar to a Baeyer-Villiger rearrangement (q.v.) and might therefore have a similar mechanism, i.e. a nucleophilic carbon-to-oxygen migration.

The hydroxy-ketone was elaborated by a standard Wittig methylenation (8) and Jones oxidation (9). The resulting 6-methylenecyclodecyl-acetic acid was converted into 19P by the usual procedures [(10) and (11) - Ch 2.17].

5.7 Kinetics Experiments. Thermal decomposition of 19P in the presence of T in the usual manner afforded cis-19'T and trans-19'T. The identity of the isomers was established by spectral analysis of prepared samples and by HPLC coinjection of the authentic cis and trans isomers prepared from cis- and trans-9-decahydronaphthyl-acetic acid via their tert-butyl peresters (see Exp.). The unrearranged product was not resolved by HPLC but the

\[ \text{(1) O}_2/AIBN \ 100^\circ \text{C (2%), (2) } \phi \text{COCl/pyridine (98%), (3) MeOH reflux (60%), (4) KOH/aq-MeOH (86%), (5) MeP} \phi^+\text{Br-/DMSO/NaH at } 50^\circ \text{C (82%), (6) } \text{B}_2\text{H}_6/\text{THF at } -5^\circ \text{C then } \text{H}_2\text{O}_2/\text{NaOH (98%), (7) Br}_2/\text{HMPA/CH}_2\text{Cl}_2/aq-\text{NaNCO}_3 (90%), (8) Same as (5),(78%) (9) Jones' Reagent, (10) OxCl}_2, (11) \text{t-BuOOH/pyridine.} \]
NMR spectrum of a sample of \textit{trans-19'T}, prepared by HPLC resolution of a reaction mixture 0.3M in \textit{T}, revealed a small singlet resonance at \( \delta 4.96 \), comparison with the spectrum of 6-methylene-cyclodecanol indicated that this arose from \textit{19T}; i.e. that \textit{19T} was coeluted with \textit{trans-19'T}. Based on this assumption, the following product concentration ratios were obtained, (a) by HPLC analyses of reaction mixtures (\( \Rightarrow \text{cis : trans} \) ratios) and (b) by NMR analysis of samples prepared under the specified conditions (\( \Rightarrow \text{trans-19'T : 19T} \)); total yields were estimated to be in the range 60-70%.

80°C, 4hr, [\textit{T}] = 0.30M, [\textit{19P}] = 0.10M: \( \text{cis-19T} : \text{trans-19T} : \text{19T} = 2.7 : 1.0 : 0.082 \)
80°C, 4hr, [\textit{T}] = 0.60M, [\textit{19P}] = 0.21M: \( \text{cis-19T} : \text{trans-19T} : \text{19T} = 2.8 : 1.0 : 0.18 \)
123°C, 0.3, [\textit{T}] = 0.30M, [\textit{19P}] = 0.10M: \( \text{cis-19T} : \text{trans-19T} : \text{19T} = 2.1 : 1.0 : 0.041 \)  
(±5\% for cis : trans and ±12\% for trans : 19'T ratios).

The data indicate, \( k_{c\,\text{cis}} = 1.2 \times 10^{10} \text{ s}^{-1} \) and \( k_{c\,\text{trans}} = 4.5 \times 10^{9} \text{ s}^{-1} \) at 80°C and \( k_{c\,\text{cis}} = 1.9 \times 10^{10} \text{ s}^{-1} \) and \( k_{c\,\text{trans}} = 9.2 \times 10^{9} \text{ s}^{-1} \) at 123°C from which the approximate temperature variation equations are (\( \theta = 2.3RT \text{ kcal/mol} \))

\[
\log k_{c\,\text{cis}} = 11.9 - 3.0/\theta \quad (5.5)
\]
\[
\log k_{c\,\text{trans}} = 12.5 - 4.6/\theta \quad (5.6)
\]

\section*{5.6 Discussion.}

There are several reported spectral and chemical manifestations of \textit{transannular} non-bonded interactions in 8- to 11-membered ring compounds\(^{183}\) and most appear to be caused by the proximity of groups at the 1-position to those at the 5- or 6-positions.

Of relevance here is the report that the 6-oxo-cyclodecyl radical cyclizes in the presence of 1.3M tributylstannane (60°C) to afford the reduced rearranged radicals, viz. \textit{cis-} and \textit{trans-9-decalinol}, in high yield (95\%) but with just 4\% yield of the unrearranged reduced product. This demonstrates that the cyclization or 'ring fusion' is remarkably rapid,\(^{184}\) i.e. the total \( k_{c} = 1.0 \times 10^{8} \text{ s}^{-1} \) at 60°C which is some 100 times faster than hex-5-enyl or 1000 times faster than the more closely related 5-oxo-pentyl radical.\(^{185}\) The report also demonstrated that, although \textit{cis} cyclization is kinetically favoured (\( \text{cis : trans} = 3.7 \)), the \textit{trans} fused radical is more
stable. Schiesser found that the analogous transannular addition to a carbon-carbon double bond, i.e. ring fusion of 19, was irreversible and gave mostly the cis-9-methyl decalin but with no detectable amount of the unrearranged radical product, methylenecyclodecane; a lower limit of $5 \times 10^8 \text{s}^{-1}$ was therefore calculated for the total cyclization rate constant at 80°C. The fact that the cis : trans ratio fell from 3.2 at 60°C to 2.3 at 122°C indicated that the cis cyclization had a lower activation energy. The regio-selectivity of the reaction was opposite to that predicted by MM2 calculations which have proven highly reliable for ordinary cyclizations (see Intro.).

No explanation has been given for this discrepancy but it occurs to the present author that, in view of the extreme rapidity of the reaction, the preferential cis fusion might be a 'memory effect', i.e. the radical 'remembers' or holds the conformation of its precursor molecule long enough for fusion to take place. It is a simple matter to calculate that, since the energy barriers between stable conformations in similar rings are of the order of 7-12 kcal/mol, the rate constant for 'flipping' between conformations is probably in the range $4 \times 10^5$ to $5 \times 10^8 \text{s}^{-1}$ (at 80°C with $\log A = 13$); this is clearly much slower than the ring fusion rate of 19 ($10^{-10} \text{s}^{-1}$) and perhaps it is also slower than ring fusion for the 6-cyclodecanone radical. The hypothesis is illustrated below. [NB, "transoid" 19P $\rightarrow$ "cisoid" 19 and vice versa].
barriers for conformational changes in acyclic species are small.

Eq 5.5 and 5.6 suggest that much of the large difference between the rate constants for ordinary 5-hexenyl cyclizations and the transannular radical additions, e.g. 19, lies in the pre-exponential term. Typical log $A$ terms for 5-hexenyl cyclizations are in the range 10.0 to 10.4 ($\Delta S^\# = -14 \text{ eu}$), whereas the data for 19 give $\log A = 12.3$ ($\Delta S^\# = -5 \text{ eu}$). The origin of the increased frequency factor for the latter reaction is intuitively obvious; 5-hexenyl cyclization entails a large loss of internal freedom (mostly rotational) as the 'floppy' acyclic species is constrained to the cyclic transition state, by contrast, ring fusion is attended by only a relatively small loss of internal freedom since both the radical and the double-bond groups are rotationally constrained before addition takes place.

(III)

Two Cyclobutylcarbinyl Ring Openings$^{82,188}$

As mentioned in Chapter Two the cyclobutylcarbinyl radical ring openings are generally too slow to be calibrated by the radical-trapping method (e.g., $k_1$ (13) $< 10^5 \text{ s}^{-1}$ at 80°C). However, investigations by Moad and Beckwith$^{82}$ have shown that ring opening is strongly promoted by alkyl substituents at the $\gamma$-position. Consequently, the calibrated ring opening of 5 could be used as a radical 'clock' (see Ch 2.7). In this section the ring fission rate constant for 5 is confirmed and compared with that of the $\delta$-oxo substituted radical 20.

Results

5.7 Synthesis. (−)Methyl (2,2-dimethyl-3-oxo-cyclobutane)-acetate 20E was prepared from $\alpha$-pinene via (−)pinonic acid in five steps by a procedure described by Subramanian,$^{121}$ (see below). The ketone group was removed from 20E by desulphuration of its thioacetal with Raney nickel. Esters 20E and 5E were converted into the corresponding diacyl peroxides 20P and 5P by the usual procedures.
Chapter 5: Alkyl Radical Rearrangements

Preparation Scheme for 5P and 20P

\[ \text{α-pinene} \rightarrow (1) \rightarrow (-\text{pinonic acid}) \rightarrow (2) \rightarrow \text{CO}_2\text{Me} \rightarrow (3) \rightarrow \text{CO}_2\text{Me} \rightarrow (4) \rightarrow \text{CO}_2\text{Me} \rightarrow (5) \rightarrow \text{CO}_2\text{Me} \rightarrow (6) \rightarrow \text{CO}_2\text{Me} \rightarrow (7) \rightarrow \text{CO}_2\text{Me} \]

(1) \( a) \text{KMnO}_4/\text{NaHSO}_4/\text{ice}, b) \text{MeOH}/\text{BF}_3\)-etherate. (2) MCPBA. (3) \( a) \text{KOH/aq-MeOH}, b) \text{MeOH}/\text{BF}_3\)-etherate, c) Jones' Reagent. (4) see 'general procedures' of Ch. 2.17. (5) Ethanedithiol/\text{BF}_3\)-etherate. (6) Raney-Nickel W2. (7) see (4).

5.9 Kinetics. Alkoxyamines 5T and 5'T could not be resolved by HPLC, the ratios 5'T/5T were calibrated by NMR analysis of the HPLC prepared mixtures. Kinetic data obtained for radical 5 were given in Chapter Two (cf. Table 2.4, Sup. Table 2.5, Ch 2.7 and 2.17). The radical-trapping kinetic data with \( k_T = 1.4 \times 10^9 \text{M}^{-1}\text{s}^{-1} \) give eq 5.7 for the ring opening rate constant at 80°C in cyclohexane.

\[ k_i (5 \rightarrow 5') = (5.7 \pm 0.85) \times 10^6 \text{ s}^{-1} \quad (5.7) \]

The stannane calibration of Moad and Beckwith\(^\text{82}\) gave a rate constant of 7.4 \times 10^6 \text{ s}^{-1} at 80°C.

Thermal decomposition of 20P in the presence of T in the usual manner afforded alkoxyamines 20T and 20'T in moderate yields (45-55%). Analysis of duplicate ampoules after prolonged heating indicated that 20'T was not stable under reaction conditions. This was not unexpected in view reports from other workers that similar alkoxyamines, i.e. trapped
products of tertiary \(\alpha\)-cyano or \(\alpha\)-carbonyl radicals, decompose above about 60°C. However, the decay of \(20'T\) was less rapid than that of the precursor \((20P)\) so that by extrapolating data obtained at various reaction times back to \(t = 0\), the kinetically determined product concentration ratios could be estimated.

### Kinetic Scheme for Radical 20

![Kinetic Scheme for Radical 20]

---

### Table 5.3 Alkoxyamine Yields from 20P at 80°C versus Reaction Time

<table>
<thead>
<tr>
<th>[T] (^{b}), mM</th>
<th>time, hr</th>
<th>20T, % (^{c})</th>
<th>20'T, % (^{c})</th>
<th>20'T/20T</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.0</td>
<td>2.0</td>
<td>4.5</td>
<td>5.0</td>
<td>1.11</td>
</tr>
<tr>
<td>8.8</td>
<td>5.1</td>
<td>6.5</td>
<td>3.8</td>
<td>0.58</td>
</tr>
<tr>
<td>8.8</td>
<td>10.0</td>
<td>6.6</td>
<td>2.1</td>
<td>0.32</td>
</tr>
<tr>
<td>8.8</td>
<td>22.0</td>
<td>6.6</td>
<td>0.47</td>
<td>0.072</td>
</tr>
<tr>
<td>15</td>
<td>2.0</td>
<td>4.9</td>
<td>3.5</td>
<td>0.71</td>
</tr>
<tr>
<td>14</td>
<td>10.0</td>
<td>7.1</td>
<td>1.63</td>
<td>0.23</td>
</tr>
</tbody>
</table>

\(^{a}\) Cyclohexane solvent. \(^{b}\) Corrected for thermal expansion and for consumption of T. \(^{c}\) Assigned percentages of total HPLC area, actual yields based on 20P were 45-55%.

By least-squares fitting the data to the form, \(\log R/U = \log [R/U]_{t=0} - k_D \times t(\text{hr})\), we obtain,

\[
[T] = 8.8 \text{ mM} \quad 20'T/20T = 1.26 \exp[- 0.15 t (\text{hr})] \quad (5.6)
\]

\[
[T] = 15 \text{ mM} \quad 20'T/20T = 0.94 \exp[- 0.14 t (\text{hr})] \quad (5.7)
\]

Eq 5.6 and 5.7, combined with eq 2.1 and \(k_T = 1.4 \times 10^9 \text{ s}^{-1}\), give

\[
k_i(20 \rightarrow 20') = 1.5 \times 10^7 \text{ s}^{-1}\text{ at 80°C} \quad (5.8)
\]
and also indicate that the first-order rate of decay of $20'T$ is $k_D = 4.2 \times 10^{-5} \text{s}^{-1}$ (i.e. $t_{1/2} = 4.2 \text{ hr}$ at 80°C).

5.9 Discussion

Radical $20$ was examined with the expectation that the stabilizing carbonyl group would strongly enhance the ring fission reaction. The data above indicate only a small increase in the ring opening rate relative to $5.82$ However, closer examination of the reaction shows that delocalization of the radical orbital onto the carbonyl group may be precluded by stereo-electronic factors (see Kinetic Scheme above). That is to say, $\pi$-bonding in the carbonyl group is held nearly orthogonal to the incipient radical orbital by the ring structure and thus cannot effectively overlap the SOMO at the transition state.

(IV)

1,1-Dideuterio-2-(9-anthracene)-ethyl Radical ($21$) and Investigations of Reactions of $T$ with Stabilized Radicals

The title radical ($21$) is reported to undergo a rapid rearrangement ($k_i > 5.10^7 \text{ s}^{-1}$) to give the corresponding 2,2-dideuterio species ($21'$).$^{189}$ However, it was also demonstrated that the obvious intermediate for this reaction, viz. the spirocyclopropyl radical $22$, did not ring open under similar conditions. It was hoped that radical-trapping might help to solve this mechanistic puzzle.

Results

5.10 Synthesis. 9-Anthracenemethanol, prepared by LiAlH$_4$ reduction of the
commercially available aldehyde, was converted into 3-(9-anthracene)-propanoic acid by the reaction sequence shown below. The acid was α-deuteriated (97% D₂) by heating its sodium salt in D₂O at 150°C for four hours. Conversion by the usual procedures afforded the diacyl peroxide but this was found not to be a practical radical precursor since it was insoluble in hydrocarbon solvents, e.g. benzene. The tert-butyl perester 21P was soluble in benzene but not in cyclohexane.

**Preparation Scheme for 21P**

![Chemical Reaction Diagram](image)

1. SOCl₂ (88%).
2. Diethyl Malonate/NaH in DMF.
3. a) LiCl/DMSO/H₂O, 160°C, b) KOH/aq-MeOH.
4. D₂O/Na(1 eq.) 150°C, 4 hr.
5. as above.

5.11 Kinetics Experiments. A solution of 21P (95% α-D₂) and T (5 mol equiv., 50mM) in benzene was heated to reflux under N₂ for 4 hr. The reaction mixture was then resolved by flash chromatography on fine mesh silica to afford a mixture of 21T and 21'T (70%). A complex mixture of by-products was also noted; these presumably arose from reactions of the concomitant tert-butoxy radical with the solvent, the precursor, and the products (anthracenes are excellent radical traps themselves) – no spiro-cyclopropyl products were observed.

NMR analysis (see below and Exp.) of the alkoxyamine fraction indicated equimolar amounts of 21T and 21'T to within random uncertainties. Based on the assumptions that NMR analysis would distinguish 10% excess of either isomer (i.e. if the ratio was > 55:45) and...
that \( k_T = 1 \times 10^9 \text{ M}^{-1}\text{s}^{-1} \), eq 5.9 indicates a lower limit of \( k_i = 2 \times 10^8 \text{ s}^{-1} \) for the rearrangement — see kinetic analysis below.

### Radical-Trapping Reaction Scheme for Isomerization of Radical 21

<table>
<thead>
<tr>
<th>21P</th>
<th>21</th>
<th>21'</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>H</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
21P \xrightarrow{k_i} 21 \xleftarrow{k_i} 21' \quad T \xrightarrow{k_T} 21T \xrightarrow{\delta 4.10} 21'T \xrightarrow{\delta 4.34} 21''T
\]

**Kinetic Equations**

Steady-state radical concentrations require that,

\[
[21] \ k_i = [21'] (k_i + k_T[T])
\]

\[
\therefore \ \frac{[21]}{[21']} = \frac{1}{1 + k_T[T]/k_i}
\]

Rate constant definitions and pseudo-first-order conditions thus give the following relationship between the product concentration ratios and the rate constants (cf. Appendix).

\[
\frac{[21T]}{[21'T]} = \frac{1}{1 + k_T[T]/k_i}
\]

Here \([T] = 0.05\text{M} \) and \( k_T = 1.0 \times 10^9 \text{ M}^{-1}\text{s}^{-1} \) so that \( [21T]/[21'T] < 55:45 \Rightarrow k_i > 2 \times 10^8 \text{ s}^{-1} \)

(5.9) (5.10)

### Does Radical 22 Ring-Open?

#### 5.12 The Radical Precursor.

Hydrogens in the 9- or 10-positions in 9,10-dihydroanthracene are highly activated towards hydrogen atom abstraction. Consequently, the aim was to generate radical 22 under mild conditions (e.g. 10 min at 60°C) by reaction of the spiro hydrocarbon 22H with di-tert-butyl peroxyxalate (DBPO).
Synthesis. Treatment of 10-methylene-9-anthrone, prepared by a Knoevenagel type reaction of anthrone with formaldehyde\(^{189}\), with diazomethane afforded a spiro 1-pyrazoline compound. This compound, which was not isolated in the literature preparation,\(^{190}\) rapidly extruded N\(_2\) upon exposure to light to give spiro10-cyclopropylanthrone in nearly quantitative yield. Reduction with LiAlH\(_4\)/AlCl\(_3\) in THF afforded 22H.

\[
\begin{array}{c}
\text{O} & \overset{(1)}{\text{N}} & \text{O} \\
\text{1.38} & \delta 4.09 & \delta 4.09 \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} & \overset{(3)}{\text{O}} & \overset{(4)}{\text{O}} \\
\text{1540cm}^{-1} & \delta 4.97 & \delta 2.10 \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} & \overset{(3)}{\text{N}} & \overset{(4)}{\text{O}} \\
\text{1730cm}^{-1} & \delta 1.90 & \delta 1.90 \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} & \overset{(4)}{\text{O}} \\
\text{1665cm}^{-1} & \delta 1.90 & \delta 1.90 \\
\end{array}
\]

\(1\) Aq-CH\(_2\)O/piperidine (tr.) in MeOH (85%). \(2\) CH\(_2\)N\(_2\) in MeOH, \(3\) hv (98%). \(4\) LAH/AlCl\(_3\) (85%)

5.13 Kinetics Experiments. Two mixtures of 22H (5% w/w), DBPO (1 mol. equiv.), and T (50mM, 5mol. equiv.) in benzene were heated at 60°C, one for 10 min and the other for 1 hr then analysed by HPLC – the reaction mixtures appeared identical. A larger scale reaction mixture, resolved by flash chromatography, revealed the presence of four major aromatic components apart from the starting materials;

(a) 10-spirocyclopropylanthrone \(5\text{B}\) (15%),

(b) 2,2'-(9-anthryl)-ethoxy-1,1,3,3-tetramethylisoindoline \(5\text{C}\) (45%),

(c) 1,1,3,3-tetramethylisoindoline \(5\text{D}\) (12%) and

(d) 9-ethyl-anthracene \(5\text{E}\) (10%).

The presence of \(5\text{C}\), in \textit{ca} 45% yield based on DBPO, demonstrates that, contrary to the previous report, 22 may ring open under suitable conditions. At first, component (a) was thought to have arisen from air oxidation either of the substrate directly\(^{191}\) or of radical 22.
(followed by the usual decay of a peroxyl radical); however, the presence of $^5$D indicates another mechanism, viz. that the radical is trapped by $T$ but the product decomposes either spontaneously or by a bimolecular reaction with $T$ (see below).

In order to draw conclusions from this experiment, one must know whether or not the radical trap $T$ could form a stable coupling product with $22$. The scavenging efficiency of $T$ towards a series of stabilized radicals was tested under conditions similar to those described above. Reaction of the specified hydrocarbon with DBPO in the presence of $T$ gave the following results:

<table>
<thead>
<tr>
<th>h'carbon radical product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph--Ph</td>
</tr>
<tr>
<td>Ph--Ph</td>
</tr>
<tr>
<td>(75% - stable, less crystals)</td>
</tr>
<tr>
<td>T-H +</td>
</tr>
<tr>
<td>(65%)</td>
</tr>
</tbody>
</table>

It is interesting that, whereas $T$ forms a stable alkoxyamine product with the
Chapter 5: Alkyl Radical Rearrangements

diphenylmethyl radical, the two dihydroanthryl radicals do not form any identifiable coupling products. Products from the unsubstituted species probably arise by the mechanism proposed for the 1,4-cyclohexadiene radical (Ch 3.2), i.e. transfer of a hydrogen atom at the 10-position to the nitroxide (this can be seen as a radical disproportionation rather than hydrogen atom abstraction). The 10,10-dimethyl substituted radical can not undergo this reaction and its failure to form stable coupling products with T implies that there is a substantial difference in stability between a biphenylcarbinyl radical in which the rings are free to rotate and one in which the rings are held co-planar (space filling models of the relevant product species suggest only a small difference in strain energy).

In summary, test reactions of T with 22 and with other highly stabilized species indicate, (a) T couples with diphenylmethyl radical but not with species similar to 22 and, consequently, (b) that 22 ring opens in the presence of T but probably only because the nitroxide is unable to trap the ring closed form – indeed, the presence of 10-spirocyclopropylanthrone in the product mixtures suggests that the ring-opening may be slow.

Discussion

The radical-trapping data indicate that radical 21 rearranges rapidly to 21' \((k_i > 2 \times 10^8 \text{ s}^{-1})\). The data for 22 do not rigorously preclude this radical as an intermediate. That is, a rapid ring closure followed by a slow ring opening may have the appearance of a rapid deuterium migration because whereas the ring open form is efficiently trapped, the putative intermediate species is not. However, the absence of a detectable amount 10-spirocyclopropylanthrone in reaction mixtures from the \(21 \rightarrow 21'\) rearrangement reinforces Alberti and Perdulli's conclusion\(^\text{189}\) that the rearrangement does not proceed via 22.

If 22 does not lie along the reaction pathway from 21 to 21' then the transition structure must be of lower energy than that for ring closure of 21. The only suggestion the present author can offer is that, in view of the marked tendency for anthracene and biphenylene ring systems to undergo charge transfer reactions, the transition state is polarized possibly with a negative charge 'in the cyclopropane ring' and the anthracene element adopting a favourable
radical cation configuration. A precedent for this type of mechanism can be found in the acetoxyl rearrangement (q.v.)\(^{192}\) which has been demonstrated to proceed not via the obvious 5-membered ring radical intermediate but via a lower energy dipolar pathway.

**Experimental Section.**

Instrumentation and general kinetic techniques have been described in Ch 2.16. HPLC analysis conditions and results are listed in the Supplementary Tables.

### 5.15 Starting Materials.

**9,9-Dimethyl-anthracene** mp 47-49°C (lit.\(^{192}\) mp 51.5-52.0°C) (Sect. 5.13) was prepared by the literature procedure\(^{192}\) except that the cyclization of 2-(2-benzylphenyl)-2-propanol was accomplished with polyphosphoric acid.

**O- Allyl OO-tert-Butyl Monoperoxymalonate (16P).** Malonyl dichloride (6.1 g, 43 mmol) was added slowly to a chilled solution of allyl alcohol (5.0 g, 86 mmol) in ether (10 mL). The reaction mixture was heated under reflux for 3 hr, then washed successively with water, sat. aq NaHCO\(_3\) (4 x) and sat. brine; evaporation and distillation *in vacuo* afforded diallyl malonate (6.5 g, 82%) bp 88-92°C at 5mm (lit.\(^{193}\) bp 205°C). The resulting malonate ester (3.7 g, 20 mmol) was added to a solution of NaOH (conc. sol. in H\(_2\)O, 18 mmol) in allyl alcohol then left overnight. Evaporation and the usual procedure for isolation of the acidic component (Ch 2.17) afforded allyl hydrogen malonate\(^{194}\) as a viscous oil (1.6 g, 55%) bp 90°-95°C at 5mm. \(^1\)H NMR (CCL\(_4\), 100 MHz) \(\delta\) 3.05 (s, 2H), 4.0 (d, 2H), 5.0 (m, 1H), 5.8 (m, 2H); IR \(v_{\text{max}}\) 1735, 1750 (C=O) cm\(^{-1}\). The acid was converted into the title perester 16P by general procedures 2 and 4 of Ch 2.17. \(^1\)H NMR (CCL\(_4\), 100 MHz) \(\delta\) 1.12 (s, 9H), 3.02 (m, 4H), 3.95 (m, 2H), 5.0 (m, 2H), 5.9 (m, 1H); IR \(v_{\text{max}}\) 1760, 1775 (C=O) cm\(^{-1}\).

