THE CYCLOPROPYLMETHYL FREE RADICAL CLOCK

THE CYCLOPROPYLMETHYL FREE RADICAL CLOCK. CALIBRATION FOR THE RANGE 30-90°C

BY

Lukose K. Mathew, M.Sc.

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TO MY LOVING WIFE

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TITLE: The Cyclopropylmethyl Free Radical Clock. Calibration for the Range 30-89°C.

AUTHOR: Lukose K. Mathew, M.Sc.

(Calicut University, India)

SUPERVISOR: Professor John Warkentin

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ABSTRACT

The Arrhenius equation for the ring opening isomerization of cyclopropylmethyl radicals (R•) to 3-buten-1-yl radicals (R•') for the 303-362 K temperature range was determined by thermolysis of cyclopropylmethyl [1-hydroxy-1-methylethyl] diazene in the presence of excess 1,1,3,3-tetramethylisoindolin-2-yloxyl (Y•).

Rate constants for coupling of R• with Y• were assumed to be proportional to diffusion controlled rate constants (k_d) and rate constants (k_i) for the isomerization were calculated from k_d (corrected) and product ratios (RY/R'Y). The temperature dependence of k_i, given by $\log(k_i/s^{-1}) = (13.9 \pm 0.4)-(7.6 \pm 0.1)/\theta$, is significantly different from that determined by Ingold and co-workers by kinetic epr spectroscopy in the temperature range 128-153 K; $\log(k_i/s^{-1}) = (11.34 \pm 0.85)-(5.94 \pm 0.57)/\theta$, where $\theta = 2.3\ RT$ kcal mol^{-1}.

ACKNOWLEDGEMENTS

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INTRODUCTION

In the last two decades free radical chemistry has received much attention because of its almost unlimited applications not only in the industrial fields like plastics and polymers, but also in the mechanistic and kinetic areas. The enormous increase in the amount of kinetic data for free radical reactions in the last decade shows the growing demand for a deeper understanding of this rapidly developing field of chemistry. Earlier quantitative work on free radical reactions was mostly done in the gas-phase and therefore a number of compilations of kinetic data are available for gas-phase reactions.[1-4] Most of these rate constants have been determined by the most commonly used 'rotating sector' technique[5]. Measurements of absolute rate constants for radical reactions, especially the ones having very low activation energies, are subject to very large errors (± 50%)[6], using this technique. Another method used in the gas-phase radical kinetic studies is kinetic Absorption Spectrscopy (KAS). For example, the rate constant for methyl radical coupling has been studied by this technique[7,8]. The absorption at 216.4 nm by methyl radicals is used for the calculation of absolute concentrations of these radicals from which rate constants are calculated.

A great deal of kinetic data is also available for solution phase radical chemistry. The major areas for which the kinetic data have been derived are unimolecular radical reactions such as rearrangements and β-scissions and for bimolecular radical reactions such as radical coupling, addition to multiple bonds and abstraction of atoms (H or halogen) from molecules. The importance of the knowledge of these rate constants can never be overemphasized! The direct measurement of absolute rate constants for a number of radical reactions in solution comes from a variety of experimental techniques such as rotating sector (RS)[9,10], kinetic absorption spectroscopy (KAS)[11,12], steady-state electron spin resonance spectroscopy (SSESR)[13,14] and kinetic electron spin resonance spectroscopy (KESR)[15-17].

Due to the experimental difficulties in measuring the absolute rate constants for radical reactions, it is a common practice to measure relative rate constants and the literature data are much more extensive for relative rate constants than for absolute rate constants. The relative rate constants for a series of related reactions will be more reliable because in such cases the systematic errors are mostly cancelled.