**OO-tert-Butyl O-Ethyl Pent-4-enylmonoperoxymalonate (17P).** Diethyl malonate was alkylated with 5-bromopent-1-ene using the literature procedure to afford diethyl pent-4-enylmalonate (68%).\(^{196}\) The malonate ester was partially hydrolysed as above to give ethyl hydrogen 4-pentylmalonate (55%) bp 125°-127°C at 3mm. This was converted by general procedures 2 and 4 of Ch 2.17 into the title peroxide (48%) of 94% purity (iodometric): \(^1\)H NMR (CCL\(_4\), 100 MHz) \(\delta\) 1.05 (s, 6H), 1.50 (t, 2H), 2.10 (m, 2H), 2.35 (s, 2H), 5.00 (m,
Bis-[trans-7-cyclopropyl-3,3-dimethyl-hept-6-enoyl] Peroxide (18P). A mixture of triphenylphosphine (14.4 g, 50 mmol) and dicyclopentylmethanol (5.6 g, 50 mmol – prepared by LAH reduction of dicyclopentylketone) in DMF was stirred for 30 min then chilled to -10°C and maintained at this temperature while bromine (2.67 mL = 8.3 g, 50 mmol) was slowly added. After being stirred overnight at room temperature the reaction mixture was flash distilled in vacuo (0.5 mm) into an acetone/dry-ice trap until a head temperature of 50°C was reached. A solution of the distillate in pentane was washed with water then dried and distilled to afford trans-4-bromo-1-cyclopropyl-1-butene (5.61 g, 65%) in excellent purity (96% by GC analysis, 7:1 trans: cis) bp 76-78°C at 12 mm. Diethyl isopropylidenemalonate (5.0 g, 25 mmol) was added to a cooled (-30°C) mixture of trans-4-cyclopropylbut-3-enylmagnesium bromide [formed from the bromide (4.7 g, 25 mmol) of by a standard procedure197] and CuCl (0.5 g) in ether (200 mL) then allowed to warm slowly to room temperature. The usual work-up gave diethyl 5-cyclopropyl-1,1-dimethylpent-4-enylmalonate (4.6 g, 62%), bp 120-134°C at 0.5 mm; pure by NMR and TLC. 1H NMR (CCl4, 100 MHz) δ 0.3 (m, 2H), 0.6 (m, 2H), 1.05 (s, 6H), 1.2 (m, 1H), 1.3 (t, 6H, 7 Hz), 1.95 (m, 2H), 3.3 (s, 1H), 4.1 (q, 4H, 7 Hz), 4.9-5.3 (m, 2H); IR νmax 1741 (C=O) cm⁻¹. The malonate ester (4.0 g) was decarbethoxylated by Krapcho's method119 to give ethyl 7-cyclopropyl-3,3-dimethyl-hept-6-enoate as a colourless oil (2.8 g, 82%), bp 80-82°C at 0.5 mm (91% GC); 1H NMR (CCl4, 100 MHz) δ 0.3 (m, 2H), 0.6 (m, 2H), 0.95 (s, 6H), 1.2 (m, 1H), 1.25 (m, 5H), 1.95 (m, 2H), 2.05 (s, 2H), 3.95 (q, 4H, 7 Hz), 4.9-5.3 (m, 2H); IR νmax 1745 (C=O) cm⁻¹. The ester was converted via general procedures 1 (84%), 2 (94%), and 3 (80%) of Ch 2.17 into the title peroxide, 18P, of 92% iodometric purity: 1H NMR (CCl4, 100 MHz) δ 0.3 (m, 4H), 0.6 (m, 4H), 0.95 (s, 12H), 1.2 (m, 2H), 1.25 (t, 4H, 8 Hz) 1.95 (m, 4H), 2.25 (s, 4H), 4.9-5.3 (m, 4H); IR νmax 1765, 1795 (C=O) cm⁻¹.

tert-Butyl 6-Methylene-cyclodecane-peroxycarboxylate (19P). A suspension of oil-free NaH (440 mg, 18 mmol) in dry DMSO (20 mL) was stirred at 70°C intil gas ceased to be evolved (ca 45 min). Methyltriphenylphosphonium iodide (7.5 g, 20 mmol) in DMSO (25
Chapter 5: Alkyl Radical Rearrangements

mL) was then added and the mixture was stirred for 10 min at 70°C before addition of a solution of 6-hydroxymethyl-cyclodecanone\textsuperscript{181} (1.60 g, 9.0 mmol) in DMSO (25 mL). After 2 hr at 70°-75°C, the reaction mixture was diluted with water (100 mL), extracted with pentane (5 x 30 mL), evaporated, and chromatographed on fine mesh silica (60 g) with CH\textsubscript{2}Cl\textsubscript{2}/ether (10:1) elution to afford 6-hydroxymethyl-methylenecyclodecane as a viscous colourless oil (1.28 g, 78%). \textsuperscript{1}H NMR (CCl\textsubscript{4}, 100 MHz) \( \delta \) 1.3-2.0 (m, 13H), 2.1-2.5 (m, 5H), 3.35 (d, 2H), 4.75 (s, 2H). Jones' Reagent\textsuperscript{195} was added dropwise to a solution of the alcohol (180 mg, 1.0 mmol) in acetone (4 mL) until the brown colour of the unreduced reagent persisted for 10 min. Filtration (Celite), evaporation and the usual purification of the acidic component (Ch 2.17) afforded pure (NMR and TLC) 6-methylene-cyclodecanecarboxylic acid (180 mg, 92%) plates from pentane, mp 65-67°C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \( \delta \) 1.4-1.8 (m, 13H), 2.15 (m, 4H), 2.61 (m, 1H), 4.86 (s, 2H); IR \( \nu_{\text{max}} \) 1759 (C=O) cm\(^{-1}\). The acid was converted by procedures 2 and 4 of Ch 2.17 into the title perester \textsuperscript{19P} (61%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \( \delta \) 1.31 (s, 9H), 1.4-1.8 (m, 13H), 2.15 (m, 4H), 2.61 (m, 1H), 4.86 (s, 2H); IR \( \nu_{\text{max}} \) 1778, 1794 (C=O) cm\(^{-1}\).

Bis-[(2,2-dimethyl-3-oxo-cyclobutane)acetyl] Peroxide (20P). (-) Methyl (2,2-dimethyl-3-oxo-cyclobutane)acetate (cf. ref 121. and the text) was converted into the title peroxide, of 96% iodometric purity, by general procedures 1 (88%), 2 (95%) and 3 (65%) of Ch 2.17. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \( \delta \) 1.04 (s, 6H), 1.12 (s, 6H), 2.5 (m, 6H), 2.81 (d, 2H), 3.12 (m, 2H); IR \( \nu_{\text{max}} \) 1765, 1778, 1792 (C=O) cm\(^{-1}\).

tert-Butyl 3-(9-Anthracene)-2,2-dideuterio-peroxypropanoate (21P). NaBH\textsubscript{4} (0.51 g, 13 mmol) was added to a cooled (ice-bath) suspension of 9-anthracenecarboxaldehyde (Fluka) (5.0 g, 24 mmol) in ethanol (100 mL) – immediate conversion was observed (dark yellow \( \rightarrow \) cream colour). After 20 min at room temperature the reaction mixture was diluted with dil. aq-HCl (250 mL x 0.25 M) then filtered to afford crude 9-anthracenemethanol (4.5 g which was purified by recrystallized from CCl\textsubscript{4}/CHCl\textsubscript{3} (4.01 g, 80%) mp 155-156°C (lit.\textsuperscript{197} mp 156-158°C). The alcohol was added portionwise to a rapidly stirred solution of SOCl\textsubscript{2} (5 mL) in dry dioxan (30 mL) – TLC indicated complete conversion in ca 15 min at room temperature.
The reaction mixture was evaporated, dissolved in CH$_2$Cl$_2$/CHCl$_3$ (1:1, 50 mL), washed with sat. aq-NaHCO$_3$, dried (MgSO$_4$), and, finally, the volume was reduced to ca 20 mL (in a hot water bath) and the product was allowed to crystallize slowly. Filtration and drying afforded 9-chloromethyl-anthracene (2.9 g, 86%) mp 136-137°C (lit. mp 137-138°C). $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 5.52 (s, 2H), 7.3 - 8.5 (m, 9H). The chloride was added to a solution of sodium diethyl malonate in DMF (15 mL), formed by treatment of diethyl malonate (1.70 g, 11 mmol) with NaH (0.24 g, 10 mmol); after 1 hr TLC indicated complete conversion. Dilution with water and filtration afforded crude diethyl 9-anthrylmethyl-malonate (3.1 g, 100%); $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 1.05 (t, 3H, 8Hz), 3.8 - 4.1 (m, 6H), 7.3 - 7.7 (m, 4H), 7.7 - 8.3 (m, 5H). The diester was decarbethoxylated by heating it to reflux for 3 hr in a mixture of LiCl (2.2 g) and H$_2$O (160 µl, 1.05 mol. equiv.) in DMSO (50 mL). The reaction mixture was poured into water and the crude ethyl 3(9-anthryl)-propanoate filtered at the pump (2.10 g, 85%) (pure by TLC) mp 61-63°C. Hydrolysis with KOH in aq-EtOH (cf. general procedure (1) of Ch 2.17) gave the crude acid (1.8 g, 90%) which was purified by recrystallization from EtOAc/CDCl$_3$ (3:1) to afford analytically pure 3(9-anthracene)-propanoic acid (1.65 g, 85%). mp 193-195°C (lit. mp 194-195°C); $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 2.86 (t, 2H, 7.5 Hz), 4.00 (t, 2H, 7.5 Hz), 7.53 (m, 4H), 8.02 (d, 2H, 12 Hz), 8.28 (d, 2H, 12 Hz), 8.39 (s,1H). IR $\nu_{max}$ (CDCl$_3$) 1735 (C=O) cm$^{-1}$. Anal. Calcd for C$_{17}$H$_{14}$O$_2$: C, 81.61, H, 5.64; Found: C, 81.92, H, 5.35.

$\alpha$-Dideuteriation: aq-NaOH (4.3 M x 230 µl = 1 mol. equiv.) was added to a warm solution of the acid (250 mg) in ethanol (5 mL) – a pH of 9 indicated equivalence. Evaporation gave sodium 9-anthracene-propanoate as a pale yellow powder (273 mg, 100%). The sodium salt (273 mg, 1 mmol) was dissolved in a solution of NaOD in D$_2$O (1 mL x ca 0.1 M = 0.1 mol. equiv.) formed by adding shavings of Na to D$_2$O; the solution was flame sealed in a small silica (NMR) tube then heated in a stainless steel bomb, one third filled with water, at 150°C for 12 hr. Careful acidification and recrystallization gave 3-(9-anthracene)-2,2-dideuterio-propanoic acid (220 mg, 88%) mp 194-195°C. $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 2.86 (s, 2H), 4.00 (s, 2H), 7.53 (m, 4H), 8.02 (d, 2H, 12 Hz), 8.28 (d, 2H, 12 Hz), 8.39 (s,1H). The acid was converted by general procedures (2) (100%) and (3) (64%) of Ch 2.17 into the title perester.
Chapter 5: Alkyl Radical Rearrangements

21P. $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.32 (s, 9H), 2.91 (s, 2H), 4.02 (s, 2H), 7.53 (m, 4H), 8.02 (d, 2H, 12 Hz), 8.28 (d, 2H, 12 Hz), 8.39 (s, 1H).

Spiro[anthracene-9(10H),1'-cyclopropane] (22). A solution of 10-spirocyclopane-9-anthrone$^{190}$ (1.10 g, 50 mmol) in THF (15 mL) was added to a stirred suspension of LiAlH$_4$ (0.5 g) in THF (20 mL). After 1 hr at 50°C, a solution of dry AlCl$_3$ (1.65 g) in THF (15 mL) was added to the reaction mixture which was then maintained at 50°C for a further 1 hr before being cooled and quenched by the H$_2$O/NaOH method (Fieser and Fieser$^{195}$). Work-up by filtration, evaporation, dilution with water and isolation with EtOAc was followed by chromatography on fine mesh silica with pentane/CH$_2$Cl$_2$ (4:1) to afford the pure title compound 22 as a colourless liquid which solidifies on freezing (-18°C). $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.38 (s, 4H), 4.09 (s, 2H), 7.0 (m, 2H), 7.2 (m, 4H), 7.4 (m, 2H). Anal. Calcd for C$_{16}$H$_{14}$: C, 93.16, H, 6.84; Found: C, 92.89, H, 6.74.

NB: 22 (colourless) was slowly oxidized back to the anthrone (yellow, fluorescent under UV) on exposure to air but it was established by TLC (which is extremely sensitive for anthracenes) that the anthrone formed in the kinetics experiments (Sect. 5.13) was not present in the starting material.

5.16 Products. All products except those from the anthracene experiments were isolated by preparative HPLC on Column #2 or #3. The anthracene products and those from the 'product stability test reactions' (Sect. 5.13) were resolved by flash chromatography on fine mesh silica with elution by progressively more polar mixtures of CH$_2$Cl$_2$ and pentane.

Allyl 1,1,3,3-Tetramethylisoindolin-2-yloxy-acetate (16T): $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.42 (br s, 12H), 4.95 (s, 2H), 5.2 (m, 2H), 5.32 (d, 2H), 6.15 (m, 1H), 7.04 (m, 2H), 7.15 (m, 2H); IR $\nu_{\text{max}}$ 1742 (C=O) cm$^{-1}$.

4-(1,1,3,3-Tetramethylisoindolin-2-yloxy-methyl)-oxacyclopentan-2-one (16'): $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.44 (br s, 12H), 2.4-2.85 (m, 3H), 3.95 (d, 2H, 7 Hz), 4.4-4.6 (m, 2H), 7.04 (m, 2H), 7.15 (m, 2H); IR $\nu_{\text{max}}$ 1770 (C=O) cm$^{-1}$.
Chapter 5: Alkyl Radical Rearrangements

2-(1-Ethoxycarbonyl-hex-5-en-1-oxy)-1,1,3,3-tetramethylisoindoline (17T):

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.28 (m, 2H) overlaps with 1.31 (t, 3H, 8 Hz) and 1.35 (s, 6H), 1.50 (d, 6H), 1.7 (sex, 2H), 1.95 (m, 3H), 3.94 (d, 2H, 7.2 Hz), 4.95 (m, 2H), 5.85 (m, 1H), 7.08 (m, 2H), 7.11 (m, 2H); IR $\nu_{\text{max}}$ 1738 (C=O) cm$^{-1}$.

2-(2-Ethoxy-carbonylcyclopentylmethoxy)-1,1,3,3-tetramethylisoindoline (17'T):

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.33 (t, 3H, 8 Hz), 1.44 (br s, 12H), 1.62 (m, 2H), 1.85 (m, 4H), 2.52 (m, 1H), 2.85 (m, 1H), 3.94 (d, 2H, 7.2 Hz), 4.05 (q, 2H, 8 Hz), 7.03 (m, 2H), 7.11 (m, 2H); IR $\nu_{\text{max}}$ 1738 (C=O) cm$^{-1}$.

2-(6-Cyclopropyl-2,2-dimethyl-5-hexen-1-oxy)-1,1,3,3-tetramethylisoindoline (18'T):

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 0.33 (m, 2H), 0.62 (m, 2H), 0.94 (s, 6H), 1.2 (m, 2H), 1.44 (br s, 12H) overlaps with 1.41 (m, 1H), 1.9 (m, 2H), 4.9-5.4 (m, 2H), 7.06 (m, 2H), 7.14 (m, 2H).

2-(3',3'-Dimethylcyclopentyl-cyclopropyl-methoxy)-1,1,3,3-tetramethylisoindoline (18'T):

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 0.01 (m, 2H), 0.31 (m, 2H), 1.01 (s, 6H), 0.95 (m, 1H), 1.31 (br s, 6H), 1.47 (d, 6H), 1.53-1.90 (m, 6H), 2.21 (m, 1H), 3.99 (m, 1H), 7.02 (m, 2H), 7.11 (m, 2H).

2-[4-(3,3-Dimethylcyclopentyl)but-3-en-1-oxy]-1,1,3,3-tetramethylisoindoline (18''T):

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.03 (s, 6H), 1.41 (br s, 6H), 1.53-1.90 (m, 6H), 2.1 (m, 2H), 2.91 (m, 1H), 3.89 (t, 2H, 7 Hz), 5.0-5.3 (m, 2H), 7.05 (m, 2H), 7.14 (m, 2H).

2-(cis-decahydronaphthalene-9-methoxy)-1,1,3,3-tetramethylisoindoline (cis-19'T). Prepared by heating a solution of authentic bis-[cis-decahydronaphthalene-acetyl] peroxide$^{199}$ and 2 mol. eq. T in benzene to reflux for 4 hr (71%). $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.21 (s, 6H), 1.53-1.95 (m, 18H), 2.18 (m, 4H), 3.93 (s, 2H), 7.05 (m, 2H), 7.14 (m, 2H).
2-(trans-decahydro-naphthalene-9-methoxy)-1,1,3,3-tetramethylisoindoline (cis-19'T): Prepared by heating a solution of authentic bis-[trans-decahydro-naphthalene-acetyl] peroxide\(^{199}\) and 2 mol. eq. \(T\) in benzene to reflux for 4 hr (74\%). \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.23 (br s, 6H), 1.50-1.90 (m, 18H), 2.18 (m, 4H), 3.70 (s, 2H), 7.05 (m, 2H), 7.14 (m, 2H).

2-(2-Dimethyl-3-oxocyclobutyl-methoxy)-1,1,3,3-tetramethylisoindoline (20T)
\(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.26 (s, 3H), 1.29 (s, 3H), 1.45 (br s, 12H), 2.45 (m, 1H), 2.88 (dd, 1H, 21 Hz/6 Hz), 3.21 (dd, 1H, 21 Hz/8 Hz), 4.10 (m, 2H), 7.08 (m, 2H), 7.22 (m, 2H); IR \(\nu_{\text{max}}\) 1782 (C=O) cm\(^{-1}\).

2-(2-Methyl-3-oxo-hex-5-en-2-oxy)-1,1,3,3-tetramethylisoindoline (20'T):
\(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.20 (s, 6H), 1.25-1.5 (m, 12H), 3.45 (d, 2H, 9 Hz), 5.10 (m, 2H), 5.95 (m, 2H), 7.08 (m, 2H), 7.22 (m, 2H); IR \(\nu_{\text{max}}\) 1742 (C=O) cm\(^{-1}\).

2-[2-(9-Anthracene)-1,1-dideuterio-1-ethoxy)-1,1,3,3-tetramethylisoindoline (21T): Deduced from the spectrum of the mixture 21T + 21'T; \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.45 (br s, 12H), 4.11 (s, 2H), 7.08 (m, 2H), 7.22 (m, 2H), 7.50 (m, 4H), 8.02 (d, 2H), 8.51 (d, 3H, 11 Hz).

2-[2-(9-Anthracene)-2,2-dideuterio-1-ethoxy)-1,1,3,3-tetramethylisoindoline (21'T): Deduced from the spectrum of the mixture 21T + 21'T; \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.45 (br s, 12H), 4.32 (s, 2H), 4.10 (m, 2H), 7.08 (m, 2H), 7.22 (m, 2H), 7.50 (m, 4H), 8.02 (d, 2H), 8.51 (d, 3H, 11 Hz).

2-[2-(9-Anthracene)-1-ethoxy]-1,1,3,3-tetramethylisoindoline (22'T): mp 95-97°C. \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.45 (br s, 12H), 4.11 (t, 2H, 8 Hz), 4.32 (t, 2H, 8 Hz), 4.10 (m, 2H), 7.08 (m, 2H), 7.22 (m, 2H), 7.50 (m, 4H), 8.02 (d, 2H), 8.51 (d, 3H, 11 Hz).
CHAPTER SIX

Solvent Effects upon $k_T$ and Product Stability and a Kinetic Model for the Trapping Reaction

Abstract

In this chapter the argument of diffusion as opposed to energetic control of the radical-trapping reaction is pursued in the light of a systematic investigation of solvent effects upon product distributions. A general kinetic model for reactions 'near to diffusion control' is presented (in Part II) and some predictions regarding the values and Arrhenius parameters of $k_T$ at various degrees of diffusion control are made. A good free energy correlation of solvent effects with solvent strength, as gauged by the solubility parameter ($\delta$)\textsuperscript{200} rather than with viscosity, accords well with the view that $k_T$ is, for the most part, energetically controlled. However, other experiments suggest that the rate becomes diffusion controlled with high solvent viscosities (and hence also at low temperatures).

PART I

Solvent Effects

6.1 Introduction

By analogy with other radical-radical reactions and in the absence of experimental evidence to the contrary, there has been a general expectation that the coupling of radicals with nitroxides is a diffusion-controlled reaction.\textsuperscript{50,63} However, recent radical clock and direct calibrations have established that radical-trapping of alkyl radicals by TEMPO and by T occurs with rate constants appreciably lower than those of normal radical recombinations in hydrocarbon solvents, e.g. the $k_T$ for primary alkyl radicals ($1.3 \times 10^9$ s\textsuperscript{-1} at 80°C) is about a factor of five lower than estimates for the termination rate constants ($2k_t$) of similar radicals.\textsuperscript{200} The difference is even more pronounced in the temperature dependence equations where log $A$ and $E_A$ terms for radical trapping, viz. 9.5-10.5 and 0.3-1.5 kcal/mol respectively, are significantly lower than those for radical termination (typically 11.5 and 3.0 kcal/mol).\textsuperscript{201} The low $E_A$ terms are particularly surprising; for instance, direct calibration of the benzyl/TEMPO reaction in
isooctane gave $E_A = 0.6$ kcal/mol (Ch.1 Table I) and some clock calibrations even suggest a negative $E_A$ (1)\textsuperscript{57} – fully diffusion-controlled reactions should have activation energies of at least 2 and usually around 3 kcal/mol in common solvents (see Part II).\textsuperscript{201,202}

In order to investigate this anomaly further and for obvious practical reasons it was decided to test the effect of a wide variety of solvents upon the trapping rate constant $k_T$ using the radical clock method.

**Results**

**6.2 Calibration Method.** Radical-trapping rate constants were measured by the *radical clock* method described in Chapter Two from which the radical and product numbering is retained (see Ch.2 Table 2.1). Isomerization of 2,2-dimethyl-3-butenyl radical (7 $\rightarrow$ 7') was the *clock* reaction used most extensively for this study both for practical and for theoretical reasons; viz. (a) the products 7T and 7'T are well separated and have high retention on RP-HPLC and thus are not liable to be confused with by-products from solvent/radical and trap/peroxide reactions (q.v. Ch.1.5 and 3.1), (b) it is a relatively fast *clock* reaction ($k_C = 4 \times 10^7$ s\(^{-1}\) at 80°C) which is competitive with trapping in solutions up to 100mM in T – this allows the analysis of 'neat' reaction mixtures, typically by HPLC resolution of ca 10 µl of reaction mixture (- reaction mixtures from the slower clocks are too dilute for this procedure), and (c) the radical is non-polar and, being compact, its cyclization is likely to cause only a small amount of solvent displacement, therefore the rate constant is not expected to be sensitive to solvent effects.\textsuperscript{203}

A wide range of solvents can be used for the nitroxide trapping reactions – many more than can be employed for stannane reduction reactions where the chain carrying stannyl radicals are liable to reduce any unsaturated or otherwise reducible groups in the solvent (q.v. Ch.2.14). The series of solvents chosen for this study contains those commonly used for radical reactions and displays the full spectrum of solvent polarity from aliphatic hydrocarbons to methanol. Diethyl malonate and methyl acrylate were tested because of the report by Burnett *et al*\textsuperscript{204} that they display particularly strong binding with nitroxide radicals.
Reactivity of the clock radicals towards the solvents was assessed in each case by using two (or more) trap concentrations for each solvent. Steady-state kinetic analysis of the reaction scheme below reveals that participation of the solvent (S-X) in the quenching of rearranged clock radicals (r) can be detected by a positive \([T] = 0\) intercept in a plot of \(U/R\) versus \([T]\) – the equation below is derived in Appendix A3.2. On the other hand, extraneous reactions of u should not affect the \(U/R\) ratios but merely reduce the yield (this is an important point because u is often more reactive than r, e.g. u (aryl or cyclopropyl) \(\rightarrow\) r (alkyl), cf. Ch 8.

By itself the failure to observe trapped solvent derived products is not conclusive evidence for the absence of solvent reaction because the solvent derived products may be unstable (e.g. T-CCl₃ which decomposes during analysis) or may be disguised by some fortuitous factor in the HPLC resolution (e.g. some trapped acrylonitrile adducts are co-eluted with T).

\[
\begin{align*}
[Solvent \ derived \ products] \\
S-X \xrightarrow{k_S} S-X' \xrightarrow{k_S'} \\
\text{[Solvent derived products]} \\
\text{u} - \text{CO}_2)_2 \rightarrow \text{u} \cdot \xrightarrow{k_C} \text{r} \cdot \\
\text{[Solvent derived products]} \\
U \xrightarrow{k_T} T \xrightarrow{k_T'} R \\
\text{[Solvent derived products]} \\
\text{Kinetic Equation for Trapping in Reactive Solvents} \\
\frac{U}{R} = \frac{k_T}{k_T'} \frac{k_S'}{k_C} [S-X] + \frac{k_T}{k_C} [T]
\end{align*}
\]

6.3 Kinetic Data. Data obtained from reactions in 28 solvents using the 7 \(\rightarrow\) 7' clock are summarized in Table 6.1. In each case the data were consistent with a pseudo-first-order irreversible kinetic equation, i.e. \([7T]/[7'T] = U/R = k_T/k_C [T]\), to within experimental uncertainties except for carbon tetrachloride (#7) and methyl acrylate (#14). In the exceptional solvents radical/solvent reactions were evident both in the \(U/R\) versus \([T]\) function.
# Chapter 6: Solvent Effects

## Table 6.1 Solvent Effects on $k_T/k_C (7)$ at 80°C

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>$[T]_1^a$</th>
<th>$7T/7'T$</th>
<th>$[T]_2$</th>
<th>$7T/7'T$</th>
<th>$k_T/k_C^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isooctane</td>
<td>17.9 mM</td>
<td>0.619</td>
<td>35.5</td>
<td>1.29</td>
<td>35.5(4)</td>
</tr>
<tr>
<td>1a</td>
<td>Dodecane</td>
<td>17.4</td>
<td>0.557</td>
<td>35.2</td>
<td>1.08</td>
<td>31.4(8)</td>
</tr>
<tr>
<td>2</td>
<td>Hexane</td>
<td>17.6</td>
<td>0.612</td>
<td>35.7</td>
<td>1.23</td>
<td>34.6(2)</td>
</tr>
<tr>
<td>3</td>
<td>Pentane</td>
<td>17.7</td>
<td>0.638</td>
<td>35.6</td>
<td>1.24</td>
<td>34.8(3)</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexane</td>
<td>17.9</td>
<td>0.504</td>
<td>35.6</td>
<td>1.03</td>
<td>28.5(4)</td>
</tr>
<tr>
<td>5</td>
<td>Benzene</td>
<td>17.9</td>
<td>0.280</td>
<td>35.7</td>
<td>0.559</td>
<td>16.0(0)</td>
</tr>
<tr>
<td>5a</td>
<td>Perfluorobenzene</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.614</td>
<td>17.1</td>
</tr>
<tr>
<td>6</td>
<td>1:1 (V/V) #4:#5</td>
<td>17.9</td>
<td>0.39(2)</td>
<td>-</td>
<td>-</td>
<td>21.8(9)</td>
</tr>
<tr>
<td>7</td>
<td>Carbon Tetrachloride</td>
<td>Data in Chapter 8</td>
<td></td>
<td></td>
<td></td>
<td>15.5(4) c</td>
</tr>
<tr>
<td>8</td>
<td>Acetone</td>
<td>35.8</td>
<td>0.508</td>
<td>87.7</td>
<td>1.265</td>
<td>14.5(2)</td>
</tr>
<tr>
<td>9</td>
<td>Methylene Chloride</td>
<td>16.6</td>
<td>0.128</td>
<td>85.7</td>
<td>0.659</td>
<td>7.69(18)</td>
</tr>
<tr>
<td>10</td>
<td>Diethyl Ether</td>
<td>11.9</td>
<td>0.288</td>
<td>35.3</td>
<td>0.800</td>
<td>22.7(4)</td>
</tr>
<tr>
<td>11</td>
<td>Chloroform</td>
<td>18.0</td>
<td>0.211</td>
<td>35.9</td>
<td>0.438</td>
<td>12.2(4)</td>
</tr>
<tr>
<td>12</td>
<td>Ethyl Acetate</td>
<td>-</td>
<td>-</td>
<td>44.4</td>
<td>0.670</td>
<td>15.8</td>
</tr>
<tr>
<td>13</td>
<td>Diethyl Malonate</td>
<td>17.9</td>
<td>0.262</td>
<td>35.7</td>
<td>0.535</td>
<td>14.8(2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71.2</td>
<td>1.024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Methyl Acrylate</td>
<td>See Chapter Six</td>
<td></td>
<td></td>
<td></td>
<td>10.9(15) c</td>
</tr>
<tr>
<td>15</td>
<td>50% (V/V) #13:#2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>18.6</td>
</tr>
<tr>
<td>16</td>
<td>Dimethoxyethane</td>
<td>35.1</td>
<td>0.520</td>
<td>70.7</td>
<td>1.053</td>
<td>14.9</td>
</tr>
<tr>
<td>17</td>
<td>Acetonitrile</td>
<td>-</td>
<td>-</td>
<td>79.1</td>
<td>0.644</td>
<td>8.14</td>
</tr>
<tr>
<td>18</td>
<td>DMSO</td>
<td>36.5</td>
<td>0.401</td>
<td>72.1</td>
<td>0.820</td>
<td>11.2(2)</td>
</tr>
<tr>
<td>19</td>
<td>DMF</td>
<td>36.3</td>
<td>0.438</td>
<td>71.9</td>
<td>0.892</td>
<td>12.2(2)</td>
</tr>
<tr>
<td>20</td>
<td>Propylene Carbonate</td>
<td>-</td>
<td>-</td>
<td>72.2</td>
<td>0.845</td>
<td>11.7</td>
</tr>
<tr>
<td>21</td>
<td>t-Butyl Alcohol</td>
<td>29.5</td>
<td>0.374</td>
<td>-</td>
<td>-</td>
<td>12.7</td>
</tr>
<tr>
<td>22</td>
<td>Isopropyl Alcohol</td>
<td>17.8</td>
<td>0.198</td>
<td>70.7</td>
<td>0.788</td>
<td>11.1(3)</td>
</tr>
<tr>
<td>23</td>
<td>Ethanol</td>
<td>35.4</td>
<td>0.391</td>
<td>71.4</td>
<td>0.820</td>
<td>11.3(2)</td>
</tr>
<tr>
<td>24</td>
<td>Methanol</td>
<td>35.8</td>
<td>0.365</td>
<td>89.3</td>
<td>0.915</td>
<td>10.2(3)</td>
</tr>
<tr>
<td>24a</td>
<td>1:3 (V/V) H2O:#24</td>
<td>-</td>
<td>-</td>
<td>67.7</td>
<td>0.87</td>
<td>12.8</td>
</tr>
<tr>
<td>25</td>
<td>THF</td>
<td>35.6</td>
<td>0.52</td>
<td>70.7</td>
<td>1.07</td>
<td>15.1(4)</td>
</tr>
<tr>
<td>26</td>
<td>Ethylene Glycol</td>
<td>14.2</td>
<td>0.440</td>
<td>28.8</td>
<td>0.881</td>
<td>30.6(0)</td>
</tr>
</tbody>
</table>

---

**Notes:**

- Initial concentrations at 22°C were 20.0, 40.0, 80.0, 100 mM; corrections for thermal expansion and the reaction's trap decrement were made using $[T] = (100+\%T)/200 \cdot (1-58°C \cdot \alpha \cdot [T])$, where $\alpha$ is the thermal expansion coefficient of the solvent (Partington).

- Average value. Standard deviations in brackets are in units of the last significant figure.

- From a linear regression of $U/R$ versus $[T]$ (Appendix A3.2).
### Table 6.2 Solvent Effect Compared with Some Solvent Properties

<table>
<thead>
<tr>
<th>Solvent No.</th>
<th>$\varepsilon_{20}^a$</th>
<th>$K_{20}$</th>
<th>$\delta_{80}^b$</th>
<th>$\eta_{20}$</th>
<th>$\ln(k_T/k_C)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.96</td>
<td>0.195</td>
<td>6.62</td>
<td>0.489</td>
<td>3.57</td>
</tr>
<tr>
<td>1a</td>
<td>1.98</td>
<td>0.20</td>
<td>6.56</td>
<td>0.94</td>
<td>3.45</td>
</tr>
<tr>
<td>2</td>
<td>1.89</td>
<td>0.201</td>
<td>6.70</td>
<td>0.326</td>
<td>3.54</td>
</tr>
<tr>
<td>3</td>
<td>1.84</td>
<td>0.202</td>
<td>6.68</td>
<td>0.24</td>
<td>3.55</td>
</tr>
<tr>
<td>4</td>
<td>2.02</td>
<td>0.219</td>
<td>7.57</td>
<td>0.96</td>
<td>3.35</td>
</tr>
<tr>
<td>5</td>
<td>2.28</td>
<td>0.229</td>
<td>8.74</td>
<td>0.625</td>
<td>2.77</td>
</tr>
<tr>
<td>5a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.96^w</td>
<td>2.84</td>
</tr>
<tr>
<td>7</td>
<td>2.24</td>
<td>0.223</td>
<td>8.7</td>
<td>0.969</td>
<td>2.74</td>
</tr>
<tr>
<td>8</td>
<td>20.7</td>
<td>0.464</td>
<td>9.15</td>
<td>0.326</td>
<td>2.67</td>
</tr>
<tr>
<td>9</td>
<td>9.08</td>
<td>0.420</td>
<td>10.14</td>
<td>0.431</td>
<td>2.04</td>
</tr>
<tr>
<td>10</td>
<td>4.34</td>
<td>0.341</td>
<td>7.52</td>
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<td>3.12</td>
</tr>
<tr>
<td>11</td>
<td>4.81</td>
<td>0.356</td>
<td>8.96</td>
<td>0.58</td>
<td>2.50</td>
</tr>
<tr>
<td>12</td>
<td>6.02</td>
<td>0.384</td>
<td>8.40</td>
<td>0.455</td>
<td>2.76</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>8.5</td>
<td>2.71</td>
<td>2.69</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>-</td>
<td>9.35</td>
<td>0.44</td>
<td>2.39</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>7.9</td>
<td>-</td>
<td>2.70</td>
</tr>
<tr>
<td>17</td>
<td>36.0</td>
<td>0.479</td>
<td>11.4</td>
<td>0.36</td>
<td>2.10</td>
</tr>
<tr>
<td>18</td>
<td>46.7</td>
<td>0.484</td>
<td>13.0</td>
<td>-</td>
<td>2.41</td>
</tr>
<tr>
<td>19</td>
<td>36.7</td>
<td>0.480</td>
<td>12.8</td>
<td>-</td>
<td>2.50</td>
</tr>
<tr>
<td>20</td>
<td>64.5</td>
<td>0.488</td>
<td>13.3</td>
<td>-</td>
<td>2.46</td>
</tr>
<tr>
<td>21</td>
<td>17.4</td>
<td>0.458</td>
<td>10.5</td>
<td>ca3.5</td>
<td>2.54</td>
</tr>
<tr>
<td>22</td>
<td>19.4</td>
<td>0.462</td>
<td>11.5</td>
<td>2.50</td>
<td>2.41</td>
</tr>
<tr>
<td>23</td>
<td>24.3</td>
<td>0.468</td>
<td>12.9</td>
<td>1.20</td>
<td>2.42</td>
</tr>
<tr>
<td>24</td>
<td>32.6</td>
<td>0.477</td>
<td>14.3</td>
<td>0.597</td>
<td>2.32</td>
</tr>
<tr>
<td>25</td>
<td>7.39</td>
<td>0.399</td>
<td>9.5</td>
<td>ca0.5</td>
<td>2.71</td>
</tr>
<tr>
<td>26</td>
<td>37.7</td>
<td>0.480</td>
<td>14.5</td>
<td>19.9</td>
<td>3.42</td>
</tr>
</tbody>
</table>

---

*a* $\varepsilon$, $K$, and $\eta$ were taken from ref. 10 and 8.  
*b* Calculated at 80°C (see text) from data in ref. 10 and with corrections to molar volumes using thermal expansion coefficients from Partington (ref.4).  
^w^ Warkentin's data (ref 63)
Figure 6.1 \( \log \left( \frac{k_f}{k_r} / M \right) \) versus the Kirkwood polarity parameter, 

\[
K = \frac{(\varepsilon - 1) / 2E + 1}{\varepsilon}
\]

where \( \varepsilon \) is the dielectric constant.

\[
\log \left( \frac{k_f}{k_r} / M \right) = 3.76 - 3.28 K, \langle r \rangle = -0.69
\]
Figure 6.2 \( \log \left( \frac{k_T}{k_r} / M \right) \) versus \( E_T \) at 80°C

\[
\log \left( \frac{k_T}{k_r} / M \right) = 6.0 - 0.90 E_T, <r> = -0.815
\]
Figure 6.3: $\log \left( \frac{k_f}{k_i} / M^{-1} \right)$ for clock 7$\rightarrow$7$'$ versus the Hildebrand Solubility Parameter ($\delta$) at 80°C

$\log \left( \frac{k_f}{k_i} / M^{-1} \right) = 6.64 - 0.46 \delta$, $\langle \delta \rangle = 0.978$

1. Isooctane
2. Hexane
3. c-Hexane
4. Benzene
5. CCl$_4$
6. Acetone
7. CH$_2$Cl$_2$
8. Ether
9. CHCl$_3$
10. Ethyl Acetate
11. Ethane
12. THF
13. Diethyl Malonate
14. Dimethoxyethane (DME)
and by direct observation of the solvent derived products, i.e. T-CCl₃ in CCl₄ and various trapped monomeric and telomeric adduct radicals in methyl acrylate. The data for these solvents are interpreted in Chapter 8; suffice it to say here that the slope of the U/R versus [T] plot gives the desired rate ratio, \( k_T / k_C \), regardless of radical/solvent reactions.

Historically the solvent properties most commonly used in solvent effect studies²⁰⁵-²⁰⁷ are the dielectric constant (\( \varepsilon \)), the Hildebrand solubility parameter²⁰⁷ (\( \delta \)), the Kirkwood polarity parameter²⁰⁶ \( K = (\varepsilon - 1)/(2\varepsilon + 1) \), and (for diffusion-controlled reactions) the solvent viscosity (\( \eta \)). These are listed in Table 6.2 against the experimental solvent dependence of \( k_T / k_C (7) \) at 80°C. Not listed but also examined were the various spectroscopic measures of solvent polarity e.g. Dimroth's \( E_T \)²⁰⁸ (Fig. 6.2), the acceptor number \( A_N \) (Ch.1.3)²⁰⁹ and the donor number \( D_N \).²¹⁰

As is customary in the analysis of solvent effects, a linear relationship is sought between a solvent property and the logarithm of rate ratios, i.e. a linear free energy relationship.²⁰⁴,²¹¹ Graphical and linear regressive analyses of data in Table 6.2 (e.g. Figs 6.1-6.2) show that \( \ln (k_T / k_C) \) correlates poorly with \( \varepsilon, K, \) and \( \eta \) and with the spectroscopic parameters mentioned above. On the other hand, the correlation of \( \ln (k_T / k_C) \) with \( \delta \) is very good for the less polar solvents (#1 to 12) but breaks down completely for the more polar and especially for the hydroxylic solvents (Fig 6.3).

Despite the claim that diethyl malonate complexes strongly with tert-butyl mesityl nitroxide²⁰⁴ at the radical centre, the relative trapping rate in diethyl malonate (#13) is not anomalous in the trend of solvent dependence. On the other hand, the significance of radical complexation in methyl acrylate (#14)²⁰⁴,²¹² (see Ch 8) is confirmed by the anomalously low rate ratio both in the pure solvent and in a mixture with hexane [#15 = 50:50 v/v = 1.1:1.0 mol/mol #14/#2]; in \( \log \) terms the rate ratio in #15 is the mean of those in #2 and #14.
6.4 Discussion

Before the kinetic data are discussed, it must be emphasised that the radial clock method measures the trapping rate constant relative to that of the clock reaction. Consequently, an undefined proportion of the solvent effects observed in the relative trapping rate $k_T/k_C$ might be caused by solvation of the clock reaction. There appears to be no conclusive evidence that radical rearrangements are less susceptible to solvent effects than bimolecular radical reaction rates although Benson has argued that, on theoretical grounds, unimolecular reactions should in general be less solvent dependent than bimolecular reactions.

Schiesser has recently studied a number of 1,5- and 1,6-radical cyclizations using tributylstannane in aprotic and protic solvents. His data indicated that generally the solvent dependence of $k_C/k_H$ was small, e.g. 1-methyl-5-hexenyl radical’s relative cyclization rate $k_C/k_H$ was not significantly altered by changing the solvent from hexane to DME or to $n$-propanol. This could mean that $k_H$ (the hydrogen atom transfer rate constant) and $k_C$ fortuitously have about the same solvent dependence but since both the stannane reduction and rearrangement reactions are clearly nonpolar there remains a strong implication that the rearrangement rate constants are not sensitive to solvation. In addition, the following radical-trapping data show that the solvent dependence of rate ratios $k_T/k_C$ are not greatly affected by the choice of clock reaction – which is an indication that it is changes in $k_T$ that we are observing not changes in $k_C$. Nonetheless, it must be admitted that solvent effects on $k_T$ per se can only reliably be measured by direct methods.

The most notable feature of the kinetic data presented in Table 6.2 is the lack of correspondence between solvent viscosity and the relative trapping rate. For instance, for $7 \rightarrow 7'$; the rate ratio in ether ($\eta = 0.23$ c-poise at $20^\circ$C) is just slightly lower than in cyclohexane ($\eta = 0.96$) but about three times higher than in methylene chloride ($\eta = 0.43$), and the rate ratio in hexane ($\eta = 0.33$) is only slightly higher ($+10\pm5\%$) than it is in dodecane ($\eta = 0.95$). The last example is the most compelling since it is hard to imagine that increasing the chain length of the hydrocarbon solvent could significantly alter $k_C$. The lack of viscosity dependence confirms other indications (vide supra and Part II) that the radical-trapping reaction is not fully diffusion
The dielectric constant $\varepsilon$, the Kirkwood parameter $K$, and several variations thereof,\textsuperscript{214} have been proposed as gauges of the electrostatic stabilization afforded to dipolar species in polar solvents. The lack of correspondence with these parameters might thus suggest that the radical trapping and clock reactions proceed without large charge separations in their transition states. However, many unambiguously polar reactions show a poor correlation\textsuperscript{205} with $K$ and $\varepsilon$ so that a polar transition state cannot be ruled out on these grounds.

In contrast, the Hildebrand model of salvation was developed for nonelectrolytes in low polarity solvents (see Appendix A5). Good correlations between $\delta$ and rate effects have been demonstrated in a number of reaction systems (including some rather more polar than for which it was intended\textsuperscript{205,207}). Some breakdown of the correlation (Fig. 6.3) beyond CH$_2$Cl$_2$ ($\delta = 10.3$) would not be surprising in view of the model's design but the complete reversal of the trend does warrant further comment - see Part II.

Experiments using other radical clocks in cyclohexane, benzene, acetone and CH$_2$Cl$_2$ are summarized in Table 6.3. It can be seen that the rate ratios are affected similarly to $7 \to 7'$ except that for $1 \to 1'$ the solvent effect is somewhat less pronounced; e.g. $k_T/k_C$ for $7 \to 7'$ in methylene chloride is reduced by a factor of five from its value in cyclohexane whereas for $1 \to 1'$ the corresponding solvent effect is a factor of three – the difference might lie in the solvent dependence of $k_C$ or it may represent a genuine variation in the solvent dependence of $k_T$. Interestingly, $k_T/k_C$ obtained from the relatively polar alkoxy carbonyl clock radicals 12 and 13 are only slightly more solvent dependent than those from 7.

Arrhenius parameters were estimated for some solvent/clock systems, the results are given in Table 6.4. For low polarity organic solvents (#1 to 12) it appears that most of the solvent effect is manifested in the preexponential term. Smaller changes in the activation energy are probably not experimentally significant. For the polar aprotic and hydroxylic solvents, the trend to lower frequency factors with increasing polarity is reversed; this suggests that the
Table 6.3. Effect of Solvents upon $k_F/k_C$, M$^{-1}$ for Various *Clock* Reactions at 80°C$^b$

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Clock Reaction</th>
<th>1→1'</th>
<th>2→2'</th>
<th>7→7'</th>
<th>8→8'</th>
<th>9→9'</th>
<th>13→13'</th>
</tr>
</thead>
<tbody>
<tr>
<td>hexane</td>
<td></td>
<td>1220</td>
<td>1.2</td>
<td>86</td>
<td>1.1</td>
<td>32</td>
<td>1.2</td>
</tr>
<tr>
<td>cyclohexane</td>
<td></td>
<td>1030</td>
<td>1.0</td>
<td>77</td>
<td>1.0</td>
<td>26</td>
<td>1.0</td>
</tr>
<tr>
<td>benzene</td>
<td></td>
<td>780</td>
<td>0.76</td>
<td>48</td>
<td>0.62</td>
<td>15</td>
<td>0.58</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td></td>
<td>350</td>
<td>0.34</td>
<td>19</td>
<td>0.25</td>
<td>5.3</td>
<td>0.20</td>
</tr>
<tr>
<td>EtOH</td>
<td></td>
<td>460</td>
<td>0.40</td>
<td>8.8</td>
<td>0.34</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Mean of data from two concentrations of T (see Experimental); experimental scatter was less than 7% of the stated figures.  $^b$ Figures in *italics* are the rate ratios relative to those obtained in cyclohexane.  $^c$ Erratic analysis possibly due to ethanolysis of the 'carbonate' product.

Table 6.4 Relative Arrhenius Coefficients for the Competition of Radical-Trapping with *Clock* Rearrangements of 1, 7 and 9 in Various Solvents in the Range 60°-125°C$^{a,b,c}$

<table>
<thead>
<tr>
<th>Solvent</th>
<th>1→1'</th>
<th>7→7'</th>
<th>9→9'</th>
</tr>
</thead>
<tbody>
<tr>
<td>log $A_{T/C}$</td>
<td>Δ$E_{T/C}$</td>
<td>log $A_{T/C}$</td>
<td>Δ$E_{T/C}$</td>
</tr>
<tr>
<td>isoctane</td>
<td>-0.7</td>
<td>6.2</td>
<td>-</td>
</tr>
<tr>
<td>hexane</td>
<td>-0.9</td>
<td>6.4</td>
<td>-1.8</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>-1.0</td>
<td>6.4</td>
<td>-2.0</td>
</tr>
<tr>
<td>benzene</td>
<td>-1.3</td>
<td>6.7</td>
<td>-2.4</td>
</tr>
<tr>
<td>C$_6$F$_6$</td>
<td>-1.2</td>
<td>6.5</td>
<td>-</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>-1.5</td>
<td>6.5</td>
<td>-3.0</td>
</tr>
<tr>
<td>EtOH</td>
<td>-1.3</td>
<td>6.5</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

$^a$ log $k_F/k_C = \log A_{T/C} - \Delta E_{T/C}/\theta$, ($\theta = 2.3RT$ kcal/mol), where $A_{T/C} = A_T/A_C$ (M$^{-1}$), and $\Delta E_{T/C} = \Delta E_T - \Delta E_C$ (kcal/mol).  $^b$ Estimated random errors (2xSD) are ±0.3 in log $A_{T/C}$M$^{-1}$ and ±0.5 (kcal/mol) in $\Delta E_{T/C}$.  $^c$ Calculated from data in Supplementary Table 5.1.
unexpected increase in the relative trapping rate after the minimum at methylene chloride could result from favourable entropy factors. One rationale that presents itself is that the solvent entropy is likely to increase when the polar reactant T is converted into the non polar product T-R. That is to say, specific binding or ligation of the solvent to T involves a loss of entropy in the solvent/solute system; the coupling reaction disrupts the solvation and thus increases the entropy of the system. However, alternative explanations are possible.

Implications of the solvent effects described above are further discussed in Part II on the basis of the kinetic model proposed for radical-trapping.

6.5 Product Stabilities.

As noted in Chapter Two, trapped products of tertiary alkyl radicals decompose at elevated temperatures; products of secondary and primary radicals also decompose but only under more severe conditions than those used for the kinetic calibration experiments. Because product stability is a critical factor in the application of radical-trapping in reactions of highly hindered or stabilized radicals it was of considerable importance and interest to ascertain the factors which determine the rate and the mechanism of their decomposition.

6.6 Method. The decay of 7'T and 9T was examined by analysing reaction mixtures subjected to prolonged heating. The decay of 7'T was calibrated by monitoring the alkoxyamine product ratio 7'T/7T in 'radical clock' product mixtures, i.e. product mixtures generated by heating 7P with 10 mol. equiv. of T in the test solvent (see Experimental Section for techniques). A slightly different technique and exemplary data are described for 9T below – the kinetic data obtained for 7'T over a range of temperatures, trap concentrations, and solvents are given in Sup/Table 6.2.

6.7 Mechanism and Kinetics. The decomposition of trapped products R-T can be envisaged to occur by one or more of the following mechanisms: (a) dissociation of R-T by NO-R bond fission followed by disproportionation of R· with T·; (b) fission of the NO-R bond followed by disproportionation of R· with T· within the solvent cage, (c) an
intramolecular hydrogen atom or proton transfer, N-OR bond fission, and (e) bimolecular hydrogen atom abstraction of a $\beta$-hydrogen on the $R$ group by the radical $T^\cdot$. Mechanisms (a) and (b) are illustrated below.

At first sight $N$-$O$ bond fission may seem unlikely since it produces highly reactive alkoxy and aminyl radicals and it is not favoured by the product radical resonance which assists the $NO$-$R$ bond fission. However, $N$-$O$ bond fission can not be ruled out on these grounds alone because $N$-$O$ bonds are substantially weaker than $C$-$O$ bonds (by about 26 kcal/mol$^{25}$). In these experiments $N$-$O$ fission would be detected by the trapped radicals derived from reaction of the alkoxy and aminyl radicals with the solvent; such were not detected in these experiments [ruling out (d)]. Although (d) is not an important pathway here, there is some evidence that when $R$ is aryl it may be the main mode of decay – a rationale being that $Ar$-$O^\cdot$ radicals are resonance stabilized by some 10-15 kcal/mol, cf. Ch 7 Sect. (4).

Kinetic analysis reveals that the decay rate of $T$-$R$ would be independent of $[T]$ for each mechanism, including (a), but excluding (e) (see above). The data given in Sup. Table 6.2
show that the rate of change of 7'T/7T is indeed sensibly independent of [T] - this rules out mechanism (e) as a major mode of product decay.

Mechanism (a) was tested by thermolysis of the tertiary alkoxyamine 9T: dissociation via the first mechanism would, in the presence of T, lead to the formation of 9'T whereas mechanisms (b) or (c) would not allow leakage to 9'T. To avoid ambiguity, pure 9T was prepared, mixed with T in cyclohexane, degassed and heated at 126°C in small ampoules. Analysis after 1 hr, 4.5 hrs, and 22 hrs (Table 6.4) revealed a logarithmic decrement of 9T but without detectable formation of 9'T. The radical clock kinetic data (cf. Ch 2.7) show that under these conditions rearrangement would take place if (dissociated) 9 were produced in the thermal decay.

**Thermolysis of 9T in the presence of T**

In contrast, alkoxyamine species similar to the trapped cyanoisopropyl radical have been used as radical sources in what Rizzardo et al have termed "quasi-living" free radical polymerizations. The discrepancy can not be resolved on the basis of the present data but it might be associated with the polar nature of α-cyano-alkyl or α-alkoxycarbonyl-alkyl radicals.

The above experiment gave a first-order rate of decay ($k_D$) of 9.3 x 10^{-6} s^{-1} ($<r> = 0.998$) at 126°C. Similar experiments at 90°C, and 146°C for 9T and data for 7'T gave the following Arrhenius expressions,

$$\log k_D (9T) = 12.5 - 32.1/\theta, \quad <r> = 0.989$$
$$\log k_D (7'T) = 11.8 - 30.2/\theta, \quad <r> = 0.991$$

The frequency factors are a little low for a dissociation reaction; i.e. the equations above imply Δ$S^\ddagger = -4$ eu and -6 eu respectively, whereas for bond dissociation Δ$S^\ddagger$ is usually positive (log $A > 13.5$). On comparing $k_D(9T)$ to $k_D(7'T)$ one is tempted to speculate that the higher rate and lower frequency factor of the latter is due in some way to allylic activation of the
β-hydrogen.16

Table 6.5  Kinetic Data for Decomposition of 9T

<table>
<thead>
<tr>
<th>temp (°C) a</th>
<th>solvent</th>
<th>time (hr)</th>
<th>[T] (mM) b</th>
<th>[9T]/[IS] b</th>
<th>$k_D$ (10^{-7} s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>c-C_{6}H_{12}</td>
<td>0.0</td>
<td>17</td>
<td>2.3±0.1</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>c-C_{6}H_{12}</td>
<td>48</td>
<td>17</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>c-C_{6}H_{12}</td>
<td>404</td>
<td>16</td>
<td>1.85±0.08</td>
<td>1.3</td>
</tr>
<tr>
<td>126</td>
<td>c-C_{6}H_{12}</td>
<td>0.0</td>
<td>16</td>
<td>2.3±0.1</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>c-C_{6}H_{12}</td>
<td>1.0</td>
<td>16</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>c-C_{6}H_{12}</td>
<td>4.5</td>
<td>16</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>c-C_{6}H_{12}</td>
<td>22</td>
<td>14</td>
<td>1.07±0.05</td>
<td>94</td>
</tr>
<tr>
<td>126</td>
<td>c-C_{6}H_{12}</td>
<td>0.0</td>
<td>4.0 c</td>
<td>2.3±0.1</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>c-C_{6}H_{12}</td>
<td>22</td>
<td>3.7</td>
<td>1.16±0.07</td>
<td>86</td>
</tr>
<tr>
<td>146</td>
<td>c-C_{6}H_{12}</td>
<td>0.0</td>
<td>15</td>
<td>2.3±0.1</td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>c-C_{6}H_{12}</td>
<td>4.5</td>
<td>13</td>
<td>0.91±0.02</td>
<td>570</td>
</tr>
</tbody>
</table>

a ±0.4°C  b HPLC area ratios; decreases in [T] and 9T were measured relative to the internal standard (IS), concentrations are corrected for thermal expansion. c Made by dilution of the 20mM stock.

Rate constants for the decay of 7'T (1.2 x 10^{-5} s^{-1}) and 9T (2.6 x 10^{-5} s^{-1}) are lower than those reported for tri-tert-butylhydroxylamine at 130°C (4.7 x 10^{-4} s^{-1}).62 This can probably be attributed to a reduction of non-bonded interactions between the tertiary alkyl group and the nitroxide's methyl groups which is brought about by the constrained geometry of the alkoxyisoindoline; in particular, that the methyl groups on the 5-membered isoindoline ring are 'tied back' from the R group.

Solvent effects upon the rate of decomposition was tested by decomposition of 7'T at 126°C in c-C_{6}H_{6}, CH_{2}Cl_{2}, acetone and ethanol: The results, i.e. $k_D$ = 1.5, 3.8, 4.9 and 6.4 x 10^{-5} s^{-1} respectively (Sup. Table 6.2), show a steady increase of $k_D$ with solvent polarity which implies a moderately dipolar transition state for the reaction.205,217
PART TWO

A Kinetic Model for the Trapping Reaction and Further Analysis of Solvent Effects

6.8 Diffusion Control: Is $k_T$ Diffusion Limited?²¹⁹

A diffusion controlled reaction is one in which chemical reaction occurs at each encounter.²¹⁸ When reactants "encounter" in the liquid phase more than a simple collision is implied - the equivalent of 10 to 100 collisions are thought to occur before they diffuse apart i.e. escape the so-called solvent cage. For normal radicals the solvent cage effect is thought to be sufficient for reaction anisotropy to be fully sampled²⁰¹,²¹⁸,²¹⁹,²²⁰, that is, although many collisions do not result in coupling (because the reactants are not correctly oriented), the sheer number of collisions within the solvent cage ensures a high probability of reaction.

For such reactions the rate is limited by the speed at which the reactants diffuse through the solvent to form encounter pairs. Theoretical models such as that of von Smoluchowski predict that the rates will depend on the diffusion coefficients of the reactants in the solvent ($D_A, D_B$) and on the reactant size ($r_A, r_B$). For non polar species,²⁰¹,²¹⁹

$$k_{\text{diff}} = 4\pi(r_A + r_B)(D_A + D_B) \times 10^3 N_o \text{ (SI units)}$$ (6.1)

To a good approximation (in non-polar solvents at least²⁰¹,²¹⁹) the diffusion coefficients are inversely proportional to the solvent viscosity ($\eta$), e.g. the Stokes-Einstein relation modified to a molecular scale is that $D_A = kT/4\pi\eta r_A$.²¹⁹ Moreover because the temperature dependence of the viscosity of most solvents is very well approximated by Andrade's Law, viz. $\eta^{-1} = \eta_\infty^{-1}\exp(-E_v/RT)$,²¹⁹ eq 5.1 can be fitted to an Arrhenius equation with the energy term being,

$$E_{\text{visc}} = E_v + RT.$$ $E_{\text{visc}}$ is about one third the heat of vaporization, i.e. 2.5-3.5 kcal/mol for most common solvents ($\eta_\infty = 0.4-1.5$ c-poise). A meticulous study of $2k_T(t\text{-butyl})$ in wide range of solvent viscosities by Schuh and Fischer²¹⁹ has shown this expression to be substantially
correct, the empirical expression being \( E_{\text{viss}} = E_v + RT/2 \). A survey of reactions believed to be diffusion controlled\(^{202}\) reveals that virtually all reliable Arrhenius energy estimates lie in this range - reports of energies less than about 2 kcal/mol are rare (for non-ionic reactions).