There is no direct way of measuring the rate constant for a radical-molecule reaction such as eq.1,

$$R\bullet + AB \xrightarrow{k_1} RA + B\bullet \qquad [1]$$

for which the rate of reaction is given by

$$-\frac{d[AB]}{dt} = \frac{d[RA]}{dt} = k_1[R\bullet][AB] \qquad [2]$$

Calculation of the rate constant (k_1) for this reaction requires that the absolute concentrations of both the reacting radical (R•) and the reagent (AB) be known accurately. Since most radicals are very reactive, their absolute concentrations are very low in solution and therefore their accurate measurements are almost impossible. But if reaction 1 is done in competition with another reaction of the same radical (R•) with a reagent CD (eq. 3.), in the same solution,

$$R\bullet + CD \xrightarrow{k_3} RC + D\bullet \qquad [3]$$

$$-\frac{d[CD]}{dt} = \frac{d[RC]}{dt} = k_3[R\bullet][CD] \qquad [4]$$

the relative rates of reactions (1 and 3) can be expressed in terms of their rate constants as in eq. 5.

$$\frac{-d[AB]/dt}{-d[CD]/dt} = \frac{d[RA]/dt}{d[RC]/dt} = \frac{k_1}{k_3} \times \frac{[AB]}{[CD]} \qquad [5]$$

From the product ratio and from the concentrations of AB and CD, the ratio of rate constants (k_1/k_3) can be calculated. If eq.3 is a reaction whose absolute rate constant (k_3) is already known, then it is possible to calculate the absolute rate constant for reaction 1 (k_1). In this case reaction 3 acts as a radical 'clock'[18] which simply means that the absolute rate constant for that reaction is known. In some cases, where the radical (R•) isomerizes to radical R'• (R• $\xrightarrow{k_i}$ R'•) with a rate constant ki, the competition kinetics can be carried out without the use of a second reagent (eg, CD in eq. 3). Once the rate constant for the isomerization (k_1) is known, the rate constant for the competing reaction 1 (k_1) can be calculated from the ratio of the concentrations of products RA and R^1A using eq.6.

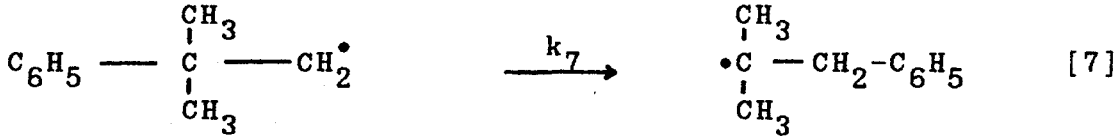
$$\frac{RA}{R'A} = \frac{k_1[AB]}{k_i} \qquad [6]$$

There are a number of unimolcular radical reactions for which the absolute rate constants are known[18] and quite often they have been used as clocks for other radical-molecule reactions. The accuracy of the rate constant calculated from this type of competition kinetics depends mainly on the accuracy of calibration of the 'clock'. A more detailed

discussion about the calibration of a few of these 'free radical clocks' will be given in a later section. The best known free radical 'clocks' which have been calibrated include some unimolecular radical reactions such as rearrangements[18] and some bimolecular reactions such as H-abstraction from trialkyltin or triaryltin hydrides by a variety of carbon centered radicals.[10,19] In some cases radical-radical reactions, which occur at or near the diffusion controlled limit,[20,21] can also be used to 'clock' other radical reactions, especially those with very high rate constants. A brief survey of a few of these radical rearrangements, some of their absolute rate constants, and the application of some of them as kinetic probes will be discussed.

1.1.0 Free Radical Rearrangements.

A large number of free radical rearrangement reactions have been recognized and are well studied in recent years. This particular topic has been reviewed several times by different authors.[22-25] The neophyl rearrangement (eq. 7) discovered by Urry and Kharasch[26] in 1944 was the first free radical rearrangement studied in solution.



1 2 [7]

The neophyl rearrangement involves the 1,2-migration of a phenyl group resulting in the thermodynamically more stable tertiary radical (2). The neophyl and related rearrangements represent an active area of research, even today. The absolute rate constants for this and similar radical rearrangements have been determined by different research groups.[27-29] According to a recent estimate[29] the rate constant for the neophyl rearrangement at 25°C is 762 s^{-1}. This value is close to that reported by the e.s.r. technique[27] approximately $10^3 s^{-1}$.