By contrast; (a) radical clock and accurate direct calibrations\(^{57,60}\) of \( k_T \) give activation energies of -0.2-1.4 kcal/mol with a median value of about 0.5 kcal/mol in cyclohexane where \( E_{\text{viss}} \) should be about 3.0 kcal/mol [Schuh et al\(^{221}\) have estimated 2.1 kcal/mol for 2\( k_1 \) (tert-butyl) in this solvent] and (b) the rates are about a factor of five smaller than those predicted for diffusion controlled radical-trapping by combining relevant experimental data\(^{219a}\) with a correction for the size of \( T \).\(^{219b}\) In concert, these factors support the "solvent effect" conclusion that radical trapping is not fully diffusion controlled. To elaborate further on the factors influencing \( k_T \) we need a model for reactions with partial diffusion control.

### 6.9 A Model for Radical-trapping

Reactions near to diffusion control can be analysed through the steady-state approximation by treating the encounter pair as an intermediate state; the rate of formation of this 'state' is limited by the reactants' bimolecular diffusion rates and its rate of decay is the sum of unimolecular rate constants \( k_2 \) and \( k_{\text{diss}} \).

\[
\begin{align*}
\text{r} + \text{T} & \quad \xrightarrow{k_{\text{diff}}} \quad \frac{k_{\text{diff}}}{k_{\text{diss}}} \quad \left[ \text{r}, \text{T} \right]_e \quad \xrightarrow{k_2} \quad \text{r-T}
\end{align*}
\]

steady-state concentrations require that,

\[
-d[r]/dt = k_T[T][r] = [T][r] k_2 k_{\text{diff}}/(k_2 + k_{\text{diss}})
\]

\[
\therefore \quad k_T = k_2 k_{\text{diff}}/(k_2 + k_{\text{diss}}) = k_2 K_e / (1+\alpha)
\]

where \( \alpha = k_2/k_{\text{diss}} \), and \( K_e = k_{\text{diff}}/k_{\text{diss}} \).

This is a general model for reactions in solution and one can see that for ordinary reactions where \( k_2 \) is much less than \( k_{\text{diss}} \), \( k_T = K_e k_2 \). In this case the postulated intermediate "encounter pair" is not necessary to define the reaction kinetics since, by the Curtin-Hammet
Postulate (q.v.), the rate is determined solely by the free energy of the (solvated) transition state relative to that of the dissociated species. At the other extreme as \( k_2 \) becomes larger than \( k_{\text{dis}} \) the reaction's rate constant tends to a diffusion limited value \((k_{\text{diff}})\) which is not dependent on the transition state's free energy but rather on the transport properties of the solvent/reactant system. In between these extremes, differentiation of eq 6.1 (combined with Andrade's and the Stokes-Einstein approximations) with respect to \( \phi = 1/RT \) shows that an Arrhenius plot of \( k_T \) (and therefore of \( k_T/k_c \)) should be curved where \( k_T \) is near the diffusion limit e.g. at low temperatures or high \( \eta \). Moreover the magnitude of the curvature \((\partial^2 \ln k_T/\partial \phi^2)\) is greatest at \( \alpha = 1 \), i.e. \( k_T = 0.5 \, k_{\text{diff}} \) (cf. Appendix). Attempts to demonstrate this effect in ethylene glycol \#26 \((E_{\text{visc}} = 6-7 \, \text{kcal/mol})\) at normal reaction temperatures were inconclusive because over the available temperature range \((60^\circ \text{ to } 125^\circ \text{C})\) the expected curvature fell within the experimental scatter and attempts gain low temperature data by photolysis of 7P in \#26 were unsuccessful because of the photoactivity of the nitroxide (Ch.1.9).

6.10 Why is Radical-Trapping Not Diffusion Controlled?

The experimentally determined frequency factors for the radical-trapping reaction are about midway between those of diffusion controlled reactions and those of 'normal' bimolecular reactions. Frequency factors for radical recombinations in the gas phase are usually in the range \(10^{10} \text{ to } 10^{11} \, \text{M}^{-1}\text{s}^{-1}\) and the activation energies are negligible; thus in solution radical recombinations are diffusion controlled because the 'intrinsic' rate constant is higher than the rate at which encounter pairs diffuse apart or dissociate. On the other hand, frequency factors for most other bimolecular reactions in solution lie in the range \(10^8 \text{ to } 10^9 \, \text{M}^{-1}\text{s}^{-1}\) (and slightly lower in the gas phase) so that even in the absence of any significant enthalpy barrier \((\Delta H^\ddagger = 0)\) the rate constants would lie within or below the range \(5 \times 10^7 \text{ to } 5 \times 10^8 \, \text{M}^{-1}\text{s}^{-1}\). This is less than the diffusion limit and suggests that such hypothetical reactions would be determined by their free energies of activation \((\Delta G^\ddagger)\) rather than the transport properties of the solvent.

To extend the argument further; it can seen that reactions with frequency factors of about \(10^9 \text{ to } 10^{10} \, \text{M}^{-1}\text{s}^{-1}\) (\(= 10^8 \text{ to } 10^9 \, \text{M}^{-1}\text{s}^{-1}\) in the gas phase) are not likely to be (fully) diffusion controlled except in relatively viscous solvents or at low temperatures (where \( \eta \) is
high for all solvents). For reasons discussed below, the author proposes that radical-trapping falls into this category. Consequently the reaction’s rate constant is determined by the free energy barrier for coupling which in turn is dominated by the entropy term, i.e. \( \Delta G^\ddagger = \Delta H^\ddagger - T.\Delta S^\ddagger = -T.\Delta S^\ddagger \) when \( \Delta H^\ddagger = 0 \). Reactions with similar kinetic parameters, viz. highly exothermic reactions with low enthalpy barriers such as radical addition to activated vinyl groups, are known to be controlled by a combination of polar, frontier orbital, and steric factors and perhaps the trapping reaction’s rate constant is similarly determined. 

On the molecular scale, the main difference between radical recombination and, say, radical addition to an olefin is the degree of electronic reorganisation required for each process. The former consists only of bond formation whereas the latter involves breaking of the olefin’s \( \pi \)-bond (bond strength \( \text{ca.} \ 26 \) kcal/mol) and formation of a \( \sigma \)-bond. Radical-trapping can be seen to lie between these extremes since it breaks the nitroxide’s 3-electron radical bond (bond strength \( \text{ca.} \ 30-32 \) kcal/mol) but roughly speaking this involves the movement of one rather than two electrons. That is to say, as the coupling takes place electron density must be transferred from the nitrogen centre to the embryonic \( R-O \) \( \sigma \)-bond in much the same way that the two \( \pi \)-electrons must be redistributed in radical addition reactions and it is this requirement that reduces the "spacial flexibility" of the reaction’s transition state thus lowering the \( \log A \) term.

In summary, the low frequency factors for the radical-trapping reaction compared with other radical recombinations might be attributed to the following terms: (a) a low frontier orbital density; only about 50% of the radical orbital (SOMO) density resides on the oxygen centre, this reduces the probability of a reactive overlap (Ch 1.3), (b) radical coupling to nitroxides is opposed by the loss of about 30 kcal/mol resonance energy in the nitroxyl group – this may lead to a tighter transition state, (c) non-bonded interactions with the trap’s four methyl groups may further diminish the probability of reaction, and (d) since \( T \) is polar (= 3 Debye) and \( R-T \) are non polar the coupling reaction must cause some degree of solvent reorganization (see below).
6.11 More about Solvent Effects

The solvent effects reported in Part I are presumed to be associated with factors (a) and (d). The former is involved to the extent that polar solvents are known to reduce the spin density on the oxygen centre (Ch 1.2) and consequently may also reduce the reactivity of the nitroxyl group; hence the general trend towards lower $k_T$ with increasing solvent polarity. On this basis we might expect the coupling rate to correlate with the spin density on $N$ which in turn has been shown to correlate well with acceptor number ($A_N$) of the solvents;\textsuperscript{14} however, as shown in Part One there is is only a moderate correspondence between spectroscopic solvent parameters such as $A_N$ and the trapping rate constant – this implies that factors other than spin density on $Q$ are important.

With regard to factor (d), the kinetic solvent effect depends on the free energy of solvation of the transition state relative to that of the reactants: the effect of polar solvents is to promote or retard reactions according as the transition state is more or less polar than the reactant(s) respectively. It is the radical orbital (SOMO) which gives rise to the nitroxyl group’s polarity (Ch.1.3), therefore the $T + R$ transition state would be less polar than $T$ to the extent of $NO-R$ bond formation in the transition state.\textsuperscript{220}

From radical clock and direct $k_T$ data one can calculate that the median enthalpy of activation ($\Delta H^\ddagger$) for radical-trapping is negligible, i.e. $\Delta H^\ddagger = E_A - RT = 0$. The energetic effects of solvation discussed above do not appear as increased energies of activation (perhaps because radical coupling is an intrinsically attractive interaction) but rather as reduced frequency factors. Solvation is thought to delay, i.e. tighten, the transition state.\textsuperscript{220} However, when the solvent is organised about the nitroxide by specific interactions or ligation there might be a favourable solvent entropy effect opposing the above general trends.
6.12 Conclusions

The findings of this chapter are summarised by the following points:

* Relative radical trapping rates $k_T/k_C$ show a strong dependence on solvent polarity but not on solvent viscosity.

* Variations in radical-trapping product distributions from radical rearrangements in many solvents can be predicted by their solubility parameters ($\delta$) or internal pressures ($\delta^2$).

* Anomalously low rates in methyl acrylate and acrylonitrile (Ch. 8) suggest some special binding of $T$ (and/or of the clock radical) to these solvents.

* Decomposition of tert-alkoxyamines occurs mostly via a non-dissociative process.

* Arrhenius expressions for $k_T$ and solvent effects upon $k_T/k_C$ indicate that the trapping reaction is basically under energetic control at ordinary temperatures in the commonly used solvents.

Finally, while it is conceded that there is a degree of ambiguity regarding how much of the observed changes in $k_T/k_C$ can be attributed to changes in the clock rate ($k_C$), it should be noted that it is effects on $k_T/k_C$ per se which are of chief practical importance since it is these ratios that determine product distributions in the various solvents. Thus with the aid of data in Tables 6.1-4 one can, with some degree of confidence, relate kinetic data ($k/k_T$) obtained in one solvent with those which would be obtained in another solvent where $k_T$ is better defined, i.e. cyclohexane or isooctane.
Chapter 6: Solvent Effects

Experimental Section.

Solvents 1 to 4, 7, and 23 (Table 5.1) were Ajax 'Spectrosol' grade, 5, 17, and 24 Mallinckrodt 'Nanograde', 8 to 12, 21, 22 and 26 Ajax A.R., 18 and 19 Mallinckrodt A.R., 16 Aldrich 98%+ and 20 was BDH A.R. grade - all used without further purification. Ajax 'Spectrosol' chloroform (#11) was filtered through a column of basic alumina to remove the ethanol stabilizer. Methyl acrylate (Fluka) was purified by flash distillation under nitrogen just prior to use; only the first fraction (about one third) was used in the kinetics experiments.

Stock solutions were accurately made up at room temperature (22°- 23°C) and each ampoule (500 µl of stock plus 0.1 equivalents of 7P) was degassed, heated (5 hrs at 80°C) and the neat solution was analysed by HPLC with column #2 eluted with 92% aq-MeOH, (for details see Chapter 2).

Radical clocks representative of (unhindered) primary, secondary, and tertiary alkyl and alkoxy carbonyl radicals, i.e. 1, 2, 8, 9, 12 and 13 respectively (see Ch.2 Table I) were similarly calibrated in solvents #2, 4, 5 and 9. Ampoules were of identical make-up except for the precursor which was added as a concentrated solution in cyclohexane. 2, 8, and 9 were calibrated using the same trap concentrations as used for 7, i.e.100 mM and 50 mM. Slower clocks 1~ 1' and 12~ 12' were tested in 10 mM and 2.0 mM solutions of T in these solvents.

Stabilities of the product ratios were tested by the prolonged heating of a duplicate reaction mixture for each clock/solvent combination. Alkoxyamine products of primary, secondary and alkoxy carbonyl radicals were found to be stable under the reaction conditions employed for calibrations of $k_T/k_C$. The 'kinetic' products were also stable under analysis conditions (i.e. product ratios were not affected by the presence of aqueous methanol at ambient temperature, cf. Ch 2). However, the product of chlorine atom abstraction of CCl₄ by the clock radicals, i.e. trapped trichloromethyl T-CCl₃, was partially solvolized during analysis by the HPLC eluent (viz. aqueous methanol); the reactions and kinetics involved in this scheme are examined in Chapter 8.

Thermal stability calibrations were performed on product mixtures containing trapped tert-alkyl radicals. Experiments at 125°C and below were performed simply by heating ampoules of identical make-up (i.e. precursor with 10 mol. equiv. of T and a trace of biphenyl as an internal standard) then analysing them at appropriate time intervals. For tests above 125°C a stock of the product mixture was preformed in a large ampoules (4 mL) at 100°C (4 hrs), then distributed into smaller ampoules (500 µl), degassed and then heated at the test temperature. This procedure was required to eliminate the variable amount of peroxide decay which occurs during the rise to temperatures above 125°C.
CHAPTER SEVEN

Aryl and Cyclopropyl Radicals

Abstract

In this chapter, radical-trapping investigations of some highly reactive carbon-centred radicals are reported. The material has been divided into the following sections: (I) methods for generating aryl radicals in the presence of T and calibration of the ring closure reaction of the o-(alkenyl)aryl radical 23, and (II) ring closures of alkenyl-cyclopropyl radicals 25 and 26 and, for comparison, that of the alkenyl-cyclobutyl radical 27.

(I) Aryl Radicals

7.1 Introduction. The 1,5- and 1,6-cyclizations of suitably constituted aryl radicals recently have become the subject of considerable interest. The regio- and stereochemistry of these rearrangements have been investigated in these laboratories and synthetic applications have also been made. Like the analogous o-alkenyl species, the initial cyclizations predominantly afford exocyclic radicals but in some circumstances the latter may undergo neophile-type rearrangements to their endocyclic isomers.

Abeywickrema, Beckwith and Gerba have investigated several of these rearrangements by the stannane method (e.g. 23 and 24). Although the relative rate constants, \( k_c/k_{H^1 \text{aryl}} \), could readily be assessed from the product distributions, absolute \( k_c \) values could not be (directly) derived from these data because \( k_{H^1 \text{aryl}} \) has not been calibrated.
Chapter 7: Aryl and Cyclopropyl Radicals

In this section, radical-trapping investigations directed towards the calibration of aryl radical reactions in general, and of the cyclization of 23 in particular, are reported.

Results and Discussion

7.1 Aryl Radical Precursors. Considerable difficulty was encountered in finding a 'clean' source of aryl radicals which was compatible with the kinetic application of radical-trapping. The following radical sources were tested.

Diaroyl Peroxides. These are readily prepared from aryl-carboxylic acids by procedures which have been described for the aliphatic diacyl peroxides (cf. Ch 2.17). However, unlike the latter, diaroyl peroxides are known to decompose via relatively long lived intermediate species, viz. the acyloxyl radicals (ArCOO•). This can lead to complications if these peroxides are used as sources of aryl radicals, e.g. reaction of the acyloxyl radicals with hydrogen donor solvents leads to the formation of the acid and solvent radicals (see eq 7.3). Other complications arise when nitroxides are present, i.e.; (a) nitroxides can induce the decomposition of diaroyl peroxides\(^3\) \(\text{eq } 7.2\) and (b) it has been established laser flash photolysis (LFP) data\(^6\) \(\text{eq } 7.5\) that a rapid radical quenching reaction \(k_q = 3 \times 10^8 \text{ M}^{-1}\text{s}^{-1}\) occurs between the nitroxide and the aroyloxy radical (eq 7.5). Since typical aroyloxyl radicals decarboxylate with rate constants in the order of \(10^6\) to \(10^7 \text{s}^{-1}\) at \(25^\circ\text{C}\) it can be seen even low concentrations of T may drastically reduce the yield of aryl radicals, e.g. 0.1 M of nitroxide would intercept most aroyloxy radicals before they could decarboxylate \((|T| < 3 \times 10^8 \text{ M}^{-1}\text{s}^{-1} > 10^6-10^7 \text{s}^{-1})\). The exact nature of this 'quenching' reaction is not known but presumably it is an electron transfer reaction as indicated in eq 7.5 (see Ch 1.11).

\[
\begin{align*}
1/2 \text{ArCOO}_2^2 & \rightarrow \text{ArCOO}^* \quad (7.1) \\
\text{or} \quad \text{ArCOO}_2^2 + T & \rightarrow \text{ArCO}_2^- + \text{T}^* + \text{ArCOO}^* \quad (7.2) \\
\text{ArCOO}^* & \rightarrow \text{Ar}^* + \text{CO}_2 \quad (7.3) \\
\text{ArCOO}^* + \text{S-H} & \rightarrow \text{ArCO}_2\text{H} + \text{S}^* \quad (7.4) \\
\text{ArCOO}^* + T & \rightarrow \text{ArCO}_2^- + \text{T}^* \quad (7.5) \\
\text{Ar}^* + T & \rightarrow \text{T-Ar} \quad (7.6) \\
\text{Ar}^* + \text{S-H} & \rightarrow \text{Ar-H} + \text{S}^* \quad (7.7)
\end{align*}
\]
Test reactions performed with benzoyl peroxide and T (20 and 100 mM = 2.2 mol equiv.) at 100°C in benzene or cyclohexane afforded low to moderate yields of the trapped phenyl radicals T-Φ (30-40%). In the latter solvent, the presence of trapped cyclohexyl radical indicated hydrogen atom abstraction of the solvent by either benzoyloxy (eq 7.4) and/or by phenyl radicals (eq 7.7). The yield of trapped phenyl appeared to depend on the nitroxide concentration; in accord with eq 7.5 the yield of T-Φ was indeed significantly lower at the high trap concentration, i.e. 31% at [T] = 100 mM versus 40% at [T] = 20 mM. However, the complexity of the overall reaction is such that one cannot conclude that the reduced yield of T-Φ arises from this source.

An attempt was made to study the ring closure of radical 24 by thermal decomposition of bis-[o-allyloxy-benzoyl] peroxide, i.e. (24-CO₂)₂. HPLC analysis revealed a complex mixture of polar products. In order to simplify the analysis the reaction mixture was separated into acidic and non-acidic components by base (aq-Na₂CO₃) extraction. The acidic component was then esterified with diazomethane (-5°C) and resolved by column chromatography.

The products were consistent with the following reaction scheme (yields based on...
peroxide). A quantity of methyl o-allyloxybenzoate (45%) was detected in the acidic product mixture but the only major alkoxyamine product was 7A (see above). 24T and 24'T were not detected in the non-acidic product mixture. The expected co-product of 7A, viz. the alternative coupling product of the allylic radical - 7B, was not found but this may not be a true reflection of the 'kinetic' product distribution because 7B, the product of a highly stabilised radical, is likely to be labile under the reaction/analysis conditions - see also radical 10 in Ch 2.

These results are interesting in themselves and suggest that radical-trapping may be useful for mechanistic studies involving aroyloxy radicals but they also demonstrate that peroxides are poor to useless as sources of ortho-substituted aryl radicals.

(2) Diazonium Salts. Aryldiazonium tetrafluoroborates are accessible by diazotization of the appropriate primary amines and are usually stable under refrigeration in the dark.

Investigations in these laboratories by Beckwith and Meijs and more recently by Nonhebel indicate that nitroxides rapidly reduce diazonium salts to afford aryl radicals (see above and Ch 1.5). The former work is of particular interest because it suggests the application of radical-trapping for the synthesis of alcohols (see scheme below). Although there are good methods available for the incorporation of halo or cyano groups onto a radical site there appears to be no other practical methods for the direct introduction of an oxygen function.

Nonhebel found that a problem with this reaction was the production of variable amounts of phenols especially from the alkyl-phenyl-diazonium salts; the mechanism of the
phenol production has not been determined.

(3) The Stannane/Halide Reaction. The feasibility of producing radicals in the presence of T via the stannane/halide reaction was tested. The reaction scheme and conditions employed were similar to those described for the silane reactions below. Although some reaction mixtures were moderately fruitful, it was discovered that T is reduced quite rapidly by the stannane and this excluded the method as a radical precursor for kinetics experiments (cf. Ch 1.4).

(4) The Silane/Halide Reaction. A method commonly used for generating radicals in ESR experiments is to photolyze a mixture of di-tert-butylperoxide, triethylsilane and an appropriate halide. In this reaction scheme tert-butoxyl radicals are generated, these react with the silane to give silyl radicals (eq 7.8) which then very rapidly abstract halogen atoms from the halide to afford carbon centred radicals (and the silyl halide) (e.g. eq 7.9). Under radical-trapping conditions the tert-butoxyl radicals were produced by heating either di-tert-butyl peroxyl oxalate (DBPO) or di-tert-butyl hyponitrite (TBHN). The general reaction scheme is as follows.

\[
\text{Et}_3\text{SiH} + \text{t-BuO}^\bullet \rightarrow \text{Et}_3\text{Si}^\bullet + \text{t-BuOH} \tag{7.8}\\
\text{Et}_3\text{Si}^\bullet + \text{Ar-X} \rightarrow \text{Ar}^\bullet + \text{Et}_3\text{Si-X} \tag{7.9}\\
\text{Ar}^\bullet + \text{T} \rightarrow \text{Ar-T} \tag{7.10}
\]

When a mixture of T (30 mM = 3 mol equiv.), triethylsilane (15% v/v), bromobenzene (2% v/v = 12 mol equiv.), and DBPO was heated in benzene (60°C for 15 min) a moderate yield of trapped phenyl\(^5\) \(7E\) was obtained (~ 55%). Major by-products were the silane derived species \(7F\) and the oxammonium bromide \(7D\); the latter were crystallized when the reaction mixtures were cooled and diluted with pentane. \(7F\), which was initially thought to be the trapped triethylsilyl radical, was identified by the characteristic spectral features illustrated above. \(7D\) was a colourless crystalline compound when freshly prepared but
decomposed slowly to a brown powder upon exposure to air; paramagnetic broadening in the NMR spectrum of this material and HPLC evidence indicated that $T$ was liberated in the decomposition. Precedents suggest that $7F$ originates from hydrogen atom abstraction of the $\alpha$-position in the silane though a disproportionation/addition reaction between the silyl and nitroxyl radicals cannot be ruled out.

When the above reaction mixture was more strongly heated (2 hr at 100°C) phenol and 1,1,3,3-tetramethylisoindoline were identified by HPLC analysis. The implication is that $7E$ decomposes by $N-O$ bond fission (see Ch 6).

When $o$- and $p$-bromo-toluene and $o$-bromo-anisol were treated with $T$ and DBPO under the conditions described above they afforded the corresponding trapped methyl-aryl and methoxy-aryl radicals in 37%, 45% and 42% yields respectively. By-products, presumed to arise from hydrogen atom abstraction (by tert-butoxyl radical) of the activated positions, were observed for these substrates and were especially prominent in the case of $o$-bromo-anisol (see Scheme below). Yields of these by-products could be reduced by increasing the silane/bromide concentration ratio in the reaction mixtures (excess triethylsilane is readily removed by evaporation in vacuo). On the other hand, reduction of the bromide concentration relative to $[T]$ led to a fall in the overall yield of (isolable) alkoxyamine products, probably because this makes the silyl/trap reaction more competitive with the desired silyl/bromide reaction ($k_{Br,sily} = 10^8$ M$^{-1}$s$^{-1}$ for alkyl bromides but relevant data are not available for the aryl bromides). The reaction may possibly be improved by use of the corresponding iodides in lower concentrations.

$o$-Bromo-anisol effectively competed with the silane for tert-butoxyl radicals and so it was expected that the problem would be prohibitive for the potential precursor for radical 24, viz. $o$-bromo-allyloxy-benzene, in which the $\alpha$-oxy-alkyl position is also allylic.
7.2 Ring Closure of \( o-(3\text{-Butenyl})\text{phenyl} \) Radical

Radical 23 was generated by the silane/halide reaction method. The precursor, \( o\)-bromo-(3-butenyl)-benzene, was readily prepared by the Wurtz coupling reaction of allylmagnesium bromide and \( o\)-bromo-benzylbromide (lachrymator!) in THF.\(^{235}\)

The reaction of the bromide (0.2 M) with T (0.10 M), triethylsilane (1.5 M) and DBPO (0.02 M) in benzene solution afforded a mixture of \( 7F, \) \( 23T \) and \( 23'T \) and two minor products in the alkoxyamine region of the HPLC trace (see footnotes to Table 7.1 for conditions). The minor products were not isolated but their HPLC retention (cf. Ch 2.18) and the dependence on silane concentration shown in other experiments were consistent with their being the hydrogen atom abstraction products \( 7G \) (cis and trans) and \( 7H. \)

Once generated, radical 23 may follow one of four likely pathways to non-radical products:

(i) it may be reduced by \( Et_3SiH, \)

(ii) react with the solvent,

(iii) couple with T,

(iv) or it may rearrange to \( 23' \) which then couples with T.

The reaction of the alkyl radical \( 23' \) with the solvent (benzene) or with \( Et_3SiH \) \( (k_{Si-H}^{alkyl} = 10^4 \) M\(^{-1}\)s\(^{-1}\)) \(^{236}\) would not be competitive with radical-trapping under these conditions (cf. below).
Chapter 7: Aryl and Cyclopropyl Radicals

Though reactions (i) and (ii) may be competitive with radical trapping, and consequently reduce the alkoxyamine yields, it can be shown, by steady-state kinetic analysis, that extraneous reactions of the initial species in a rearrangement do not affect the product ratios (cf. Appendix A3.2).

Kinetic data obtained at 80°C are summarized in Table 7.1; linear regression analysis of these data gives eq 7.11, where \([T]_i\) is the initial nitroxide concentration (M), and \(<r>\) is the correlation coefficient.

\[
\frac{[23]}{[23']} = 0.016 + 3.27 [T]_i, <r> = 0.996
\] (7.11)

The small intercept in eq 7.11 confirms that the solvent reactions of the rearranged species 23' are not significant (cf. Ch 6.2 and Ch 8 and A 3.2).

Table 7.1. Kinetic Data for Radical 23 at 80°C

<table>
<thead>
<tr>
<th>([T]_i),M (^b)</th>
<th>23T ,% (^c)</th>
<th>23'T ,% (^c)</th>
<th>23'T/23T (d)</th>
<th>(k_c/k_T),M (^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.31</td>
<td>3.52</td>
<td>0.76</td>
<td>0.99</td>
<td>0.30</td>
</tr>
<tr>
<td>0.125</td>
<td>4.12</td>
<td>2.10</td>
<td>2.3</td>
<td>0.23</td>
</tr>
<tr>
<td>0.051</td>
<td>3.25</td>
<td>4.05</td>
<td>5.7</td>
<td>0.29</td>
</tr>
<tr>
<td>0.0020</td>
<td>0.07±0.03</td>
<td>1.59</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(a\) ±0.3°C reactions performed in \(\text{Et}_3\text{SiH}\) (1.5M) in benzene; HPLC analysis, 90% MeOH/col.#1, product (retention times/sec): 23'T (550), 23T (580), 7G, 7H (697,715), 7F (930). \(b\) Initial nitroxide concentration at 22°C. \(c\) Percentages of total HPLC area with UV detection at 280nm; actual yield from preparation \(ca\) 35-45% with \([T]\) = 0.1M (based on DBPO). \(d\) Area ratios corrected for relative response factor i.e. 23'T/23T \(= 4.6 \times 23'T\%/23T\%\) (280nm). \(e\) \(k_c/k_T = (23'T/23T) \times [T]\).