The main classes of free radical rearrangements involve (i) group transfer processes (ii) ring-closure reactions and (iii) ring-opening reactions. According to Beckwith and Ingold[25] these reactions can be represented as follows:

i) Group Transfers

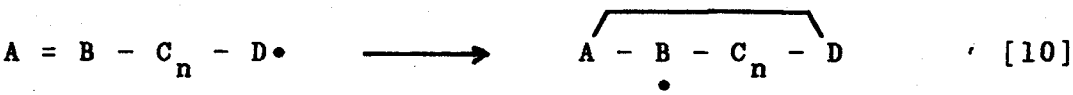
[8]

The most common group-transfer reactions involve 1,2-shifts (n=0), 1,4-shifts (n=2) and 1,5-shifts (n=3).

ii) Ring-Closure Reactions

These reactions normally involve an intramolecular addition to an unsaturated centre, which can be represented by eq. 9 and 10.

[9]



[10]

iii) Ring-Opening Reactions:

These reactions are exactly the reverse of ring-closing reactions, which can be represented as in eq. 11.

$$\bullet A - B - C_n - D \longrightarrow A = B - C_n - D\bullet \qquad [11]$$

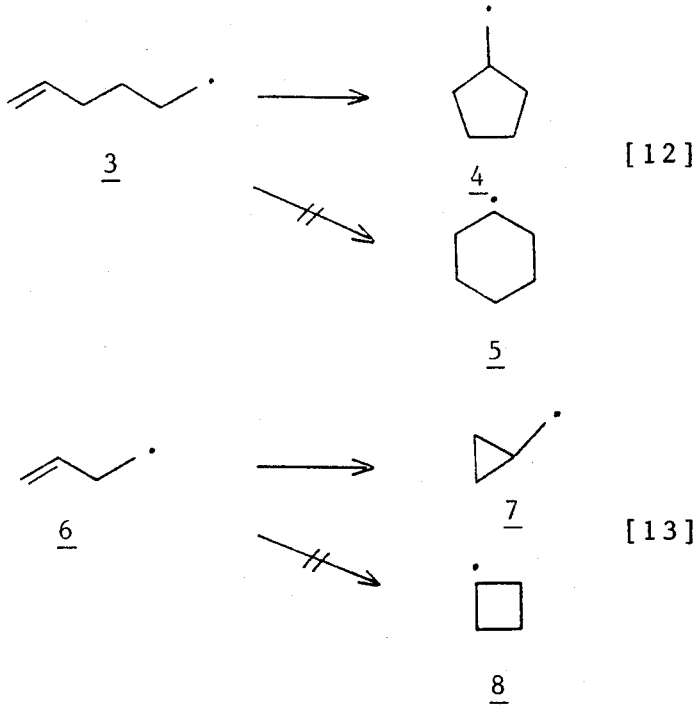
Due to the large number of examples of group-transfer reactions, only the ring-closure and ring-opening reactions, which are more relevant to the present work, are going to be discussed in the next sections.

1.2.0 Ring-Closing Rearrangements:

Intramolecular radical addition to an unsaturated site in the molecule leads to the formation of a cyclic, rearranged radical. Usually radical addition to unsaturated centers follows the more exothermic path to form the most stable possible product. Thus, a tertiary alkyl radical is formed in preference to a secondary which in turn is formed in preference to a primary radical.[30] In the case of ring-forming reactions, in addition to the exothermicity of the reaction, the steric and polar effects also have to be taken into account.[31,32] In the case of small-ring forming rearrangements, the ring-strain effects in the transition states also play an important role[33,34] in determining whether

the ring-closure is going to be in the exo- (eq. 9) or the endo- (eq. 10) sense. The enthalpy factor favours larger-ring formation in preference to small rings in intra molecular radical additions. Thus, the relative rates should be in the order six - > five - >> four - > three-membered rings. Intramolecular additions are faster than the corresponding intermolecular analogues, which can be easily explained on the basis of the difference in entropy changes. The intermolecular addition involve the loss of a substantial amount of translational kinetic energy, whereas the intramolecular processes involve only the internal rotational degrees of freedom. The entropy factor alone favours small-ring formation in preference to larger rings.

If two modes of cyclization are available, the reactions proceed through that transition complex which is of lowest energy. For intramolecular additions, in most cases, the exo-cyclization (eq. 9) is more favourable than the endo-cyclization,[35,36] (eq. 10). The best known example of this is seen in the modes of cyclization of 5-hexenyl and 3-butenyl radicals, which give exclusively the exo-cyclization products $\underset{\sim}{4}$ and $\underset{\sim}{7}$ respectively (eq. 12, 13).



3 4 5 [12]

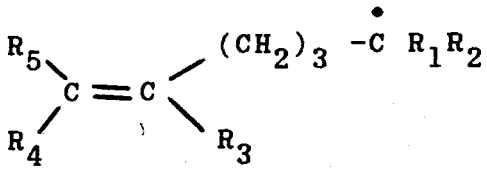
6 7 8 [13]

1.2.1 The 5-Hexenyl Cyclizations:

The 5-hexenyl rearrangement (eq. 12), is the most extensively investigated free radical rearrangement. The mechanistic and kinetic applications of this rearrangement have been well-established by various research groups over the last two decades.[35-44] In the case of the unsubstituted 5-hexenyl radical (3), the ratio of the 5-membered to the 6-membered ring is very high.[45-50] The effects of substituents on the ratio of products formed from the two different modes of cyclization have been well established by Walling[45], Beckwith[46], and Julia.[47] Table 1 lists the effect of some

methyl substituents on the rate constant for the 5-exo- ($k_{1,5}$) and the 6-endo- ($k_{1,6}$) cyclizations. All the rate constants are expressed relative to the rate constant for 5-hexenyl radical itself. The general trend observed is that when R_1 or R_5 is an alkyl group (Table 1) the rate constant for 5-exo cyclization is increased and the effect on the 6-exo cyclization is very little. The substituent effect is much more pronounced when R_5 is an alkyl group in which case the rate constant for 5-exo cyclization is dramatically decreased. Combination of a number of factors such as steric, inductive and polar effects could explain the general trend observed.[46,47]

Table 1

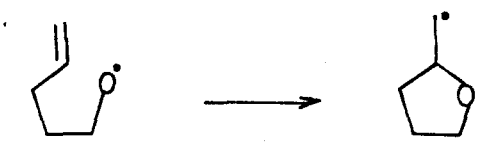
Cyclization of  at 65°-70°C

Radical	$k_{1,5}$(rel)	$k_{1,6}$(rel)	$k_{1,5}/k_{1,6}$	Ref.
R_1-R_5=H	1.0	0.02	50	46
R_1=CH_3 R_2-R_5=H	1.4	0.02	70	46
R_1-R_2=CH_3 R_3-R_5=H	1.4	0.02	70	46
R_4=CH_3 R_1-R_3=R_5=H	1.0	<0.01	>1000	47
R_4=R_5=CH_3 R_1-R_3=H	2.4	<0.01	>240	46
R_3=CH_3 R_1=R_2=R_4=R_5=H	0.022	0.04	0.05	46
R_3=R_4=CH_3 R_1=R_2=R_5=H	0.11	0.20	0.55	47
R_1=R_5=CH_3 R_2-R_4=H	0.16	<0.002	>80	47
R_1-R_3=CH_3 R_4=R_5=H	<0.0002	0.2	>0.010	46

The absolute rate constant for the 5-hexenyl rearrangement and its extensive application has been well-demonstrated by Ingold and co-workers.[10,18] The experimental determination of the absolute rate constant for this most extensively used free-radical 'clock' will be discussed in Section 1.4.0.