The relative cyclization rate at 80°C is given by eq 7.12. The radical-trapping rate constant for aryl radicals \((k_{T\text{aryl}})\) has not been measured. However, it seems reasonable to expect that \(k_{T\text{aryl}}\) would not be much different from the value which has been estimated by Scaiano \textit{et al} (by LFP)\(^{59}\) for a species of comparable reactivity, viz. the cyclopropyl radical. Thus by assuming that \(k_{T\text{aryl}} = k_{T\text{c-propyl}} = 1.2 \times 10^9 \text{M}^{-1}\text{s}^{-1}\) at 25°C and that the temperature variation is the same as that for primary radicals (i.e. \(E_T = 0.9\) kcal/mol), one obtains the ring
Chapter 7: Aryl and Cyclopropyl Radicals

closure rate constant given by eq 7.13.
\[ k_c / k_{T-aryl} = 0.27 \pm 0.03 \text{ M} \] (7.12)
\[ k_c^{80^\circ} = 4.1 \times 10^8 \text{ M}^{-1}\text{s}^{-1} \] (7.13)

Kinetic data from reactions performed at 22°, 40°, 60° and 80°C (Table 7.2), combined with the assumptions regarding \( k_{T-aryl} \), give the temperature variation equations 7.14 and 7.15 (\( \theta = 2.3 \text{ RT kcal/mol} \)).

\[
\log \left( [k_c / k_{T-aryl}]/M \right) = 0.26 - 1.25/\theta \quad <r> = 0.977
\] (7.14)
\[
\log (k_c/s^{-1}) = 10.0 - 2.1/\theta
\] (7.15)
\[
\therefore \quad k_c^{25^\circ} = 2.9 \times 10^8 \text{ M}^{-1}\text{s}^{-1}
\] (7.16)

In the following chapter an empirical expression for \( k_T \) will be estimated from the direct competition between nitroxide T and CCl₄ for phenyl radicals; the alternative rate expression, \( \log (k_{T-aryl} / \text{M}^{-1}\text{s}^{-1}) = 10.5 - 2.4/\theta \), gives somewhat higher Arrhenius coefficients for the cyclization, viz. \( \log (A_c/s^{-1}) = 10.8 \) and \( E_c = 3.6 \text{ kcal/mol} \). Which of the two expressions for \( k_T \) is more accurate is difficult to predict from the experimental evidence (cf. Ch 8).

However, for the cyclization, one tends to favour the higher estimate for \( \log A_c \) on the grounds that it should be higher than the well established figure for hex-5-enyl, viz. 10.4. Two factors suggest this: (a) the reaction is more exothermic than the alkyl radical's ring closure (by ca 10 kcal/mol) – this implies a looser transition state, and (b) the radical centre is rotationally constrained in 23 – this should also increase \( \log A_c \) (cf. discussion of 19 in Ch 5).

Table 7.2. Temperature Variation Data for Radical 23a

<table>
<thead>
<tr>
<th>temp ,°C</th>
<th>23'T ,%</th>
<th>23'T ,%</th>
<th>23'T/23Td</th>
<th>( k_c/k_T ,\text{M}^e )</th>
</tr>
</thead>
<tbody>
<tr>
<td>22±2b</td>
<td>3.79</td>
<td>2.91</td>
<td>0.28</td>
<td>0.2</td>
</tr>
<tr>
<td>40±1b</td>
<td>3.25</td>
<td>2.10</td>
<td>0.235</td>
<td>0.23</td>
</tr>
<tr>
<td>60.0±0.2c</td>
<td>4.13</td>
<td>4.34</td>
<td>0.21</td>
<td>0.29</td>
</tr>
<tr>
<td>80.0±0.3c</td>
<td>3.91</td>
<td>4.27</td>
<td>0.20</td>
<td>–</td>
</tr>
</tbody>
</table>

a Reactions performed in Et₃SiH (1.5M) in benzene; [T]i = 60 mM, [DBPO]i = 6.0 mM b Sealed ampoule. c He purged small glass vials. d Area ratios corrected for relative response factor, viz. 23'T/23T = 4.6 x 23'T%/23T% (280nm). e \( k_c/k_T = (23'T/23T) \times [T] \).
7.5 Intramolecular Radical Additions of Cyclopropyl and Cyclobutyl Radicals

Suitably constituted ω-alkenyl-2- or -1-cyclopropyl radicals may undergo intramolecular radical addition to afford bicyclic or spiro-cyclic species, respectively (e.g. 25→25' and 26→26'). By analogy with their alkyl counterparts, the 1,5- and 1,6-ring closure reactions of cyclopropyl radicals are expected to be rapid and irreversible; in fact, these reactions are predicted to be more rapid than 'ordinary' 5-hexenyl ring closures since cyclopropyl radicals are considerably more reactive than alkyl radicals.

\[
\begin{align*}
25-\text{CO}_2\text{H} & \rightarrow \text{cis} \quad \text{trans} \\
26-\text{CO}_2\text{H} & \rightarrow \text{cis} \quad \text{trans} \\
27-\text{CO}_2\text{OBu}^+ & \rightarrow \text{cis} \quad \text{trans}
\end{align*}
\]

It appears that the only precedent for this type of radical cyclization is a study by Julia et al\textsuperscript{237} of the reduction of dibromocyclopropyl-compound 7I (and two similar species) by tributylstannane. When one equivalent of the stannane (with 0.017 mol equiv. AIBN) was slowly added to 7I, the monobromo products, 7J and 7K, were produced in the quantities and stereochemistries listed in the scheme. The reaction conditions, i.e. high stannane dilution, should favour cyclization so that the presence of 15% of 7J indicates that the cyclization may be slower than a simple analogy to 5-hexenyl cyclizations would imply.
Chapter 7: Aryl and Cyclopropyl Radicals

The radical-trapping was ideally suited for the study of cyclizations 25→25' and 26→26' because the precursors, 25P and 26P, were readily prepared via short syntheses and afforded good radical yields without significant by-products. The cyclization of the alkenyl-cyclobutyl radical 27 was calibrated for comparison with 26→26'.

Results and Discussion

7.6 Precursors. Biallyl was ethoxycarbonyl-cyclopropanated by treatment with one molar equivalent of ethyl diazoacetate and a catalytic amount of anhydrous CuSO₄ with ultrasonic agitation. The resulting mixture of esters was readily resolved upon hydrolysis to afford 25A which was converted into 25P by the usual procedures (Ch 2.17). 26E was prepared by treatment of tert-butyl cyclopropanecarboxylate with lithium cyclohexyl isopropyl amide (LCIA) then with 5-iodo-1-pentene at -35°C; acid hydrolysis (90% HCO₂H) and conversion gave 26P. Unlike the cyclopropyl case, 27E could be prepared by α-alkylation of the methyl ester by the LCIA/iodide method.

7.7 2-(3-Butenyl)-cyclopropyl Radical. Thermolysis of 25P in the presence of a ten-fold excess of T in the usual manner afforded alkoxyamines 25T cis, 25T trans, cis25'T and trans25'T in molar ratios listed in Table 7.3. 1,6-Cyclized products were not detected (by HPLC analysis or by NMR analysis of the alkoxyamine samples). 25T cis and 25T trans were not resolved by HPLC but could be discerned in the NMR spectrum of a sample of the mixed isomers; interestingly it was the trans trapped isomer which appeared to predominate but the NMR assignments were considered tentative due to the lack of a suitable model upon which to base the assignments (cf. Experimental and Ch 2.18). A trace of trapped cyclohexyl was
detected in the dilute reaction mixture. This was probably produced by hydrogen atom abstraction of the solvent by cyclopropyl radicals. Solvent reaction with the short lived cyclopropane-formyloxyl radical, formed in the initial fission of the diacyl peroxide, could be ruled out by the absence of trapped cyclohexyl in the more concentrated reaction mixtures (see following chapter).

<table>
<thead>
<tr>
<th>[T] , mM</th>
<th>25T , % c</th>
<th>( {cis}25'T , % c )</th>
<th>( {trans}25'T , % c )</th>
<th>( k_c^{cis}/k_T , \text{M}^d )</th>
<th>( k_c^{trans}/k_T , \text{M}^d )</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.5</td>
<td>3.4</td>
<td>7.8</td>
<td>3.4</td>
<td>0.020</td>
<td>0.0084</td>
</tr>
<tr>
<td>40</td>
<td>9.9</td>
<td>5.8</td>
<td>2.4</td>
<td>0.018</td>
<td>0.0078</td>
</tr>
<tr>
<td>80</td>
<td>14.3</td>
<td>4.1</td>
<td>1.74</td>
<td>0.023</td>
<td>0.0097</td>
</tr>
</tbody>
</table>

\( a \) ±0.3°C, reactions performed in cyclohexane \( b \) Initial nitroxide concentration at 22°C corrected for thermal expansion of the solvent \( c \) Percentages of total HPLC area, actual yields based on 25P were in the range 75-80% \( d \) Calculated from \( k_c/k_T = (25'T/25T) \times [T] \) for each isomer.

The kinetic data given in Table 7.3 are consistent with the scheme above and indicate relative ring-closure rates to the \( {cis} \) and \( {trans} \) isomers of eq 7.17 and eq 7.18 respectively. Scaiano’s value for \( k_T^{c-propyl} \), viz. \( 1.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1} \) at 25°C in a Freon solvent,\(^59\) can be extrapolated to 80°C by assuming that the temperature variation is the same as that for primary radicals (viz. \( E_T = 0.9 \text{ kcal/mol} \)); this gives a trapping rate constant of \( 1.8 \times 10^9 \text{ M}^{-1}\text{s}^{-1} \) at 80°C. Substituting this into the relative expressions gives absolute cyclization rate constants of
Chapter 7: Aryl and Cyclopropyl Radicals

eq 7.19 and eq 7.20.

\[ \frac{k_c^{\text{cis}}}{k_T} (25) = (2.4 \pm 0.4) \times 10^{-2} \text{ M} \] (7.17)

\[ \frac{k_c^{\text{trans}}}{k_T} (25) = (0.89 \pm 0.16) \times 10^{-2} \text{ M} \] (7.18)

\[ k_c^{\text{cis}} (25) = (4.3 \pm 0.8) \times 10^7 \text{ s}^{-1} \] (7.19)

\[ k_c^{\text{trans}} (25) = (1.6 \pm 0.3) \times 10^7 \text{ s}^{-1} \] (7.20)

7.8 1-(Pent-4-enyl)-cyclopropyl Radical. Thermolysis of 26P in the presence of T produced the expected alkoxyamine products, viz. 26T and 26'T, in good yields; HPLC analysis and NMR analysis of the alkoxyamine samples did not detect 1,6-cyclized material. As in the case of 25P, small amounts of trapped cyclohexyl were formed in the dilute reaction mixtures.

Table 7.4. Kinetic Data for 1-(Pent-4-entyl)-cyclopropyl Radical (26)

<table>
<thead>
<tr>
<th>temp °C</th>
<th>time , hr</th>
<th>[T] , M</th>
<th>26'T/26T</th>
<th>( \frac{k_c}{k_T} , \text{ M} )</th>
<th>yield , %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>48</td>
<td>37</td>
<td>1.89</td>
<td>0.070</td>
<td>56</td>
</tr>
<tr>
<td>60</td>
<td>48</td>
<td>37 (in benzene)</td>
<td>2.71</td>
<td>0.100</td>
<td>52</td>
</tr>
<tr>
<td>80</td>
<td>18</td>
<td>8.5</td>
<td>9.4</td>
<td>0.080</td>
<td>77</td>
</tr>
<tr>
<td>80</td>
<td>18</td>
<td>35</td>
<td>2.33</td>
<td>0.082</td>
<td>85</td>
</tr>
<tr>
<td>80</td>
<td>14</td>
<td>72</td>
<td>1.09</td>
<td>0.078</td>
<td>68</td>
</tr>
<tr>
<td>101</td>
<td>4</td>
<td>35</td>
<td>2.98</td>
<td>0.100</td>
<td>88</td>
</tr>
<tr>
<td>120</td>
<td>1</td>
<td>34</td>
<td>4.2</td>
<td>0.142</td>
<td>90</td>
</tr>
<tr>
<td>126</td>
<td>0.6</td>
<td>34</td>
<td>4.6</td>
<td>0.156</td>
<td>87</td>
</tr>
</tbody>
</table>

\[ a \pm 0.3 ^\circ C , \text{ reactions performed in cyclohexane} \]

\[ b \text{ Initial nitroxide concentration at } 22^\circ C \text{ corrected for thermal expansion and for consumption of } T \text{ by reaction} \]

\[ c \text{ Calculated from } k_c / k_T = (26'T / 26T) \times [T]. \]

The kinetic data (Table 7.4) when combined with the trapping rate expression suggested for 25 give the cyclization rate constant \( k_c^{26} = 1.7 \times 10^8 \text{ s}^{-1} \) at 80°C; the usual Arrhenius treatment of the kinetic data gives eq 7.22 for the temperature range 60°-125°C.

\[ \log [k_c / k_T (26)/M] = 1.1 - 3.6/\theta \]

\[ \langle r \rangle = 0.989 \] (7.21)

\[ \log (k_c^{26}/\text{s}^{-1}) = 10.9 - 4.5/\theta \] (7.22)

\[ k_c^{26} = 4.0 \times 10^7 \text{ s}^{-1} \text{ at } 25^\circ C. \] (7.24)
7.9 1-(Pent-4-enyl)-cyclobutyl Radical. Thermolysis of the tert-butyl perester $27\text{P}$ in the presence of $T$ in the manner described above afforded the trapped cyclohexyl radical, $27\text{T}$ and the spiro compound $27\text{T}'$ in moderate yields; 1,6-cyclization was not detected. The kinetic data (Table 7.6 - after Exp.) were consistent with the relative rate expression eq 7.25; this expression, combined with the trapping rate constant for a tertiary radical (i.e. $\log k_f^{27} = 9.5 - 0.9/\theta$), gives a ring closure rate constant of $1.5 \times 10^6 \text{ s}^{-1}$ at $80^\circ\text{C}$ and temperature variation given by eq 7.26.

$$\log \left[ k_c/k_T (27)/M \right] = 1.2 - 6.4/\theta \quad \langle r \rangle = 0.999$$

$$\log (k_c^{27}/\text{s}^{-1}) = 10.7 - 7.3/\theta$$

$$\Rightarrow \quad k_c^{27} = 2.2 \times 10^5 \text{ s}^{-1} \text{ at } 25^\circ\text{C}.$$

7.10 Discussion

Ring closure of $26$ is estimated to be about 200 times faster than that of its primary alkyl counterpart, hex-5-enyl radical (1), at $25^\circ\text{C}$. A comparison of the Arrhenius equations for these two reactions, Table 7.5 below, suggests that some of the difference lies in the frequency factor (viz. a factor of ca three) but that most arises from the lower activation energy for $26\rightarrow 26'$. The implied difference in the enthalpies of activation ($\Delta\Delta H^\circ = 2.3 \text{ kcal/mol}$) may originate from a larger driving force for ring closure of the cyclopropyl radical, since bond strength data suggest that the latter is more exothermic ($\Delta\Delta H^\circ = 8 \text{ kcal/mol}$). However, the analogy between reactions $1\rightarrow 1'$ and $26\rightarrow 26'$ is flawed by substantial differences in their steric parameters, e.g. non-bonded interactions, rotational constrictions and the geometry of their radical centres. A more accurate comparison may be made with the ring closures of $\alpha$-pent-4-enyl-cyclobutyl radical (27) and $\alpha$-pent-4-enyl-cyclopentyl radical (7M). The former has steric requirements quite similar to those of $26\rightarrow 26'$ except that whereas $26$ has a pyramidal radical centre that of $27$ is more or less planar. Calibrations indicate that both of these reactions have rate constants very close to that for the hex-5-enyl radical cyclization $1\rightarrow 1'$ so that the large increase in rate going from ring-closure of $1$ (or $27$) to that of $26$ must be attributed primarily to the high reactivity of cyclopropyl-type radicals though possibly with assistance from a favourable structural effect.
Chapter 7: Aryl and Cyclopropyl Radicals

Table 7.5 Global Ring-Closure Rates for some \( \omega \)-Alkenyl-cycloalkyl Radicals

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>25</th>
<th>7L</th>
<th>26</th>
<th>27</th>
<th>7M</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k^{80^\circ} ) (10^6 s^-1)</td>
<td>1.4</td>
<td>59</td>
<td>1.3 ( ^a )</td>
<td>170</td>
<td>1.5</td>
<td>1.5 ( ^b )</td>
</tr>
<tr>
<td>log ( A_c/s^{-1} )</td>
<td>10.4</td>
<td>-</td>
<td>-</td>
<td>10.9</td>
<td>10.7</td>
<td>-</td>
</tr>
<tr>
<td>( E_c ) (kcal/mol)</td>
<td>6.85</td>
<td>-</td>
<td>-</td>
<td>4.5</td>
<td>7.3</td>
<td>-</td>
</tr>
</tbody>
</table>

\( ^a \) Extrapolated using a 'reasonable' log \( A \) of 10.5 from 65°C where \( k_c(7L) = 7.6 \times 10^5 \) s^-1 and \( k_c(7M) = 9.3 \times 10^5 \) s^-1 (both data from Schiesser - ref 175).

The kinetic data collected in Table 7.5 imply (a) that alkyl substitution at the radical centre has little effect on total cyclization constant and (b) that cyclobutyl radical 27 behaves like an 'ordinary' alkyl radical in its intramolecular radical addition reaction – a result which is congruent with bond strength data, i.e. \( D_{C-H-butyl} = 96 \) kcal/mol = \( D_{C-H-sec-alkyl} \). It is interesting that a decrease in ring size from four to three has such a profound effect on the corresponding radical's reactivity. Cyclopropyl radicals are in fact more like vinyl radicals than ordinary alkyl radicals in reactivity and this adds some credibility to the view\(^{144a}\) that cyclopropanes are better described as mitigated olefins than as true cycloalkanes.

![trans-cyclization and cis-cyclization](image)

A comparison of the data for 25 with those for 7L reveals that (a) ring closure of 7L is more stereo-selective than that of 25 (3.5:1 versus 2.3:1 cis:trans respectively), (b) the annular form of 7L has little effect on the cyclization rate whereas there is a marked difference in rate between 25 and 26; the implication of this is that the cyclization of 25 may have a relatively large amount of strain energy in the transition structure.
Finally, with regard to results of Julia et al.,\textsuperscript{237} it is difficult to make any estimates of rate constants from these data because the reactions were performed under 'infinite dilution' conditions (see Intro.); the effective stannane concentration under these conditions is inversely proportional to the length of the stannane/halide radical chain; this is not known and consequently $k_e/k_H$ cannot be estimated. The higher selectivity of the $\alpha$-bromo radical's cyclization may reflect non-bonded interactions between the bromine ($X = \text{Br}$ above) and the double-bond group at the transition state; the preference for cis cyclization in 25 is proposed to arise from non-bonded interactions between the pseudo-endo hydrogens as indicated above.

**Experimental Section**

Instrumentation and general kinetic techniques have been described in Ch 2.16. HPLC analysis conditions and results are listed in the Supplementary Tables.

**7.11 Starting Materials** Commercial (i.e. wet) benzoyl peroxide was dried by dissolving it in benzene and drying the solution (i.e. washed with sat. brine then dried over anhydrous MgSO$_4$). Tributylstannane was purified by bulb-to-bulb (Kügelrohr) distillation \textit{in vacuo}. Other reagents were used without special purification. Bis-(o-allyloxy-benzoyl) peroxide 24P was donated for this study by Gerber.\textsuperscript{239} Preparation of o-(3-butenyl)-benzyl bromide (23P) from o-bromobenzylbromide and allylmagnesium bromide has been described by Koppang et al.\textsuperscript{240c}

**Bis-[2-(3-Butenyl)cyclopropyl] Peroxide (25P).** A solution of biallyl (8.3 g) in heptane (15 mL) was boiled with anhydrous CuSO$_4$ (0.3 g) for 15 min after which ethyl diazoacetate (11.4 g, 0.95 mol equiv.) was added at a rate which maintained vigorous reflux and N$_2$ evolution. After 30 min at reflux, the reaction mixture was washed successively with water, aq-NH$_3$ (4M) (x 3) and sat. brine. Evaporation and distillation \textit{in vacuo} (96°-100°C at 10 mm) afforded crude ethyl 2-(3-butenyl)-cyclopropanecarboxylate (4.0 g) which contained diethyl maleate and diethyl fumarate (formed by coupling of the ester carbene) as the only impurities. The mixture of esters was hydrolysed by general procedure 1 of Ch 2.17; the
usual purification and isolation of an acid afforded the pure 2-(3-butenyl)-cyclopropane-carboxylic acid (84% for hydrolysis, 18% overall) bp 135°C at 18 mm (Kügelrohr). \( ^1H \) NMR (CDCl\(_3\), 200 MHz) \( \delta \) 0.75 (m, 4H), 1.1-1.5 (m, 4H), 1.67 (m, 1H), 2.16 (dt, 2H), 5.00 (m, 2H), 5.8 (m, 1H), 11.5 (br s, 1H); IR \( \nu_{\text{max}} \) 1759 (C=O) cm\(^{-1}\). The acid was converted by general procedures (2) and (3) of Ch 2.17 into the title peroxide 25P (71%) of 88% iodometric purity. \( ^1H \) NMR (CDCl\(_3\), 200 MHz) \( \delta \) 0.75 (m, 8H), 1.1-1.5 (m, 8H), 1.65 (m, 2H), 2.16 (dt, 4H), 5.00 (m, 4H), 5.9 (m, 2H); IR \( \nu_{\text{max}} \) 1775, 1795 (C=O) cm\(^{-1}\).

Bis-[1-(4-Pentenyl)cyclopropaneformyl] Peroxide (26P). n-Butyllithium (7 mL x 1.6 M in hexane) was added to a solution of cyclohexyl isopropyl amine (1.61 g) in THF (10 mL) at -20°C. The solution was stirred at 0°C for 15 min then cooled to -40°C before the addition of tert-butyl cyclopropanecarboxylate (1.42 g - made from the acyl chloride by a standard procedure\(^{172e}\)\(^{240a}\) and, after 10 min, pent-4-enyl iodide\(^{240b}\) (2.15 g, 1.1 mol equiv.) in HMPA (1.5 mL). The reaction mixture was allowed to reach room temperature over a period of 1 hr then poured into a slurry of crushed ice in dilute H\(_2\)SO\(_4\); immediate isolation with pentane followed by distillation and careful column chromatography on fine mesh silica afforded tert-butyl 1-(4-pentenyl)-cyclopropanecarboxylate (45%) bp 88-91°C at 18 mm (98% pure by GC); \( ^1H \) NMR (CDCl\(_3\), 200 MHz) \( \delta \) 0.55 (m, 2H), 1.08 (m, 2H), 1.40 (s, 9H) overlaps with 1.35-1.6 (m, 4H), 2.05 (dt, 2H), 4.95 (m, 2H), 5.85 (m, 1H); IR \( \nu_{\text{max}} \) 1739 (C=O) cm\(^{-1}\). The ester (1.0 g) was heated to 70°C in 90% aq-formic acid (15 ml) for 2 hr then diluted with water. The usual isolation of an acid afforded pure 1-(4-pentenyl)-cyclopropanecarboxylic acid (89%) as a colourless oil which was converted by general procedures (2) and (3) of Ch 2.17 into the title peroxide 26P of 92% iodometric purity. \( ^1H \) NMR (CDCl\(_3\), 200 MHz) \( \delta \) 0.74 (m, 4H), 1.23 (m, 4H), 1.95 (m, 8H), 2.05 (dt, 2H), 4.81 (m, 4H), 6.00 (m, 2H); IR \( \nu_{\text{max}} \) 1750, 1792 (C=O) cm\(^{-1}\).

Bis-[1-(4-Pentenyl)cyclobutanecarboxylate (27P). Methyl cyclobutanecarboxylate (2.3 g) was \( \alpha \)-alkylated following the procedure described above; purification by column chromatography gave methyl 1-(4-pentenyl)cyclobutanecarboxylate (1.03 g, 31%).
Hydrolysis by general procedure (1) of Ch 2.17 afforded 1-(4-pentenyl)cyclobutanecarboxylic acid (86%) \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.25 (m, 2H), 1.6-2.1 (m, 8H), 2.38 (m, 2H), 4.95 (m, 2H), 5.8 (m, 1H); IR \(v_{\text{max}}\) 1739 (C=O) cm\(^{-1}\). Anal. Calcd. for C\(_{10}\)H\(_{16}\)O\(_2\): C, 71.39, H, 9.59; Found: C, 71.31, H, 9.46. The acid was converted by general procedures (2) and (4) of Ch 2.17 into the title perester \(^{27}\)P (67%) of 84% iodometric purity. \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.2 (m, 4H), 1.6-2.2 (m, 16H), 2.41 (m, 4H), 4.95 (m, 4H), 5.8 (m, 2H); IR \(v_{\text{max}}\) 1749, 1787 (C=O) cm\(^{-1}\).

7.12 Products. All products except those from the aryl radical precursor experiments were isolated by preparative HPLC on Column #2 or #3; product mixtures derived from \(^{23}\)P were flash chromatographed (2→10% ether in pentane) to remove the excess substrate (\(^{23}\)P) before the HPLC resolution. The aryl radical precursor trial experiments were analysed by HPLC but were resolved by flash chromatography on fine mesh silica with elution by progressively more polar mixtures of CH\(_2\)Cl\(_2\) and pentane. 2-Phenoxy-1,1,3,3-tetramethylisoindoline\(^5\) (\(^7\)E) has previously been described.

1,1,3,3-Tetramethyl-2-oxa-isoindolinium Bromide (\(^7\)D): Colourless needles from cyclohexane, mp 95-98°C - decomposes. \(^1\)H NMR (CDCl\(_3\), 200 MHz) [all features broadened with time unless the solution was purged (He)] \(\delta\) 2.00 (br s, 12H), 7.23 (m, 2H), 7.35 (m, 2H).

Diethyl-1-(1,1,3,3-tetramethylisoindolin-2-oxy)-ethyl-silane (\(^7\)G): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.75 (m, 4H), 1.07 (m, 6H), [1.29 (d), 1.49 (br s), 1.35 (d, 6.5 Hz)] = 15H, 3.80 (m, 1H), 3.92 (dq, 1H, 6.5 Hz/1.2 Hz), 7.03 (m, 2H), 7.15 (m, 2H); IR \(v_{\text{max}}\) 3680, 2110 (Si-H), 1485, 1455, 1372, 1360 cm\(^{-1}\).

2-(2-(But-3-enyl)phenoxy)-1,1,3,3-tetramethylisoindoline (\(^{23}\)T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.45 (s, 12H), 2.32 (m, 2H), 2.91 (t, 2H, 6.7 Hz), 4.95 (m, 2H), 5.94 (m, 1H), 7.03 (m, 2H), 7.15 (m, 2H), 7.30 (m, 2H), 7.35 (t, 1H), 7.42 (d, 1H).
Chapter 7: Aryl and Cyclopropyl Radicals

2-(1'-Indan-methoxy)-1,1,3,3-tetramethylisoindoline (23'T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.43 (br s, 12H), 2.0 +2.3 (m+m, 2H), 3.02 (m, 2H), 3.50 (m, 1H), 4.0+4.2 (m+m, 2H), 7.03 (m, 2H), 7.15 (m, 2H).

2-[2-(But-3-enyl)-cyclopropanoxy]-1,1,3,3-tetramethylisoindoline (25T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.42 (m, 1H), 0.88 (m, 1H), 1.1-1.7 (m, 15H), 2.18 (m, 2H), 3.48 (m, 1H), [cis-3.77 (m)], 5.02 (m, 2H), 5.90 (m, 1H), 7.02 (m, 2H), 7.15 (m, 2H). NMR integration was consistent with trans:cis = 2.3:1.

2-(Bicyclo[3.1.0]hexylmethoxy)-1,1,3,3-tetramethylisoindoline (25'T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.25 (m, 2H), 0.82 (m, 2H), 1.44 (br s, 12H), 1.4-1.8 (m, 4H), 2.42 (m, 2H), 3.83 (d, 2H, 6.9 Hz), 7.03 (m, 2H), 7.15 (m, 2H). The NMR integration suggested a 3:1 isomer mixture the major component was assigned cis by analogy with the corresponding alcohol (25'-OH).