Among the synthetic applications of this rearrangement are the formation of cyclopentane and cyclohexane derivatives from acyclic starting materials.[49,50]

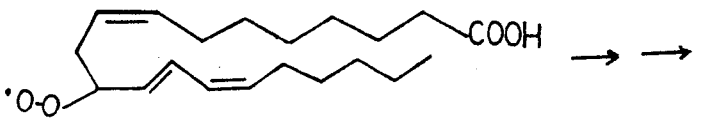
A number of rearrangements similar to the 5-hexenyl radical rearrangement, in which the unrearranged radical center is a heteroatom (O, N, or S), have also been studied. For example the oxygen-centered radical 9 rearranges to radical 10. (eq. 14).



9 10 [14]

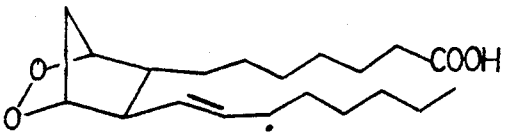
The rate constant for this rearrangement is not known accurately, but the kinetic epr data[51] suggest that the rate constant for this cyclization is much higher ($\sim 10^8 s^{-1}$) than that for the 5-hexenyl radical itself ($10^5 s^{-1}$).

The postulated mechanism for the biosynthesis of prostaglandins involves the cyclization of the peroxy radical 11 in the 5-exo sense.[52] The intermediate carbon-centered radical cyclizes again to give radical 12 (eq. 15).



[15]

11



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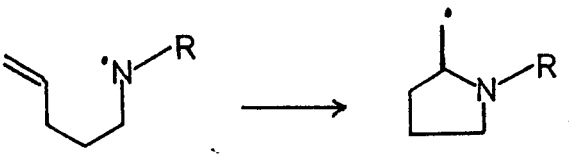
Several examples are known for the 5-hexenyl type of cyclization of nitrogen centered radicals yielding regiospecific exo-cyclization products (eq. 16).[53]

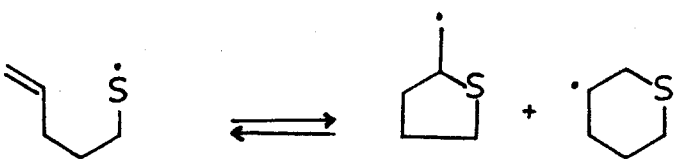


[16]

13 14

The rate constant for the rearrangement is known to be much smaller ($< 10^3 s^{-1}$)[54] than that for the corresponding carbon-centered analogues ($\sim 10^5 s^{-1}$).

Similar cyclization reactions of thiyl radicals are more complicated because of the reversibility of these reactions. Both exo- and endo-cyclization products are observed (eq. 17).[55]



[17]

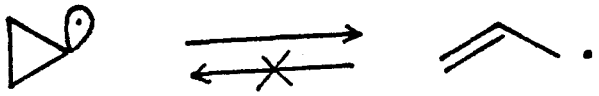
15 16 17

1.3.0 Ring-opening Reactions:

The β-scission of a cycloalkyl radical such as cyclopropyl radical or a cycloalkyl carbinyl radical (eg. cyclopropylcarbinyl radical) results in the formation of ring opened product. A few of these radical rearrangement reactions are discussed below.

1.3.1 Cyclopropyl and Related Radical Rearrangements

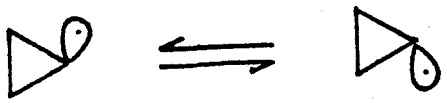
The rearrangement of cyclopropyl radical 18 to the allyl radical 19 is known to be highly exothermic (23 kcal mol^{-1}).[56-58]



18 19 [18]

Thermodynamic factors favour the forward reaction and for the same reason the reverse reaction will be extremely difficult. But it is observed that in solution, only small amounts of the rearranged products are obtained.[59-61] This means that the intermolecular reaction of these radicals can compete very well with the intramolecular rearrangement. The relatively small rate constant for the ring-opening of cyclopropyl radical, in solution, is attributed to the high activation energy. Measurements on gas-phase systems show that these ring-opening reactions have activation energies in the range 20-30 kcal mol^{-1}.[62,63]