2-(1-(Pent-4-enyl)-cyclopropoxy)-1,1,3,3-tetramethylisoindoline (26T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.1-1.9 (m, 20H), 2.22 (m, 2H), 5.05 (m, 2H), 5.99 (m, 1H), 7.05 (m, 2H), 7.17 (m, 2H). Anal. Calcd for C\(_{19}\)H\(_{27}\)NO: C, 79.95, H, 9.53. Found: C, 79.69, H, 9.15.

2-(4-Spiro[2.4]cycloheptylmethoxy)-1,1,3,3-tetramethylisoindoline (26'T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 0.4 (m, 2H), 1.45 (br s, 1H), 3.81 (m, 1H), 3.99 (m, 1H), 7.03 (m, 2H), 7.15 (m, 2H). Anal. Calcd for C\(_{19}\)H\(_{27}\)NO: C, 79.95, H, 9.53. Found: C, 80.21, H, 9.69.

2-(4-Spiro[2.4]cycloheptylmethoxy)-1,1,3,3-tetramethylisoindoline (27'T): \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 1.25 (s, 6H), 1.42 (s, 6H), 1.3-1.8 (m, 8H), 5.05 (m, 2H), 5.93 (m, 1H), 7.09 (m, 2H), 7.26 (m, 2H). IR \(\nu_{\text{max}}\) 2980, 2935, 1640 (C=CH\(_2\)), 1490, 1455, 1369, 1361 cm\(^{-1}\).
2-(4-Spiro[2.4]cycloheptylmethoxy)-1,1,3,3-tetramethylisoindoline (26’T):

$^1$H NMR (CDCl$_3$, 200 MHz) δ 1.45 (br s, 12H), 1.5-2.0 (m, 10H), 2.22 (m, 1H), 3.75 (m, 1H), 4.00 (m, 1H), 7.03 (m, 2H), 7.15 (m, 2H). IR $v_{\text{max}}$ 2930, 2850 (ringCH$_2$), 1488, 1455, 1369 cm$^{-1}$.

<table>
<thead>
<tr>
<th>temp, °C</th>
<th>[T], mM</th>
<th>27’T/27T</th>
<th>$k_c/k_T$, $10^{-3}$M</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1.82</td>
<td>1.44</td>
<td>2.62</td>
<td>56</td>
</tr>
<tr>
<td>60</td>
<td>4.8</td>
<td>0.53</td>
<td>2.54</td>
<td>52</td>
</tr>
<tr>
<td>84</td>
<td>4.6</td>
<td>0.98</td>
<td>4.5</td>
<td>63</td>
</tr>
<tr>
<td>110</td>
<td>4.4</td>
<td>1.88</td>
<td>8.3</td>
<td>67</td>
</tr>
<tr>
<td>110</td>
<td>8.6</td>
<td>1.00</td>
<td>8.6</td>
<td>77</td>
</tr>
</tbody>
</table>

*a ±0.3°C, reactions performed in cyclohexane b Initial nitroxide concentration at 22°C corrected for thermal expansion and for consumption of T by reaction e HPLC Analysis: T-c-hexyl% = 27T% + 27’T%.

CHAPTER EIGHT

Calibration of Bimolecular Reactions by Radical-Trapping

Introduction

As demonstrated in previous chapters, suitably designed experiments may utilize a competition between unimolecular radical reaction and the coupling reaction with nitroxide $T$ either to calibrate the coupling rate constant $k_T$ (i.e. *clock calibration*, Ch 2) or, conversely, to calibrate rearrangement and fragmentation rate constants (see Ch 3 - 5 and Ch 7). An obvious extension of the latter procedure is the calibration of bimolecular radical reactions through their competition with the radical-trapping reaction. For example, a radical ($R\cdot$) generated in a solution of $T$ in an 'atom-donor' solvent ($S-X$), may couple with the nitroxide or it may react with $S-X$ to give solvent radicals, $S\cdot$, which are then trapped by $T$ to afford the alkoxyamine $S-T$; under *pseudo-first-order* conditions (i.e. $[T] >> [\text{precursor}]$) the relationship between the final molar concentration ratio of products $[S-T]/[R-T]$ and the bimolecular rate constants, $k_T$ and $k_X$, is given by eq 8.1.

Scheme 8.1

![Scheme 8.1](image)

Kinetic Equation:

$$\frac{k_X}{k_T} = \frac{[T][S-T]}{[S-X][R-T]}$$

(8.1)

In principle, the *direct competition method* (e.g. Scheme 8.1) should be applicable to a wide range of atom transfer (displacement) reactions and to radical addition reactions ($R\cdot + C=C-Y \rightarrow R-C-C^*-Y$). However, there are some practical restrictions in the use of this scheme, viz. (a) the reaction must be sufficiently rapid to compete with radical-trapping, and (b) it must give rise to stable alkoxyamine products. Thus the method is limited to reactions with *pseudo-first-order* rate constants, e.g. $[S-X]k_X$, greater than, say, $10^5$ s$^{-1}$; if $S-X$ is the
solvent this means that unless $k_X$ is greater about $10^4 \text{M}^{-1}\text{s}^{-1}$ the solvent reaction would be too slow to be detected by radical-trapping under normal conditions. However, when radical addition or atom transfer reactions are this rapid it usually means that they are favoured by a strong thermodynamic driving force. This being so, the radicals formed from the substrate, $S^\cdot$, are more stable than $R^\cdot$ and so form less stable alkoxyamine products with $T$. Consequently few reactions of alkyl radicals are accessible via the direct competition method. On the other hand, aryl and cyclopropyl radicals react with variety of substrates with accessible rate constants; radical-trapping investigations of some of these are reported below.

An alternative technique, which does not require the substrate products $S \cdot T$ to be stable, utilizes the kinetics of radical clock reactions in the presence of two radical quenching agents, viz. $T$ and $S \cdot X$. The method has provided some very pleasing results in reactions of clock $7 \rightarrow 7'$ with $\text{CCl}_4$ and methyl acrylate (below). Further experimental investigations are in progress in this area.

Results and Discussion

(I) Direct Competition

8.1 $T$ versus $\text{CCl}_4$ for Phenyl (Ph), Cyclopropyl (28), and $\alpha$-Methylcyclopropyl (29) Radicals.

Methods. The title radicals were generated from the appropriate diacyl peroxides in $\text{CCl}_4$ in the presence of the nitroxide $T$. In a trial reaction, a solution of $T$ (16 mM) and benzoyl peroxide (BPO) (7 mM) in 'spectral grade' $\text{CCl}_4$ (solvent = 6.5 M) was heated to reflux under $N_2$; in appearance, the reaction mixture changed from yellow to a ruby red colour which intensified upon exposure to air (the colour change was also noted in degassed/sealed reaction mixtures). The reaction was monitored by HPLC analysis and appeared to be complete after four hours; the short reaction time (non-induced decomposition would require ca. 30 hr at this temperature) and low alkoxyamine yield (43% corrected), together with the large amount of
polar material evident in the HPLC trace, suggested that reaction occurred mostly through nitroxide induced decomposition of the peroxide (cf. Ch 1.5). The coloured material was presumed to arise from decay of the benzoyl oxammonium salt (Ch 1.5) which is implicated in this process.\textsuperscript{32} The usual product resolution and analysis procedures (HPLC/NMR) revealed the predicted alkoxyamine products, viz. the trapped trichloromethyl radical (T-CC\textsubscript{3}, 5-10\% by area at 270 nm) and trapped phenyl radical (T-Ph, 15-18\%).

\[
\begin{align*}
\text{Ph-Cl} & \quad \text{Cl}_3\text{C}^- \quad \text{Ph-Cl} \\
\text{CCl}_4 & \quad k_{Cl} \\
(\text{BPO}) & \quad k_D (= 10^7 \text{s}^{-1}) \\
T & \quad k_T^\text{Bz} (= 3 \times 10^8 \text{s}^{-1}) \\
T+ & \quad k_T^O \\
\text{T-CCl}_3 & \quad \text{H}_2\text{O/MEOH} \\
\text{T-CCl}_3 & \quad \text{T-OMe} \\
\end{align*}
\]

T-CC\textsubscript{3} was found to decompose under HPLC analysis conditions, presumably by solvolysis, to form a methyl carbonate (shown) or a carbonic acid (which would probably be too unstable to be observed). Since MeOH is a stronger nucleophile than H\textsubscript{2}O the former is expected to be the major product.

Fortunately, the half-life of T-CC\textsubscript{3} was longer than the analysis time so that by monitoring the decay under conditions of analysis, viz. in 92\% aq-MeOH at 22\textdegree C, the first-order rate constant of decay, \(k_s\), could be calibrated (see data for \(\alpha\)-methyl-cyclopropyl, Table 8.1). The kinetic data were then corrected, i.e. extrapolated back to \(t = 0\) of the HPLC analyses, based on the assumption that \(k_s\) was not appreciably affected by random variations in the analysis conditions, i.e. small fluctuations in methanol concentration. Under the conditions used for kinetic determinations \(k_s = 8.4 \times 10^{-4} \text{s}^{-1}\) and the HPLC retention time was 600''$\pm$35'' so that the correction factor was: \([\text{T-CCl}_3]_{t=0} = 1.65 \times [\text{T-CCl}_3]_{t=600''} \).
GC analysis of the reaction mixtures revealed the presence of chlorobenzene (see Scheme above). The molar concentration was approximately determined by the standard addition method, i.e. measurement of the relative peak enhancement afforded by addition of authentic chlorobenzene to a standard added concentration; the estimate given by this method is consistent with HPLC estimate for \([T-CCl_3]_{e=0} = 1.2 \text{ mM relative to an internal standard of biphenyl} \).

Similar reactions were performed with bis-cyclopropaneformyl peroxide \([27-CO_2]_2 \) and with bis-(1-methyl-cyclopropane)formyl peroxide \([28-CO_2]_2 \). These reacted to afford the expected alkoxyamine products (per Scheme 8.1) in very good yield and with only minor amounts of polar by-products. As above, the relative concentrations of T-CCl_3 in the reaction mixtures were estimated by performing timed analyses on solutions of T-CCl_3 in the respective HPLC mobile-phases, Table 8.1.

**Table 8.1. Kinetic Data for Solvolysis of T-CCl_3 in Aqueous Methanol**

<table>
<thead>
<tr>
<th>solvent^a</th>
<th>( t_e, s^b )</th>
<th>( t_e + t_r, s^c )</th>
<th>([T-R]/[T-CCl_3] )</th>
</tr>
</thead>
<tbody>
<tr>
<td>92%</td>
<td>0</td>
<td>400</td>
<td>1.38 (^d)</td>
</tr>
<tr>
<td>92%</td>
<td>1500</td>
<td>1900</td>
<td>0.72 (^d)</td>
</tr>
<tr>
<td>92%</td>
<td>2940</td>
<td>3340</td>
<td>0.40 (^d)</td>
</tr>
</tbody>
</table>

\[ [T-R]/[T-CCl_3] = 1.62 \exp [-4.2 \times 10^{-4} (t_e + t_r)] \langle r \rangle = 0.9998 \]

\[
\begin{array}{ccc}
85\% & 0 & 710 \\
85\% & 1260 & 1970 \\
85\% & 2100 & 2810 \\
\end{array}
\]

\[ [T-R]/[T-CCl_3] = 1.12 \exp [-8.4 \times 10^{-4} (t_e + t_r)] \langle r \rangle = 1.0000 \]

\(^a\) Percent by volume MeOH in aq-MeOH  \(^b\) Standing-time in HPLC mobile phase  \(^c\) \( t_r = \) retention time of T-CCl_3 by HPLC analysis  \(^d\) \( R = c-C_3H_5 \)  \(^e\) \( R = \alpha\text{-Me-c-C}_3H_5 \).

**Kinetic Data.** Competition experiments involving the title radicals were performed under the same conditions of temperature, nitroxide concentration and analysis in order to make comparisons between the radical reactivities as accurate as possible. Relative molar yields of the hydroxylamines were obtained from the HPLC areas upon application of the estimated solvolysis correction (and correction for the higher than usual response factor of T-Ph). The product data were consistent with eq 8.1 which was used to calculate the relative chlorine atom
transfer rates, $k_{\text{CV}}/k_T$, listed in Table 8.2. Data for the reactions with BPO were more scattered than those the other reactions; the scatter probably reflected the proximity of T-Ph to T-CCl$_3$ in the HPLC trace (sep. factor, $\alpha = 0.96$) rather than any differences between the contents of ampoules.

Table 8.2 Relative Alkoxyamine Yields from Reactions of CCl$_4$ with Phenyl, Cyclopropyl and $\alpha$-Methyl-cyclopropyl Radicals

<table>
<thead>
<tr>
<th>temp, $^\circ\text{C}$</th>
<th>[T], mM$^b$</th>
<th>[T-CCl$_3$]/[T-Ph]$^c$</th>
<th>[T-CCl$_3$]/[27T]</th>
<th>[T-CCl$_3$]/[28T]</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>18</td>
<td>2.0±0.3</td>
<td>0.82</td>
<td>4.4</td>
</tr>
<tr>
<td>80</td>
<td>18</td>
<td>3.0±0.3</td>
<td>1.04</td>
<td>5.2</td>
</tr>
<tr>
<td>80</td>
<td>9</td>
<td>6.5±1.0</td>
<td>2.20</td>
<td>9.8</td>
</tr>
<tr>
<td>100</td>
<td>18</td>
<td>3.3</td>
<td>1.22</td>
<td>5.6</td>
</tr>
<tr>
<td>121</td>
<td>18</td>
<td>3.5</td>
<td>1.37</td>
<td>6.7</td>
</tr>
</tbody>
</table>

$^a$ ±0.3$^\circ$C. $^b$ Initial concentration at 22°C and [CCl$_4$] = 6.5 M at 22°C; thermal correction cancels out. $^c$ Relative response factor of T-Ph is 2.6.

Table 8.3 Kinetic Data for Chlorine Atom Abstraction of CCl$_4$ by Phenyl, Cyclopropyl and $\alpha$-Methyl-cyclopropyl Radicals

<table>
<thead>
<tr>
<th>temp, $^\circ\text{C}$</th>
<th>[T], mM$^b$</th>
<th>$10^{-3} k_{\text{CV}}/k_T$</th>
<th>$10^{-3} k_{\text{CV}}/k_T$</th>
<th>$10^{-3} k_{\text{CV}}/k_T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>18</td>
<td>5.4±0.8</td>
<td>0.82</td>
<td>4.4</td>
</tr>
<tr>
<td>80</td>
<td>18</td>
<td>7.6±1.2</td>
<td>1.04</td>
<td>5.2</td>
</tr>
<tr>
<td>100</td>
<td>18</td>
<td>3.3</td>
<td>1.22</td>
<td>5.6</td>
</tr>
<tr>
<td>121</td>
<td>18</td>
<td>3.5</td>
<td>1.37</td>
<td>6.7</td>
</tr>
</tbody>
</table>

$^a$ ±0.3$^\circ$C. $^b$ Initial concentration at 22°C and [CCl$_4$] = 6.5 M at 22°C; thermal correction cancels out (see eq 8.1). $^c$ Relative response factor of T-Ph is 2.6; error is 1 x SD from 3 x HPLC runs.
The kinetic data of Table 8.3 can be summarised by the temperature variation equations eq 8.2-4 in which $\theta = 2.3\, RT\, \text{kcal/mol}$ and $\langle r \rangle$ is the correlation coefficient. for phenyl radical

$$\log (k_C/\alpha) = -1.14 - 1.57/\theta, \quad \langle r \rangle = 0.947$$

for cyclopropyl radical (28)

$$\log (k_C/\alpha) = -1.22 - 2.16/\theta, \quad \langle r \rangle = 0.993$$

and for $\alpha$-methyl-cyclopropyl radical (29)

$$\log (k_C/\alpha) = -0.87 - 1.56/\theta, \quad \langle r \rangle = 0.988$$

Scaiano et al\textsuperscript{59} have measured both $k_C$ and $k_{\text{TEMPO}}$ for the cyclopropyl radical; their data at 25°C, viz. $k_C = 1.4 \times 10^6 \, \text{M}^{-1}\text{s}^{-1}$ and $k_T = 1.2 \times 10^9 \, \text{M}^{-1}\text{s}^{-1}$, suggests a rate ratio of $k_C/k_T = 1.2 \times 10^{-3}$. This compares favourably with the figure which is obtained by extrapolation of the radical-trapping data using eq 8.3, viz. $1.6 \times 10^{-3}$ at 25°C. The temperature variation of $k_C$ was also measured; combination of their Arrhenius expression\textsuperscript{59}, $\log [k_C/\alpha] = 8.7 - 3.5/\theta$; with eq 8.3 gives eq 8.5 for trapping rate constant of cyclopropyl radicals with the nitroxide, T, in CC\textsubscript{14}.

$$\log k_T(\text{c-propyl}) = 9.9 - 1.3/\theta$$

The nitroxides T and TEMPO are likely to have about the same reactivity towards cyclopropyl radicals (cf. Ch 1.11) so that the agreement between the $k_C/k_T$ data encourages confidence in the experimental method and, furthermore, indicates that eq 8.2 and eq 8.4 would provide, at least, approximate estimates of $k_T$ (if $k_C$ were known) or of $k_C$ (if $k_T$ were known).

Accordingly, substitution of the $k_C$ for phenyl and $\alpha$-methylcyclopropyl radicals\textsuperscript{242,243} (viz. 7 x 10\textsuperscript{6} and 11 x 10\textsuperscript{6} M\textsuperscript{-1}s\textsuperscript{-1}, respectively, at 25°C) affords the trapping rate constants for these radicals (eq 8.6 and eq 8.7).

$$k_T^{\text{phenyl}} = 1.6 \times 10^9 \, \text{M}^{-1}\text{s}^{-1} \text{ at 25°C in CC} \text{Cl}_4$$

(8.6)

$$k_T^{29} = 1.1 \times 10^9 \, \text{M}^{-1}\text{s}^{-1} \text{ at 25°C in CC} \text{Cl}_4$$

(8.7)

Equations (8.6) and (8.7) suggest that the $k_T$ of cyclopropyl and phenyl radicals are not much higher than those of alkyl radicals in hydrocarbon solvents, viz. 1.0 x 10\textsuperscript{9} M\textsuperscript{-1}s\textsuperscript{-1}.
Chapter 8: Bimolecular Reactions

However, the *radical clocking* data of Ch 6 suggest that radical-trapping in CCl₄ may be somewhat slower than it is in cyclohexane [i.e., $k_T(c\text{-hexane}) = 2 k_T(CCl₄)$ based upon product data from $7\rightarrow 7'$] and perhaps a more accurate comparison may be made after inclusion of this solvent effect; the predicted trapping rate constants at 25°C in cyclohexane are $2.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ and $3.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ for cyclopropyl and for phenyl radicals, respectively.

Ingold *et al.*²⁴² have explained the relatively high reactivity of α-methyl-cyclopropyl radical towards CCl₄ as a polar effect; the α-methyl substituent makes 29 more nucleophilic than cyclopropyl and consequently it is more reactive towards atoms attached to electron withdrawing groups such as the CCl₃ fragment of CCl₄.

**Discussion**

In Chapter 7 the radical-trapping reaction of aryl radicals was used to investigate the kinetics of the ring-closure reaction of o-(but-3-enyl)phenyl radical (24); a problem was that there were no kinetic data available for the trapping reaction between aryl radicals and a nitroxide (cf. Ch 7.2). The ring-closure had been calibrated by Abewickrema *et al.* using the tributylstannane method and, initially, it was anticipated that this reaction could be used to calibrate the radical-trapping rate constant, $k_T^{aryl}$, in much the same way that alkyl radical clocks were used for $k_T^{alkyl}$ in Chapter 2. It appears, however, that rate constant for the reaction of phenyl radicals with the stannane ($k_H^{phenyl}$) were in error []; the figures quoted were probably for reaction of benzoyloxyl radical with the stannane. This being so, the radical-trapping data for 23 may possibly offer the best means to calibrate $23\rightarrow 23'$ and, consequently, $k_T^{aryl}$.

In Chapter 7 it was argued that $k_T^{aryl}$ may have a similar value to $k_T^{c\text{-propyl}}$. Nevertheless, an empirical estimate is desirable. In order to estimate the Arrhenius coefficients for $k_T^{aryl}$ one may assume that the reaction has the same energy of activation as the alkyl radicals and thus calculate log $A$ from eq 8.6; this gives eq 8.8. Alternatively, one might make 'reasonable' assumptions about the temperature variation of $k_T^{aryl}$ and derive Arrhenius...
coefficients for $k_{T\text{aryl}}$ from eq 8.2. Thus, by assuming that log $A_{Cl}$ would be slightly higher than those for a cyclopropyl radical (vide supra) we may estimate that log $k_{Cl\text{aryl}} = 9.0 - 3.2/\theta$ and arrive at eq 8.8 for $k_{T\text{aryl}}$.

$$\log \left( \frac{k_{T\text{aryl}}}{M^{-1}s^{-1}} \right) = 10.2 - 1.6/\theta$$ (8.8)

(II) The Clock/Trap Calibration Method

Investigations of clock reactions in potentially reactive media (Ch 6) suggested an alternative method for calibrating the kinetics of radical/molecule reactions. The basis of this method is that, in the presence of a nitroxide and a reactive substrate, the rate at which a radical species ($R\cdot$) is directly converted into non-radical products (i.e. 'quenched') is simply the sum of the trapping rate ($k_T[T][R\cdot]$) and the radical/substrate reaction rate ($k_X[S\cdot X][R\cdot]$). Kinetic relationship eq 8.4 is derived by application of the steady-state equation, rate constant definitions, and the pseudo-first-order approximation (in $T$ and in $S\cdot X$). Scheme 8.2 indicates an atom transfer reaction but the analysis is, of course, equally valid for radical addition and radical coupling reactions of $R\cdot$ and $U\cdot$.

Scheme 8.2. Kinetic Scheme for the Clock/Trap Calibration Method

Kinetics Analysis. Application of the steady-state approximation to the rearranged species ($R\cdot$) gives eq 8.9 for the radical concentration ratio $[U\cdot]/[R\cdot]$. Combination of eq 8.9 with the
definitions of the bimolecular rate constants, viz. $\frac{d[R-T]}{dt} = k_T[R][R^\ddagger]$, $\frac{d[S-T]}{dt} = k_5^R[S-X][R^\ddagger]$, and so forth for $U^\ddagger$, affords eq 8.10, which under pseudo-first-order conditions integrates to eq 8.11 (see Appendix).

\[
\frac{[U^\ddagger]}{[R^\ddagger]} = \frac{(k_X^R [S-X] + k_T^R [T])}{k_C}
\]  
\[8.9\]
\[
\frac{d[U-T]}{d[R-T]} = \frac{(k_T^U/k_T^R) [U^\ddagger]/[R^\ddagger]}
\]  
\[8.10\]
\[
[U-T]/[R-T] = \frac{(k_T^U/k_T^R) (k_X^R [S-X] + k_T^R [T])}{k_C}
\]  
\[8.11\]
Eq 8.11 is linear in $[T]$ and in $[S-X]$, thus a plot of $[U-T]/[R-T]$ versus $[T]$ (with $[S-X]$ kept constant) has

\[
slope = \frac{k_T^U}{k_C}
\]  
\[8.12\]
and $[T] = 0$ intercept $= (k_T^U/k_T^R) (k_X^R/k_C) [S-X]$  
\[8.13\]
or if $[T]$ is kept constant and $[S-X]$ is varied the analogous plot has

\[
slope = (k_T^U/k_T^R) (k_X^R/k_C)
\]  
\[8.14\]
and $[S-X] = 0$ intercept $= \frac{(k_T^U/k_C)}{[T]}$.  
\[8.15\]
In many cases it safe to assume that $k_T^U = k_T^R$ or to use calibrated values\textsuperscript{57,60} so that eq 8.13 or eq 8.14 gives the rate constant for the radical/substrate reaction relative to the clock’s rate constant $k_C$. It is noteworthy that use of this scheme affords estimates of $k_X$ which do not depend on the actual value of $k_T$.

8.3 Calibrations. The report that follows represents preliminary results only.

The experiments were designed to investigate the feasibility of this scheme as a method of calibration.

Experiments. Thermolysis of bis-(3,3-dimethylpent-4-enoyl) peroxide (Ch 2, 7P) in CCl$_4$ (redistilled spectral grade) in the presence of a tenfold excess of T afforded hydroxylamines 7T
and 7'T in molar ratios listed below. The data were consistent with eq 8.4 to within experimental uncertainties and suggest a relative rate constant for chlorine atom transfer to the tertiary radical 7' of \((k_T/7/k_T')\) \((k_X^R/k_C)\) = 1.0 x \(10^{-2}\) M\(^{-1}\). With \(k_C = 2.3 \times 10^7\) s\(^{-1}\) (cf. Ch 3) and \(k_T/7/k_T' = k_T^{\text{neopentyl}}/k_T^{\text{tertiary}} = 1.4\) (Chateauneuf et al\(^{60}\)), the \(k_C\) for a tertiary radical is calculated to be

\[
k_{C,\text{tertiary}} = 1.6 \times 10^5 \text{M}^{-1}\text{s}^{-1} \text{ at } 80^\circ\text{C} \tag{8.16}
\]

This figure is in fair agreement with an estimate which has been made by the CIDNP method for tert-butyl radical\(^{242}\), viz. \(0.95 \times 10^5\) M\(^{-1}\)s\(^{-1}\) at \(80^\circ\text{C}\) (extrapolated using the published temperature variation, \(\log k_{C,\text{Bu}} = 7.0 - 3.3/\theta\)) and with an estimate for primary radicals made by the laser flash photolysis method \((5.8 \times 10^4\) M\(^{-1}\)s\(^{-1}\) at \(25^\circ\text{C}\)\(^{243}\) which extrapolates to \(1.4 \times 10^5\) M\(^{-1}\)s\(^{-1}\) at \(80^\circ\text{C}\) with \(\log A = 8.0\)).

Likewise, thermolysis of 7P in solutions of T in methyl acrylate yielded the kinetic data of Table 8.4. The yields of what were presumed to be trapped radical/monomer products were quite erratic under these conditions (8 hr at \(80^\circ\text{C}\)) and this demonstrates an advantage of this indirect method over direct competition, viz. that lability of alkoxyamines derived from the substrate reaction do not affect the kinetic data.

![Diagram of radical reaction](image)

**Table 8.4. Kinetic Data for 7→7' in CCl\(_4\) and Methyl Acrylate**

<table>
<thead>
<tr>
<th>(\text{T} + \text{CCl}_4) versus 7→7'</th>
<th>(\text{T} + \text{CO}_2\text{Me}) versus 7→7'</th>
</tr>
</thead>
<tbody>
<tr>
<td>[T] (mM)</td>
<td>[7T]/[7'T]</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>6.0</td>
<td>0.165±0.009</td>
</tr>
<tr>
<td>19</td>
<td>0.368</td>
</tr>
<tr>
<td>45</td>
<td>0.76</td>
</tr>
<tr>
<td>96</td>
<td>1.44</td>
</tr>
</tbody>
</table>

\([7T]/[7'T] = 0.095 + 14.8 [T] , 0.999\)

\([7T]/[7'T] = 0.606 + 8.0 [T] , 0.991\)

\(a\) [CCl\(_4\)] = 9.5 M, \(b\) [MeAcr] = 9.9 M.
The data for methyl acrylate are consistent with a relative radical addition rate constant of \((k_T^7/k_T^7)\) \((k_A^7/k_C)\) = 9.7 \(\times 10^{-2}\) M\(^{-1}\), which gives (same assumptions as above)

\[
k_A^{\text{tertiary}} = 9 \times 10^5 \text{ M}^{-1}\text{s}^{-1} \text{ at } 80^\circ\text{C}. \tag{8.17}
\]

This value can be compared with an estimate made by Citterio et al\(^{244}\) for the addition of hex-5-enyl radical (1) to methyl acrylate. The calibration used the ring closure \(1\to1'\) as a radical clock; by using the currently accepted rate constant for this rearrangement\(^{72}\) we find that \(k_A^{\text{prim}} = 9 \times 10^5 \text{ M}^{-1}\text{s}^{-1} \text{ at } 80^\circ\text{C}\).

Conclusions.

It can be seen by the data presented above that radical-trapping may effectively be applied to the investigation of bimolecular processes. Preliminary experiments, not presented here, demonstrate that the direct competition method may readily be applied for the calibration of hydrogen transfer reactions between cyclopropyl or phenyl or strained bridgehead radicals and hydrocarbons (e.g. cyclohexane). The clock/trap method may also be used to calibrate radical coupling reactions such as those of clock radicals with galvinoxyl or with TEMPO.
Chapter 8: Bimolecular Reactions

Experimental Section.

Instrumentation and general kinetic techniques have been described in Ch 2.16. The substrates used here were volatile and were removed by evaporation before analysis.

8.4 Materials. Bis-cyclopropaneformyl peroxide mp 78-79°C (lit\textsuperscript{241} mp 80-81°C), and bis-(1-methylcyclopropaneformyl) peroxide\textsuperscript{241} were prepared from the commercially available acids (Aldrich) by procedures (2) and (3) of Ch 2.17. Benzoyl peroxide was dried (Ch 7) before use.

2-Cyclopropoxy-1,1,3,3-tetramethylisoindoline. \textsuperscript{1}H NMR (CHCl\textsubscript{3}, 200 MHz) \textdelta 0.45 (m, 2H), 0.60 (m, 2H), 1.21 (br s, 6H), 1.48 (s, 6H), 3.63 (m, 1H), 7.10 (m, 2H), 7.21 (m, 2H). IR v\textsubscript{max} 3085, 3058, 3022, 2975, 2930, 2860, 1486, 1450, 1383 cm\textsuperscript{-1}.

2-(1-Methylcyclopropoxy)-1,1,3,3-tetramethylisoindoline. \textsuperscript{1}H NMR (CHCl\textsubscript{3}, 200 MHz) \textdelta 0.55 (m, 2H), 0.70 (m, 2H), 1.21 (d, 6H) overlaps with 1.24 (s, 3H), 1.48 (s, 6H), 7.10 (m, 2H), 7.21 (m, 2H).
APPENDIX

Kinetic Equations

A1 Assumptions and Approximations

A1.1 Thermal Expansion. Because solvents expand when they are heated the molar concentrations of reaction mixtures are lower at reaction temperatures \((x^\circ C)\) than they are at the make-up temperature \((22^\circ \pm 2^\circ C)\). If the thermal expansion coefficient of the solvent, \(\alpha\), is defined by \(\Delta V = \alpha V \Delta T\), the correction that must be applied to the trap concentration \([T]\) is given by,

\[
[T]_{x^\circ C} = [T]_{22^\circ C} \left(1 + \alpha (x - 22)\right)^{-1}
\]

(A1)

For cyclohexane and benzene, \(\alpha = 0.0012\) \(^\circ\)C\(^{-1}\) so that at 120\(^\circ\)C, for instance, the thermal expansion correction factor is, \([T]_{120^\circ C} = 0.89 [T]_{22^\circ C}\). The effect is not negligible in accurate kinetic determinations, e.g. when the correction is applied to kinetic data for reactions in cyclohexane the Arrhenius \(\log A\) and \(E\) terms are increased by about 0.2 \((= +1\) eu in \(\Delta S^f\)) and 0.3 \((\text{kcal/mol})\) respectively.

A1.2 The Pseudo-first-order Approximation. The kinetic equation for the radical-trapping reaction is,

\[
ds[r]/dt = -k_T [r] [T]
\]

However, if \(T\) is used in a large excess then \([T]\) does not vary significantly during the course of reaction (i.e. \([T]_f = [T]_i\)), and the equation can be simplified to,

\[-d[r]/dt = -k_\psi [r]\]

That is, the reaction appears to be first-order in \([r]\). \(k_\psi (= k_T [T]_i)\) is called the pseudo-first-order rate constant for the trapping reaction.

The approximation can be greatly improved by using the mean rather than initial trap concentration when differential expressions obtained by kinetic analysis are integrated over the course of the reaction (\textit{vide infra}). The improvement in the approximation is equivalent to inclusion of the second term in a series expansion of the integrals in terms of \([T]_i\) and powers of \(\Delta[T] = ([T]_i - [T]_f)\).
Experimentally the mean trap concentration is found from the percentage of HPLC area assigned to \( T (= \%T) \) in the product mixture, i.e.

\[
[T] = [T]_i \frac{(100 + \%T)}{200}.
\]  

(A2)

Combination of eq A1 with eq A2 gives,

\[
[T]_{x=0 \text{C}, \%T} = [T]_{22 \text{C}} \left[ 1 + \alpha(x - 22) \right]^{-1} \frac{(100 + \%T)}{200}
\]  

(A3)

Equation (A3) has been used to calculate the effective trap concentration for all kinetic data in the present work. The final trap concentration did not need to be known with great precision because throughout the present work the nitroxide was used in greater than fivefold excess, i.e. in all cases corrections of less than 10% were applied to \([T]\). Thus even large relative errors in the estimates of \( \%T \) would not seriously affect the kinetic data.

A1.3 The Steady-State Approximation. Radical concentrations are assumed not to change significantly during the life-times of participating species. This is patently true for radical-trapping since the time scale of the radical reactions is \(10^{-9} - 10^{-6}\) s whereas that of the initiating reaction (e.g. thermal peroxide decay) is \(10^2 - 10^5\) s.

A1.4 Side Reactions. The radical-trapping reaction is assumed to be 100% efficient. This implies that:

(a) carbon-centred radicals react with \( T \) exclusively by coupling – evidence for this has been presented in Chapters One and Two,

(b) other radical quenching reactions do not compete with trapping – the trapping rate constant \( k_T \approx 10^9 \text{ M}^{-1}\text{s}^{-1} \) whereas rate constants for quenching of alkyl radicals by 'normal hydrogen donor' solvents are \( ca\ 10^3 - 10^4 \text{ M}^{-1}\text{s}^{-1} \) in the experimental temperature range. Thus solvent reactions will not compete with trapping unless the solution of \( T \) is extremely dilute i.e.\([T]\ < 10^{-4} \text{ M} \). In contrast, aryl and cyclopropyl radicals undergo quite rapid metathesis and double-bond addition reactions with common solvents – the kinetics of these reactions are explored in Chapters Eight.

It is also a simple matter to compute that the radical-radical termination rate \( (2k_T[r^*]^2) \) must be at least two orders of magnitude lower than the radical-trapping rate under normal conditions.

One bimolecular reaction that can effectively compete with trapping in dilute solutions
of T is radical quenching by molecular oxygen; the ramifications of this are examined in A3.3.

A2 Derivation of the Kinetic Equations

A2.1 Notation. For convenience, the following conventions will be adopted in the derivations of kinetic equations: **bold type** = species, **plain type** = molar concentrations of [species], **lower case** = radicals, **UPPER CASE** = corresponding hydroxylamine products (e.g. r-T = R,  [R] = R, etc.).

A2.2 Radical-trapping in Competition with an Irreversible Radical Rearrangement (or Fragmentation).

\[
\begin{array}{c|c|c}
\text{r} & \text{u} & \text{r} \\
\hline
\text{T} & \text{u}_r & \text{T} \\
\text{u} & \text{R} & \text{R} \\
\end{array}
\]

The steady-state radical concentration approximation applied to r· gives,

\[
dr/dt = 0 \Rightarrow k_r u = \tau_kT \cdot T
\]

or,

\[
u / r = \tau_kT / k_r
\]

By definition, \(dU/dt = u_kT u\) and \(dR/dt = \tau_kT r\), therefore,

\[
dU / dR = (u_kT / \tau_kT)(u / r) = u_kT / k_r
\]

Pseudo-first-order conditions imply \(dU/dR = U/R\) and that T is a constant (= T_{initial}) so that integration over the course of the reaction yields,

\[
U / R = (u_kT / k_r) T \quad (A4)
\]
Appendix: Kinetic Equations, & etc.

A2.3 Radical-trapping in Competition with a Reversible Radical Rearrangement.

\[
\frac{dr}{dt} = 0 \Rightarrow \quad k_r u = (r k_T T + k_r) r
\]

i.e.

\[
u / r = r k_T T / k_r + k_r / k_r.
\]

If we proceed as above (A2.2), the bimolecular rate constant definitions then give,

\[
U / R = (u k_T / k_r) [ (k_r / r k_T) + T ] \quad (A5)
\]

Linear regression analysis of U/R versus T affords the form U/R = a + bT; comparison with eq A5 gives, \( b = u k_T / k_r \) and \( b / a = r k_T / k_r \) (in graphical terms a is the abcissa and b is the slope of a plot of U/R versus T ). In this way the response of the hydroxylamine product ratio U/R to changes in T can be used to evaluate forward and reverse reaction rate constants and the equilibrium constant \( (K_r = k_r / k_r) \) if the trapping rate constants are known (see e.g. Ch.4).

A2.4 Radical-trapping in Competition with a Bifurcated Reversible Rearrangement.

Reversible reactions on either side of the initially formed species can be treated as above, i.e.,

\[
\frac{dr_1}{dt} = 0 \Rightarrow \quad k_{i1} u = (i k_T T + k_{i1}) r
\]

\[
\Rightarrow \quad U / R_1 = (u k_T / k_{i1}) [ (k_{i1} / i k_T) + T ] \quad (A6)
\]

\[
\frac{dr_2}{dt} = 0 \Rightarrow \quad k_{2} u = (2 k_T T + k_{2}) r
\]

\[
\Rightarrow \quad U / R_2 = (u k_T / k_{2}) [ (k_{2} / 2 k_T) + T ] \quad (A7)
\]
Appendix: Kinetic Equations, & etc.

If the right hand branch of this scheme is an irreversible reaction then eq A7 simplifies to

\[ \frac{U}{R_2} = \left( \frac{u T}{k_2} \right) T \]  

(A8)

and dividing eq A6 by eq A8 we get,

\[ \frac{R_2}{R_1} = \left( \frac{k_2}{k_I} \right) \left[ 1 + \left( \frac{k_I}{k_I} \right) T^{-1} \right] \]  

(A9)

Therefore, as is intuitively obvious: as \( T \to \infty \) then \( \frac{R_2}{R_1} \to k_2/k_I \) (= the partitioning or 'kinetic' ratio from \( u \cdot \)), and as \( T \to 0 \) then \( \frac{R_2}{R_1} \to \infty \) (= the thermodynamic product ratio).

Moreover, linear regression analysis of \( \frac{R_2}{R_1} \) versus \( T^{-1} \), i.e. \( \frac{R_2}{R_1} = a + b \cdot T^{-1} \), affords rate constants \( k_I \) and \( k_{-I} \) since \( a = \frac{k_2}{k_I} \) and \( b = \frac{k_{-1}}{k_I} \) (eq A8 gives \( \frac{u T}{k_2} \)).

A2.5 Radical-trapping in Competition with Consecutive Reversible Rearrangements.

![Diagram of reaction scheme](image)

\[ \frac{du}{dt} = 0 \implies (k_I + k_2 + u T) u = k_2 r_2 + k_{-I} r_1 \]  

(A10)

\[ \frac{dr_2}{dt} = 0 \implies k_2 u = (u T + k_2) r_2 \]  

(A11)

\[ \frac{U}{R_2} = \left( \frac{u T}{k_2} \right) \left( \frac{k_2}{k_I} \right) \left( k_2 + \frac{u T}{k_2} \right) + T \]  

(A12)

Substituting eq A11 into eq A10, using the rate constant definitions, and collecting terms we get,

\[ \frac{R_1}{R_2} = \left( \frac{u T}{k_2} \right) \left( \frac{k_I + k_2 + u T}{k_I + k_2} \right) \left( \frac{k_2}{k_I} \right) = k_2/k_{-I} \]  

(A13)

When the second rearrangement is irreversible, eq A12 and eq A13 simplify to

\[ \frac{U}{R_2} = \left( \frac{u T}{k_2} \right) T \]  

(A12')

and

\[ \frac{R_1}{(R_2 T)} = \left( \frac{k_I + k_2 + u T}{k_I k_2} \right) \]  

(A13')

It can be seen that numerical analysis of kinetic data with eq A12' and eq A13' can give rate constants for the rearrangements in the reaction scheme above relative to the trapping rate constant of the respective initial species.

A special case of this general kinetic scheme is where rearrangements leading from \( u \cdot \) are much faster than those leading towards \( u \cdot \), i.e. \( k_I ,k_2 >> k_{-I} k_2 \), in other words when \( u \cdot \) is a
high energy species, e.g. a cyclopropylcarbinyl radical - Ch.3 and 4. Here the intermediate radical is not trapped in significant quantities under conditions which allow the initial rearrangement to take place, i.e. 'low' [T]. This permits the rearrangement to be treated as a one step process (e.g. Ch.3 Scheme II) with an effective rate constant $k_r$ defined by

$$R_2 / R_1 = (k_r / k_T) T^{-1}$$

(A14)

Substitution of eq A14 into eq A13' shows that $k_r$ and $k_1$ are related by the partitioning of $u$, viz.

$$k_r = k_1 (1 + k_f / k_2)^{-1}$$

(A15)

A3 Radical-Trapping in Reactive Media.

A3.1 Radical-trapping in Competition with an Atom Transfer Reaction (Metathesis).

The steady-state approximation applied to the substrate derived radical $s\cdot$ gives,

$$\frac{ds}{dt} = 0 \Rightarrow \frac{rks}{s/r} = \frac{s}{s/r} = \frac{rks}{s/k_T} T$$

If the reaction is pseudo-first-order, i.e. with a large excess of $T$ and $S-X$, then

$$S/R = \frac{rks}{s/k_T} T$$

(A16)

Where $rks$ and $sks$ are the rate constants with which radicals $r\cdot$ and $s\cdot$ respectively are quenched by the substrate $S-X$. 
A3.2 Radical-trapping of Clock Radicals in Competition with Reactive Substrates.

\[
dr/dt = 0 \Rightarrow \quad k_C u = (r_{k_S} S + r_{k_T} T) r \\
u/r = r_{k_S} S-X/k_C + r_{k_T} T/k_C
\]

Definitions of \( u_{k_T} \) and \( r_{k_T} \)

\[
dU/dR = (u_{k_T} / r_{k_T}) r_{k_S} S-X/k_C + u_{k_T} T/k_C
\]

With a large excess of T and S-X this integrates to give

\[
U/R = (u_{k_T} / r_{k_T}) r_{k_S} S-X/k_C + u_{k_T} T/k_C \quad (A17)
\]

or iff \( u_{k_T} = r_{k_T} \),

\[
U/R = (r_{k_S} S-X/k_C + u_{k_T} / k_C) T \quad (A17')
\]

Thus a plot of U/R versus T (with S-X kept constant) has slope \( u_{k_T} / k_C \) and T = 0 intercept \( (u_{k_T} / r_{k_T})(r_{k_S} / k_C) S-X \) or if T is kept constant and S-X is varied the slope is \( (u_{k_T} / r_{k_T}) r_{k_S} / k_C \) and the (S-X = 0) intercept is \( (u_{k_T} / k_C) T \). In either case: (a) the trapping rate constant in the reactive medium, and (b) the rate constant for the radical/substrate or quenching reaction can be found relative to the known rate constant \( k_C \).

Note that the quenching rate constant found by this method is that of rearranged radical. Usually one can assume that \( u_{k_T} = r_{k_T} \) and use eq A17' or one can make a reasonable estimate for the ratio \( u_{k_T} / r_{k_T} \) based on clock or direct calibration data.
A3.3 The Effect of Oxygen on the Radical-Trapping. Oxygen, which quenches radicals with higher rate constants than \( T \), is proposed to participate in the radical-trapping reaction according to the following scheme:

**Kinetic Scheme for Radical Trapping in the Presence of Oxygen.**

Various oxygen derived products \( (\Sigma O_i) \) may arise from processes such as those suggested below:

\[
R\cdot + O_2 \xrightarrow{k_O} R-OO\cdot \\
2R-OO\cdot \xrightarrow{2k_t} R-OO-R + O_2 \\
R-OO\cdot + S-H \xrightarrow{k_H} R-OOH + S\cdot
\]

The new kinetic equation, a simplified form of eq A17, is:

\[
dU/dR = (k_O/k_r)O_2 + (k_T/k_r)T \quad (A16)
\]

which can be integrated if the total amount of oxygen derived product \( (\Sigma O_i) \) is known i.e.

\[
U/R = (1 + \alpha)(k_T/k_r)T, \quad \text{where } \alpha = \Sigma O_i/(U + R) \quad (A16')
\]

The effect (i.e. the overestimation of \( k_T/k_r \)) is of course largest for the slowest clock reactions since here the ratio \( O_2/T \) is highest. With hex-5-enyl, for instance, the initial precursor
concentration may be as low as 10^{-5} \text{ M} which means that even a small residual amount of O_2 can affect the kinetic data; moreover the effect tends to be larger at lower temperatures because here the clock's rate constant is smaller - see eq A16.

The early radical-trapping data suffered good deal of random scatter (typically 10-15\% between ampoules) which was confused with low precision (ca 10\%)* in the HPLC analysis but which was later thought to have arisen, in part, from residual oxygen in the reaction mixtures. For these reasons many of the early kinetic calibrations were repeated with scrupulous degassing of reaction mixtures and with an improved analysis procedure.* However, although Arrhenius coefficients for some reactions were appreciably revised, the median temperature (80°C) rate ratios all were found to be within ±20\% of the original data.

* [Subsequently this was improved (to ca 5\%) by use of an high efficiency analytical column without gradient elution]

**A5.1 The Hildebrand Model Applied to $k_T/k_C$**

From transition state theory it may be shown that the reaction of $T$ with $u$ in solution proceeds with a rate constant of,

$$k_T = (k_T)_0 v_u/v_T/v_{uT^+}$$  \hspace{1cm} (A5.1)

where $v_i$ is the activity coefficient of species $i$ (e.g. $v_{uT^+}$ is the activity coefficient of coupling reaction's transition state) and $(k_T)_0$ is the rate constant under standard conditions (i.e. $v_u = v_T = v_{uT^+} = 1$). Similarly, for the clock reaction ($u \rightarrow r$) the rate constant can be expressed as

$$k_C = (k_C)_0 v_u/v_u^+$$  \hspace{1cm} (A5.2)

where $v_{u^+}$ is the activity coefficient of the clock's transition state. Thus the rate ratio is,

$$k_T/k_C = (k_T/k_C)_0 v_T/v_{u^+}/v_{uT^+}$$  \hspace{1cm} (A5.3)

Hildebrand has shown that for nonelectrolytic conditions, the primary activity coefficient is given by,

$$RT \ln v_i = v_i(\delta_i - \bar{\delta})^2$$  \hspace{1cm} (A5.4)

where $\delta_i$ and $\bar{\delta}$, the solubility parameters of the solute and solvent respectively, are defined in terms of the heats of vaporization ($\Delta H_v$ kcal/mol) and molar volumes (V ml) of the species by,

$$\delta^2 = (\Delta H_{vap} - RT)/V$$  \hspace{1cm} (A5.5)
δ² has units of force/area and is often called the "internal pressure" of the solvent or solute; it is a measure of the cohesive energy density of the solvent or solute.

Thus substituting (5.4) into (5.3) and collecting the non solvent dependent residual into a constant term (C) we find that,

$$RT \ln \left(\frac{k_T}{k_C}\right) = \delta^2 (V_{uT} + V_{uT} - V_{uT} + V_{uT}) + 2\delta (V_{uT}^\dagger \delta_{uT}^\dagger - V_{uT} \delta_{uT} - V_{uT} \delta_{uT}) + C$$

It can be argued that to a good approximation $V_{uT}^\dagger = V_{uT} + V_T$ and thus,

$$RT \ln \left(\frac{k_T}{k_C}\right) = 2\delta [V_T(\delta_{uT}^\dagger - \delta_{uT}) - V_{uT} (\delta_{uT}^\dagger - \delta_{uT})] + C$$

$T$ is the most polar species involved in the calibration reactions and, consequently, has the highest solubility parameter and thus the bracketed term is predicted to be negative; this is confirmed by the experimental trend (Fig. 6.3) to lower rates in better solvents (higher δ).

One observation that may perhaps be rationalized in this model is the that clocks with polar transition states ($u^\dagger$) display more pronounced solvent effects than non-polar clocks. Thus $2 \rightarrow 2'$ which moves through a polar THF-like transition state shows a significantly stronger solvent effect than $1 \rightarrow 1'$.
SUPPLEMENTARY MATERIAL

Kinetic Data

In the tables that follow the mean trap concentration \([T]\) was calculated from the % of HPLC integrated area assigned to \(T \cdot (= \%T)\) in the product mixture i.e.

\[
[T] = \frac{\left[\frac{100 + \%T}{200}\right]}{[T]_i}
\]

where \([T]_i\) was corrected for thermal expansion of the solvent. Initial peroxide concentrations \([\text{DAP}]_i = 0.075[T]_i\) so that the trap consumption during the kinetic reactions was less than 15% and thus \([T] \geq 0.93[T]_i\). Generally \(T \cdot\) itself was used as the internal standard and the trap decrement and yields were calculated from the HPLC integration; use of an internal standard (biphenyl) resulted in amendments to \([T]\) which were less than the analytical precision obtained for the product ratios.

Where more than one analysis was performed on an ampoule the standard deviation is given after the mean value in units of the last significant figure. Data from thermal stability tests made above 120\(^\circ\)C are included in the tables; these and other data not used in calculating Arrhenius parameters are marked with an asterisk (*).

Reaction/Analysis Conditions. Unless otherwise noted: reaction solvent = cyclohexane; molarity ratio, nitroxide/precursor = 13.3 (.: optimum product area = 15% of total HPLC area); HPLC mobile phase = isocratic MeOH/H\(_2\)O. 1.3 ml/min (compositions given); detection = UV absorption at 270 nm (analytical UV cell).
Supp. Table 2.1. Hex-5-enyl (1)

HPLC mobile phase: 92% MeOH. Average retention times: T·, 156; IT, 706; 1'T, 803 (secs).

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10³ M⁻¹)</th>
<th>IT/1'T</th>
<th>kₚ/kₑ</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.4</td>
<td>44</td>
<td>0.91</td>
<td>1.52(4)</td>
<td>1670</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>1.83</td>
<td>2.97</td>
<td>1620</td>
<td>38</td>
</tr>
<tr>
<td>80.8</td>
<td>18</td>
<td>0.87</td>
<td>0.875(39)</td>
<td>1010</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>1.75</td>
<td>1.84 (8)</td>
<td>1050</td>
<td>76</td>
</tr>
<tr>
<td>*</td>
<td>18</td>
<td>0.437</td>
<td>0.451(22)</td>
<td>1030</td>
<td>61</td>
</tr>
<tr>
<td>*</td>
<td>18</td>
<td>3.94</td>
<td>4.09 (12)</td>
<td>1040</td>
<td>67</td>
</tr>
<tr>
<td>100.0</td>
<td>4</td>
<td>0.84</td>
<td>1.85</td>
<td>645</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.69</td>
<td>1.08(2)</td>
<td>640</td>
<td>81</td>
</tr>
<tr>
<td>123.5</td>
<td>0.5</td>
<td>0.83</td>
<td>0.319</td>
<td>385</td>
<td>82</td>
</tr>
<tr>
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<td>0.5</td>
<td>1.53</td>
<td>0.569(15)</td>
<td>372</td>
<td>83</td>
</tr>
<tr>
<td>*</td>
<td>4</td>
<td>1.53</td>
<td>0.558</td>
<td>365</td>
<td>79</td>
</tr>
<tr>
<td>*</td>
<td>24</td>
<td>1.53</td>
<td>0.579</td>
<td>378</td>
<td>84</td>
</tr>
</tbody>
</table>

Stock solutions were 2.00, 2.00, 0.50, and 4.50 mM in T·. 

Stock solutions were 5.0, 3.0, 1.0, and 0.1 mM in T·.
Supp. Table 2.2 2-Allyloxyethyl (2)

HPLC mobile phase: 85% MeOH. Average retention times: T·, 166; A, 301; 2T, 398; 2'T, 350 (sec). A = T-CH₂CH₂OCH₃ was a minor product (2.5% of 2T + 2'T) derived from peroxide impurity.

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10³ M⁻¹)</th>
<th>2T/2'T</th>
<th>kₜ/kₑ (M⁻¹)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.0</td>
<td>63</td>
<td>21.9</td>
<td>2.57(11)</td>
<td>107</td>
<td>34</td>
</tr>
<tr>
<td>80.2</td>
<td>12</td>
<td>11.9</td>
<td>1.31</td>
<td>101</td>
<td>35</td>
</tr>
<tr>
<td>80.4</td>
<td>*</td>
<td>4.3</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>101.2</td>
<td>3</td>
<td>21.2</td>
<td>1.27</td>
<td>59.7</td>
<td>64</td>
</tr>
<tr>
<td>123.1</td>
<td>0.4</td>
<td>19.8</td>
<td>0.914</td>
<td>46.2</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>19.7</td>
<td>0.937</td>
<td>47.6</td>
<td>79</td>
</tr>
</tbody>
</table>

Stock solutions were 50.2, 24.0, 13.0, and 5.02 mM in T·.
**Supp. Table 2.3 3.3-Dimethyl-5-hexenyl (3)**

Initial [3P]:[T] = 0.10. HPLC column #2; mobile phase, 95% MeOH, 4.0 ml/min.

Average retention times: T·, 171; 3T, 562; 3'T, 621 (sec).

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10⁻³ M⁻¹)</th>
<th>3T/3’T</th>
<th>kₜ/kₑ(M⁻¹)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.1</td>
<td>72</td>
<td>9.5</td>
<td>1.76(18)</td>
<td>182</td>
<td>16</td>
</tr>
<tr>
<td>80.2</td>
<td>17</td>
<td>9.2</td>
<td>1.19(9)</td>
<td>129</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5</td>
<td>0.53</td>
<td>117</td>
<td>78</td>
</tr>
<tr>
<td>110.0</td>
<td>4</td>
<td>8.8</td>
<td>0.67</td>
<td>77.8</td>
<td>70</td>
</tr>
</tbody>
</table>

Stock solutions were 10.2 and 5.1 mM in T·.
Supp. Table 2.4  Cyclopropylmethyl (4)

HPLC mobile phase: 85% MeOH. Average retention times: A, 130; T·, 158; B, 286; C, 343; 4T, 551; 4'T, 591; H, 1233 (sec). Resolution: R(4T, 4'T) = 2.0.

A and B, were products from induced decomposition\textsuperscript{20} prevalent below 80° C but only minor above; C = T-c-C\textsubscript{3}H\textsubscript{5} (from peroxide impurity); H = T-c-C\textsubscript{6}H\textsubscript{11}.

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] \textsuperscript{-} (x10\textsuperscript{3} M\textsuperscript{-1})</th>
<th>4T/4'T</th>
<th>k\textsubscript{r}/k\textsubscript{c} (M\textsuperscript{-1})</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.2</td>
<td>172\textsuperscript{a}</td>
<td>94.9</td>
<td>0.855</td>
<td>9.01</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>172</td>
<td>191</td>
<td>1.66</td>
<td>8.67</td>
<td>19</td>
</tr>
<tr>
<td>59.4</td>
<td>102</td>
<td>46.5</td>
<td>0.243(3)</td>
<td>5.22</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93.1</td>
<td>0.462</td>
<td>4.96</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>181</td>
<td>0.858</td>
<td>4.76</td>
<td>19</td>
</tr>
<tr>
<td>80.0</td>
<td>19</td>
<td>22.1</td>
<td>0.057</td>
<td>2.53(15)</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.6</td>
<td>0.111</td>
<td>2.49</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>89.8</td>
<td>0.218</td>
<td>2.43</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>178</td>
<td>0.458</td>
<td>2.38</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>260</td>
<td>0.632</td>
<td>2.43</td>
<td>38</td>
</tr>
<tr>
<td>100.0</td>
<td>5</td>
<td>82.9</td>
<td>0.132</td>
<td>1.59</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>168</td>
<td>0.257</td>
<td>1.57</td>
<td>64</td>
</tr>
<tr>
<td>122.0</td>
<td>0.6</td>
<td>83.0</td>
<td>0.073</td>
<td>0.876</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>160</td>
<td>0.141</td>
<td>0.881</td>
<td>76</td>
</tr>
</tbody>
</table>

Stock solutions were 25.0, 50.1, 100, 200 and 300 mM in T· at 22°C.
Supp. Table 2.5 (2,2-Dimethylcyclobutyl)methyl (5)

As noted in the experimental section 5T and 5'T had identical retention on RP-HPLC. $^1$H NMR integration of product envelopes (at 400-450 sec. on column #3, 90% MeOH, 4.5 ml/min) gave the following data with c. 5 mg material from each RM (Jeol FX-200, 100 scans with 8 sec pulse delay, 5 sec acquisition time).

<table>
<thead>
<tr>
<th>Temperature (*°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10$^3$ M$^{-1}$)</th>
<th>4T/4'T</th>
<th>k$_T$/k$_c$ (M$^{-1}$)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.1</td>
<td>6.8</td>
<td>3.0</td>
<td>0.73(11)</td>
<td>243</td>
<td>62</td>
</tr>
<tr>
<td>(Cyclohexane Reflux)</td>
<td>7.2</td>
<td>1.75(25)</td>
<td>235</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>80.2</td>
<td>6.8</td>
<td>0.2</td>
<td>1.9</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Stock solutions were 4.5 and 9.6 mM in T· and 1.8 and 3.0 mM in 5P respectively.
Supp. Table 2.6 2,2-Dimethyl-5-hexenyl (6)

Initial [6P]:[T] = 0.10. HPLC column #2; mobile phase, 95% MeOH, 4.0 ml/min. Average retention times: T, 171; 6T, 578; 6′T, 624 (sec). 6′T = 3′T by HPLC coinjection.

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10³ M⁻¹)</th>
<th>6T/6′T</th>
<th>kₜ/kₖ</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.1</td>
<td>72</td>
<td>9.5</td>
<td>1.52(11)</td>
<td>160</td>
<td>21</td>
</tr>
<tr>
<td>80.2</td>
<td>17</td>
<td>9.2</td>
<td>1.09</td>
<td>118</td>
<td>69</td>
</tr>
<tr>
<td>110.0</td>
<td>4</td>
<td>8.8</td>
<td>0.56</td>
<td>64</td>
<td>85</td>
</tr>
</tbody>
</table>

Stock solutions were 10.2 and 5.1 mM in T·.
**Supp. Table 2.7  2.2-Dimethyl-3-butenyl (7)**

HPLC mobile phase: 90% MeOH. Average retention times: T, 156; 7T, 708; 7'T, 789 (sec).

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10³ M⁻¹)</th>
<th>7T/7'T</th>
<th>kₜ/kᶜ (M⁻¹)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.9</td>
<td>48</td>
<td>11.9</td>
<td>0.519(13)</td>
<td>43.6(2)</td>
<td>25</td>
</tr>
<tr>
<td>80.6</td>
<td>15</td>
<td>18.2</td>
<td>0.504</td>
<td>26.2</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.6</td>
<td>0.309</td>
<td>26.6</td>
<td>65</td>
</tr>
<tr>
<td>*</td>
<td>8.9</td>
<td>4.46</td>
<td>0.115</td>
<td>25.8</td>
<td>68</td>
</tr>
<tr>
<td>*</td>
<td>128</td>
<td>18.2</td>
<td>0.567</td>
<td>-</td>
<td>58</td>
</tr>
<tr>
<td>*</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99.5</td>
<td>3</td>
<td>10.8</td>
<td>0.174</td>
<td>16.1</td>
<td>72</td>
</tr>
<tr>
<td>120.2</td>
<td>0.6</td>
<td>10.3</td>
<td>0.123</td>
<td>11.9</td>
<td>76</td>
</tr>
<tr>
<td>124.5</td>
<td>0.5</td>
<td>16.8</td>
<td>0.189</td>
<td>11.25(8)</td>
<td>81</td>
</tr>
<tr>
<td>*</td>
<td>122.0</td>
<td>0.8</td>
<td>16.3</td>
<td>0.189</td>
<td>11.6</td>
</tr>
<tr>
<td>*</td>
<td>11.5</td>
<td></td>
<td></td>
<td>0.453</td>
<td>-</td>
</tr>
<tr>
<td>*</td>
<td>25</td>
<td></td>
<td></td>
<td>1.498</td>
<td>-</td>
</tr>
</tbody>
</table>

Stock solutions were 10.0 and 20.0 mM of TiCl₄. Stock solutions were 5.00, 13.0, and 20.0 mM.
Supp. Table 2.8 2-Allyloxy-1-methylethyl (8)

HPLC mobile phase: 80% MeOH. Average retention times: T, 178; T-Me, 352;
8'T(cis), 461; 8'T(trans), 482; 8T, 620; H, 1920 (sec).

8'T(cis) and 8'T(trans) had a separation factor of about 1.2 which gave a ratio precision of c. 10% with the optimum integration method.

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10^3 M⁻¹)</th>
<th>8'T(cis)</th>
<th>8'T(trans)</th>
<th>8T</th>
<th>k_T/k_c</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.9</td>
<td>44</td>
<td>18.3</td>
<td>2.8</td>
<td>2.03</td>
<td>111</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>80.5</td>
<td>18</td>
<td>17.8</td>
<td>2.8</td>
<td>1.33</td>
<td>74.7</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>100.0</td>
<td>7</td>
<td>17.1</td>
<td>2.35</td>
<td>1.11</td>
<td>64.9</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>120.1</td>
<td>0.3</td>
<td>16.6</td>
<td>1.8</td>
<td>0.662</td>
<td>40.5</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>* 126.1</td>
<td>0.6</td>
<td>16.3</td>
<td>1.8</td>
<td>0.651</td>
<td>-</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Stock solutions were 10.0 and 20.0 mM in T·.
Supp. Table 2.9 2-Allyloxy-1,1-dimethylethyl (9)

HPLC mobile phase: 91% MeOH. Average retention times: T·, 144; 9'T, 311; 9T, 456; H, 630 (sec).

Stock solutions were 5, and 20 mM in T·.

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10^3 M^-1)</th>
<th>9T/9'T</th>
<th>k_T/k_c (M^-1)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.8</td>
<td>18</td>
<td>18.6</td>
<td>1.28</td>
<td>69.1</td>
<td>41</td>
</tr>
<tr>
<td>79.5</td>
<td>4</td>
<td>17.4</td>
<td>1.08</td>
<td>62.1</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.42</td>
<td>0.268</td>
<td>60.7</td>
<td>58</td>
</tr>
<tr>
<td>80.0</td>
<td>4</td>
<td>17.8</td>
<td>0.976</td>
<td>56.0</td>
<td>56</td>
</tr>
<tr>
<td>101.0</td>
<td>1.2</td>
<td>17.1</td>
<td>0.742</td>
<td>43.5</td>
<td>60</td>
</tr>
<tr>
<td>120.1</td>
<td>0.3</td>
<td>16.6</td>
<td>0.540</td>
<td>32.5</td>
<td>65</td>
</tr>
<tr>
<td>*</td>
<td>0.4</td>
<td>16.4</td>
<td>0.533</td>
<td>32.5</td>
<td>69</td>
</tr>
<tr>
<td>*</td>
<td>7</td>
<td></td>
<td>0.428</td>
<td></td>
<td>73</td>
</tr>
</tbody>
</table>
Supp. Table 2.10 3-Butenoxymethyl (10)

HPLC column #2. 90% MeOH with 0.5% NaOAc buffer, 4 ml/min. Average retention times: T·, 177; 10'T, 280; 10T, 349; H, 860 (sec). 10'T = 2'T by HPLC coinjection. Reproducible data were obtained at 60°C and 80°C however precision was low due to difficulties in working with extremely dilute solutions of labile products (10T).

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10³ M⁻¹)</th>
<th>10T/10'T (3 runs ea)</th>
<th>k_T/k_c (M⁻¹)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>48</td>
<td>1.13</td>
<td>3.50(80)</td>
<td>3100</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>0.45</td>
<td>1.71(15)</td>
<td>3800</td>
<td>51</td>
</tr>
<tr>
<td>80</td>
<td>12</td>
<td>1.09</td>
<td>2.30(30)</td>
<td>2110</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.41</td>
<td>0.81(8)</td>
<td>1910</td>
<td>63</td>
</tr>
<tr>
<td>*</td>
<td>48</td>
<td>0.41</td>
<td>0.71(6)</td>
<td>-</td>
<td>68</td>
</tr>
</tbody>
</table>

Stock solutions were 1.25 and 0.50 mM in T·.
Supp. Table 2.11  Phenylacetyl (11)

HPLC mobile phase: 90% MeOH. Average retention times: 11P, 138; T·, 155; T-Me, 238; 11T, 253; E, 618; 11'T, 651 (sec). E = T-CH(CHO)Ph(?) was labile under HPLC conditions and hasn’t been tabulated (initially %E = %11'T by area). Clusters of minor products from t-butoxyl/benzene reactions filled the 140 to 200 sec region.

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10^3 M⁻¹)</th>
<th>%11P</th>
<th>11T/11’T⁵</th>
<th>k_T/k_c (M⁻¹)</th>
<th>Yield %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.2</td>
<td>35</td>
<td>58.3</td>
<td>10</td>
<td>3.29</td>
<td>5.64</td>
<td>73</td>
</tr>
<tr>
<td>60.3</td>
<td>1</td>
<td>56.7</td>
<td>10</td>
<td>2.44</td>
<td>4.31</td>
<td>88</td>
</tr>
<tr>
<td>80.0</td>
<td>0.3</td>
<td>151</td>
<td>5</td>
<td>4.01</td>
<td>26.6</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92</td>
<td>10</td>
<td>2.81</td>
<td>30.5</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>10</td>
<td>1.38</td>
<td>25.1</td>
<td>81</td>
</tr>
<tr>
<td>*</td>
<td>5</td>
<td>55</td>
<td>10</td>
<td>1.41</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Stock solutions were 65, 105, and 180 mM in T.

a  UV: A_{270}(11T) = A_{270}(11’T) (±5%) = 1.070 so ratios weren’t corrected.

b  Yield estimated by internal standard (biphenyl) method with spectral correction.
Supp. Table 2.12 tert-Butoxycarbonyl (12)

HPLC mobile phase: 88% MeOH. Average retention times: T, 160; 12T, 250; 12′T, 680; H, 944 (sec).

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10^3 M⁻¹)</th>
<th>12T/12′T</th>
<th>k_T/k_c (M⁻¹)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.0</td>
<td>20</td>
<td>1.85</td>
<td>6.44(5)</td>
<td>3480</td>
<td>78</td>
</tr>
<tr>
<td>*</td>
<td>4.56</td>
<td>16.9</td>
<td>3800</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>59.0</td>
<td>3</td>
<td>1.74</td>
<td>2.99</td>
<td>1710</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>3.48</td>
<td>5.76</td>
<td>1660</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>81.0</td>
<td>0.3</td>
<td>1.67</td>
<td>0.922(12)</td>
<td>552</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>3.41</td>
<td>1.96</td>
<td>576</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Stock solutions were 2.00 and 5.00 mM in T·.
Supp. Table 2.13 2-Cyclobutyl-2-propoxycarbonyl (13)

Initial [13P]:[T] = 0.04. HPLC mobile phase: 91% MeOH. Average retention times: T, 147; 13T, 287; H, 614; 13'T, 875 (sec).

<table>
<thead>
<tr>
<th>Temperature (°C ± 0.3°C)</th>
<th>Reaction Time, hr</th>
<th>[T] (x10^3 M⁻¹)</th>
<th>13T/13'T</th>
<th>k_T/k_c (M⁻¹)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>22(±1)</td>
<td>180</td>
<td>1.27</td>
<td>2.90(8)</td>
<td>2280</td>
<td>49</td>
</tr>
<tr>
<td>48.3</td>
<td>6</td>
<td>4.82</td>
<td>2.92</td>
<td>597</td>
<td>55</td>
</tr>
<tr>
<td>60.0</td>
<td>2</td>
<td>9.96</td>
<td>3.46</td>
<td>347</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.98</td>
<td>1.83</td>
<td>368</td>
<td>65</td>
</tr>
<tr>
<td>78.0</td>
<td>0.5</td>
<td>9.47</td>
<td>1.58</td>
<td>167</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.72</td>
<td>0.779</td>
<td>165</td>
<td>69</td>
</tr>
<tr>
<td>*</td>
<td>5</td>
<td>4.72</td>
<td>0.701</td>
<td>-</td>
<td>71</td>
</tr>
</tbody>
</table>

Stock solutions were 10.5, 5.10 and 1.30 mM in T⁻. From 14 (see results section). A mixture of T⁻ (10.0 mM), di-tert-butyl peroxyoxalate (1.0 mM), and 14 (15% v/v) in spectral grade benzene (handled at 5-10°C) was degassed and heated in the usual way. For 80.0°C the product ratio 13T/13'T = 1.28 (±0.07) (2 ampoules, 2 analyses each) in a mean yield of 71%. This gave k_T/k_c = 149 M⁻¹. It was noted that 13T and 12T slowly decompose in aqueous methanol but the estimated decay rate (t½ = 2 hrs) was too low to affect the kinetic data (contact time, 0.07 hrs).
Supplementary Table 6.1 HPLC analytical conditions and retention times for each clock reaction were as listed in the Supplementary Tables for Chapter Two.

Rate ratios $k_T/k_C$, M$^{-1}$ for Radical Clocks in Various Solvents$^a$.

<table>
<thead>
<tr>
<th>Clock temp, °C</th>
<th>Solvent #1</th>
<th>#2</th>
<th>#4</th>
<th>#5</th>
<th>#5a</th>
<th>#9</th>
<th>#23</th>
</tr>
</thead>
<tbody>
<tr>
<td>1→ 1'</td>
<td>60</td>
<td>2130</td>
<td>1910</td>
<td>1650</td>
<td>1240</td>
<td>–</td>
<td>530</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>1170</td>
<td>1250</td>
<td>1030</td>
<td>710</td>
<td>770</td>
<td>346</td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>530</td>
<td>460</td>
<td>365</td>
<td>278</td>
<td>270</td>
<td>123</td>
</tr>
<tr>
<td>7→ 7'</td>
<td>59</td>
<td>–</td>
<td>48</td>
<td>42</td>
<td>24.6</td>
<td>8.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>36</td>
<td>32</td>
<td>26.2</td>
<td>14.6</td>
<td>14.2</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>–</td>
<td>12.2</td>
<td>9.8</td>
<td>6.8</td>
<td>6.6</td>
<td>2.91</td>
</tr>
<tr>
<td>9→ 9'</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>81</td>
<td>–</td>
<td>–</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>–</td>
<td>60</td>
<td>55</td>
<td>–</td>
<td>–</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>–</td>
<td>–</td>
<td>43.5</td>
<td>–</td>
<td>–</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>–</td>
<td>31.9</td>
<td>43.5</td>
<td>–</td>
<td>–</td>
<td>10.7</td>
</tr>
</tbody>
</table>

$^a k_T/k_C$ values were calculated from averaging data obtained with [T] = 4.0 and 2.0 for 1→1' and 100 and 50 mM for 7→7' and 9→9'. $^b k_T/k_C = [T]^{-1} [U]/[R]$ where U = 1 or 7 or 9, R = 1' or 7' or 9', respectively; [T] corrected for the solvent's thermal expansion and for consumption of T.
Kinetic Data for Product Decomposition. For 9T biphenyl was incorporated as the internal standard (IS): relative response factor = 13 at 270 nm, HPLC retention = 340" under analysis conditions (Sup. Tables 2.7 and 2.9)

Sup. Table 6.2  Solvent and Temperature Dependence of the Decay of 7'T/7T

<table>
<thead>
<tr>
<th>temp (°C)</th>
<th>time (hr)</th>
<th>solvent</th>
<th>[T] (mM)</th>
<th>7'T/7T&lt;sup&gt;a&lt;/sup&gt;</th>
<th>k&lt;sub&gt;p&lt;/sub&gt;(10&lt;sup&gt;-7&lt;/sup&gt; s&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>&lt;r&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>*</td>
<td>90</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>38</td>
<td>1.23±0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>24</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>37</td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>120</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>37</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>404</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>37</td>
<td>0.67±0.03</td>
<td>4.1</td>
<td>0.997</td>
</tr>
<tr>
<td>*</td>
<td>126</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>35</td>
<td>2.7±0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>4</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>35</td>
<td>2.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>11</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>34</td>
<td>1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>24</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>33</td>
<td>0.70±0.05</td>
<td>157</td>
<td>0.991</td>
</tr>
<tr>
<td>*</td>
<td>146</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>32</td>
<td>1.75±0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>1.2</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>32</td>
<td>1.07</td>
<td></td>
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<tr>
<td>146</td>
<td>4.2</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>30</td>
<td>0.18±0.01</td>
<td>1530</td>
<td>0.979</td>
</tr>
<tr>
<td>126</td>
<td>0.6</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>19</td>
<td>16.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>11.6</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>18</td>
<td>4.7±0.02</td>
<td>310</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>126</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>96</td>
<td>3.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>11.6</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>93</td>
<td>0.76</td>
<td>380</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>126</td>
<td>acetone</td>
<td>102</td>
<td>2.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>5.3</td>
<td>acetone</td>
<td>102</td>
<td>0.93</td>
<td>490</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>146</td>
<td>acetone</td>
<td>95</td>
<td>1.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>2.0</td>
<td>acetone</td>
<td>102</td>
<td>0.13</td>
<td>3100</td>
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<tr>
<td>*</td>
<td>126</td>
<td>ethanol</td>
<td>98</td>
<td>2.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>5.3</td>
<td>ethanol</td>
<td>98</td>
<td>0.48</td>
<td>640</td>
<td></td>
</tr>
</tbody>
</table>

* HPLC area ratio  b Composition of the preformed hydroxylamine mixture. * Marks the variable


6. For a splendid defence of trivial names (e.g. "galvinoxyl") see ref. 1 in; Bartlett, P.D.; Funahashi, T. J. Am. Chem. Soc. 1962, 83, 2596-2601.


8. (a) Rozantsev, E.G.; Sholle, V.D. Russ. Chem. Rev. 1971, 40, 233-246; the same authors have reviewed nitroxide synthesis in (b) Synthesis 1971, 190-204, and reactions in (c) Synthesis 1971, 401-412.


16. There may be some relaxation of the dipole through the σ-bond.


References and Notes

26. See references cited on pp. 59 of ref. 1.
35. Experimental observation.
43. For exceptions see ref. 1 Sect. IV, E.
47. For examples see ref. 7 and refs cited therein.
References and Notes


51. For instance, 1-ethoxy-2,2,6,6-tetramethylpiperidine and 2-ethoxy-1,1,3,3-tetramethylisoindoline are stable to capillary GC analysis (ca. 160°C) whereas O'Leary and Beckwith found considerable analytical scatter with the trapped hex-5-enyl "clock" radical products using a packed column (which allows lower oven temperatures). Mathew and Warkentin successfully analyzed products from the cyclopropylmethyl isomerization with T by GC.


54. Actually it was the square-root of these wayward termination rate constants which were used to derive $k_T$ so uncertainty from this source was about a factor of ten.


57. Beckwith, A.L.J.; Bowry, V.W.; Moad, G. *J. Org. Chem.* 1988, in press. (The subject matter of this paper is substantially reproduced in Ch. 2).


64. Ingold, K.U.; private communication of unpublished data.


References and Notes

73. Where this is not true equation (1) can be replaced by a numerically integrated expression.


75. At low trap concentrations the decomposition rates of the peroxide precursors could be estimated from these or similar species available in "Organic Peroxides"; Swern, D., Ed; Wiley-Interscience: New York, 1970.

76. GC analysis was normally unsuitable because the alkoxyamine products, especially those of tertiary alkyl and stabilized radicals, were unstable at the required injector/column temperatures; see also ref. 48, 51, and 62.

77. Investigations detailed in the chapter 3 have shown that unwanted abstraction products can be reduced or eliminated in favourable cases by the addition of 1,4-cyclohexadiene. The cyclohexadienyl radical thus generated undergoes disproportionation rather than coupling with T.


84. The open-chain and cyclized trapped species had nearly identical HPLC retention.


90. Mathew and Warkentin have used the radical trapping method (with GC analysis) to calibrate this rearrangement. The rate constant is still about three times higher than that calculated in this work from 1/1° clock. However their relative rate expression log($kT/k_i$) over the range 30-90°C is not in serious conflict with that given in Table 2.4 considering that different solvents were used (hexafluorobenzene versus cyclohexane).


References and Notes


98. (a) In their estimation of kT, Griller and Roberts97 initially used the following kinetic data for the termination of tert-butyl radicals: 2kT = 5.7 x 10^10 exp(-1000/T), = 2.10^9 M^-1 s^-1 at 298 K in di-tert-butylperoxide. However, they later suggested that the rate constant should be increased five-fold.

99. Subsequent measurements have supported the higher value, e.g. 2kT = 1.2 x 10^11 exp(-1000/T) in methylpentane,100 and 2kT = 8.1 x 10^9 M^-1 s^-1 at 298 K in di-tert-butylperoxide.102


105. There are indications that adducts of T with hindered stabilized radicals are more thermostable than those with TEMPO; cf. ref. 38 and Sect. 1.9.


108. For a recent example of 4→4' as a clock reaction see Ortez de Montellano, P.R.; Stearns, R.A. *J. Amer. Chem. Soc.* 1987, 109, 3415-3420.


References and Notes

135. The estimated stabilization energy in CPM varies from 0.7136 to 2.4 kcal/mol (most recent)137 and for benzyl 10.2 kcal/mol.139
139. Previously issued as Supplementary Material to ref. 57.
140. Calculated from combined ESR/nitroxide data9 for 2a and Effio et al’s134 calibration of k_c (1b).
145. Strain energy of cyclopropane and cyclobutane are 27.6 and 26.2kcal/mol respectively by Benson’s definition.24
References and Notes


147. In previous descriptions, this mechanism would retard $k_3$ rather than enhance $k_1$ in the fission of $\text{Q}_{\text{trans}}^\text{ir}$. 


149. These are manifested in the ready reduction of cyclopropanes by one-electron reagents.150


151. Estimated from data in ref 135 ('Table 2') with the most recent $k_H$ for isopropyl.56

152. The relevant C-H bond dissociation energy can be estimated Nonhebel and Walton's empirical relationship between ESR rotational barriers ($V_0$) in $X-\text{CH}_2^\cdot$ and $\text{CH}_2-\text{H}$ bond strengths, viz. $D(X\text{CH}_2\cdot\text{H}) = 97.7 - 0.75V_0$. thus $\Delta H^\#_{\text{stab}} = 0.75V_0 = 7 \text{ kcal/mol for } X = \text{CO}_2R$.153: Nonhebel, D.C.; Walton, J.C. J. Chem. Soc. Chem. Commun. 1984, 731-732.


154. Recently radical stabilization in species $\text{ROCOCH}_2^\cdot$, $\text{ROCH}_2^\cdot$, $\text{ROCH}_2^\cdot$, & etc have been calibrated by ab initio calculation (Pasto et al) and by bond dissociation rate methods (Luedtke et al); the theoretical and experimental data confirm the estimate from ref.152: Pasto, D.J.; Krasnansky, R.; Zercher, C. J. Org. Chem. 1987, 52, 3062-3072; Luedtke, A.; Meng, K.; Timberlake, J.W. Tetrahedron Lett. 1987, 4255-4258.

155. In this picture the kinetic effect of substitution, etc. is predicted to be a small or large fraction of the thermodynamic effect according as an early or late transition state is indicated for the reaction (e.g. by a low or high $\Delta H^\#$ for the reaction, respectively) This idea forms the basis of the "reactivity selectivity principle".37


158. In a simplified form:157 $\Delta G^\# = \Delta G_{o}^\# + \Delta G^\gamma/2 + (\Delta G^\gamma)^2/16\Delta G_{o}^\#$.


161. Calculated from bond strength data.25


163. The most recent estimate for stabilization in cyclopropylmethyl (2.4 kcal/mol) is derived from ESR data.137


165. Based on the assumption that one half of the stabilization energy is expressed in the energy barrier.

Extra steric hindrance and stabilization by the cyclopropyl group might reduce $k_r$ somewhat but it is unlikely to be less than that of a, $\alpha$-dimethylbenzyl which is only 25% lower than the figure used here (i.e. $1.2 \times 10^8$ versus $1.6 \times 10^8$ M$^{-1}$s$^{-1}$ for TEMPO in isooctane).  


Criegee, R. Ber., 1944, 77B, 22-34; 722-726.


Hay, B., personal communication (results in manuscript)


References and Notes

188. For background and discussion, see ref 82.

189. Alberti, A.; Perdulli, F. Private communication


195. Ref. 120 Vol 1, pp 142.


203. Consideration of the relative 'lateness' (cf. Ch 3) of the transition-state for 1,3-cyclization suggests that this hypothesis, viz. that clock reaction 7→7' involves less solvent displacement than the 5-hexenyl cyclizations, may have been ill-founded; however, data in the Table 6.3 indicates that, if there is a significant solvent effect on 7→7', it is no larger than for the latter rearrangements.


211. Transition state theory definitions of the free energies of activation for radical-trapping and for rearrangement give $k_T/k_C = \exp(-\Delta G^R_T - \Delta G^R_{R \rightarrow R})$, it follows that $\log(k_T/k_C)$ is proportional to the difference in free energies of activation, $\Delta G^R_T - \Delta G^R_{R \rightarrow R}$, and thus strictly speaking the solvent effects measured here can represent linear free energy relationships only to the extent that $\Delta G^R_{R \rightarrow R}$ is independent of solvent or that solvent effects for trapping are proportional to those for the rearrangement.


213. Ref 175 pp. 80; rearrangements of radicals with more bulky or more polar end groups (than 1-methyl-5-hexenyl) displayed somewhat larger relative solvent effects (i.e. up to a factor of two).

References and Notes

215. For reactions involving either the mitigation or production a charge separation the effect of the solvent entropy effect can be very large for alcoholic solvents (ΔS°# up to 50 eu), see for example: (a) Brownstein, S. Can. J. Chem. 1960, 38, 1590-1595; (b) Barrow, G.M. "Physical Chemistry" McGraw-Hill: Tokyo (1973), pp. 474.

216. One idea that presents itself for reactions in alcoholic solvents is that perhaps there is an associative effect for non-polar radicals in highly polar solvents, i.e. hydrophobic interactions with the solvent versus lipophilic interactions between the radicals T and R may create long-lived (kdiss lower) or perhaps more intimate encounter pairs (⇒ k2 higher).


218. However, for radical recombinations a statistical factor 1/4 has been asserted because only ground state singlet encounter pairs may combine; the implication being that the time scale for T→S and σ*→σ transitions is longer than the encounter period.25,23a


220. There is a serious difficulty in applying transition state theory to radical recombination: How does one define a 'transition' state for a monotonically attractive interaction? To define the transition state in terms of a Free Energy (ΔG°#) maximum and thus include the entropy term (ΔS°#) may provide an energy barrier in the 'reaction profile' but this definition may be difficult to apply on the molecular scale because Entropy and Free Energy are statistical or ensemble properties and so, unlike enthalpy, cannot be specified by a reaction coordinate.


224. Which is: (the kinetic effect of) "...the steric factor, S, is a function only of the difference in free energy between the two transition states for the rearrangement step and is independent of the conformations of the initial molecule." This follows naturally from the transition state model of reactions by application of Hess' Law and a similar formulation for the present problem, viz. the solvent effect upon a non-diffusion-controlled reaction, is self evident.

225. It is interesting that the first clear exposition of this useful postulate was made in a footnote in a report essentially of experimental results, see footnotes 9 and 10 in: Curtin, D.Y.; Crew, M.C. J. Am. Chem. Soc. 1955, 77, 354-357.


232. Nonhebel, D.C. *unpublished observations*


239. Gerber, S. *unpublished results*

240a Attempts to α-alkylate the methyl ester by this method failed due to rapid Claisen condensation of the ester.

240b Prepared from 4-penten-1-ol (Aldrich) by treatment of the mesolate with KI in acetone.