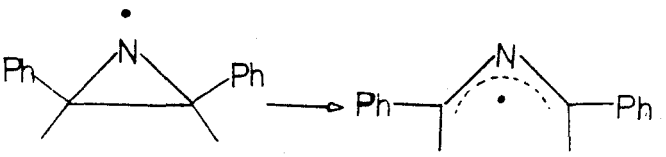
Substituted cyclopropyl radicals may undergo intermolecular reaction without much configurational change at the reaction center if the reaction is very fast.[59] This is complementary to the e.s.r. spectral evidence that cyclopropyl radical is different from other radicals.[64] Cyclopropyl radical has the unpaired electron in an sp^3 hybrid orbital, which inverts rapidly as



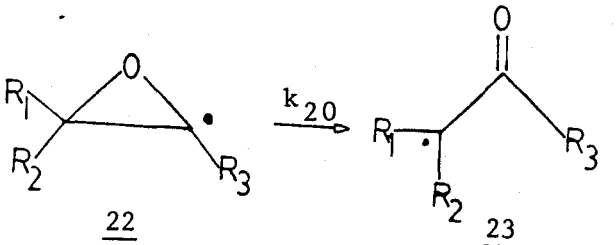
Stein and Rabinovitch[63] explained the barrier to the ring-opening of cyclopropyl systems on the basis of stereo-electronic considerations. The stereo-electronic approach is based on the hypothesis that β-scission of carbon-centered radicals proceeds most readily when the bond being broken is in an eclipsed conformation with respect to the semi-occupied orbital. This preferred transition state is very difficult to attain within a small cycloalkyl radical, since the orbital containing the free-electron is approximately orthogonal to the plane of the ring.[63]

There is no conclusive evidence as to whether the ring-opening is conrotatory but theoretical calculations suggest that there could be a preference for the disrotatory mode.[65,66]

Examples of ring-opening of three-membered heterocyclic radicals containing O and N atoms are also known. For example, the aziridinyl radical 20 rearranges to 21 (eq. 19)[67] and the oxiranyl radical 22, rearranges to the α-keto alkyl radical 23.[68-70]



20 21 [19]



22 23 [20]

a) $R_1=R_2=R_3=H$

b) $R_1=R_2=H$; $R_3=Me$

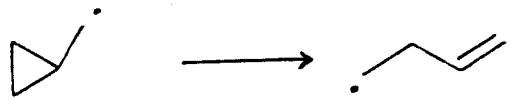
c) $R_1=R_2=R_3=Me$

d) $R_1=R_2=H$; $R_3=t\text{-}Bu$

Itzel and Fischer[68] have determined the absolute rate constants for a number of substituted oxiranyl radicals. For the unsubstituted oxiranyl radical 22a the rate constant for isomerization (k_{20}) is found to be $<10^3 s^{-1}$ at room temperature, whereas substituents increased the rate constant up to $10^4 s^{-1}$. The Arrhenius parameters for the rearrangement of 22b are given by $\log (A/s^{-1}) = 15 \pm 1$ and $Ea = 15 \pm 2$ kcal/mole.[68]

1.3.2 Cyclopropylcarbinyl and Related Radical Rearrangements

Extensive work has been done on the cyclopropyl carbinyl-allylcarbinyl radical rearrangement (eq. 21).

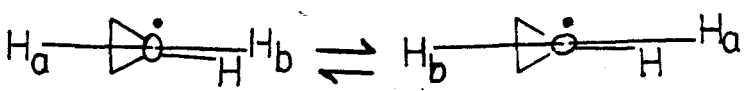


24 25 [21]

This rearrangement, which is also known as the homoallylic rearrangement, has received a lot of attention in recent years due to its mechanistically interesting features. The absolute rate constant for this rearrangement has been determined by the kinetic epr technique.[71] Because it is one of the fastest free radical 'clocks', people generally use the rate constant for this reactions to determine the rate constant for certain radical-molecule reactions which are otherwise very difficult to measure. The circumstances which led us to the re-investigation of the rate constant for this rearrangement at and above room temperature and the development of a new Arrhenius expression for the rate constant for this rearrangement will be discussed in a later section.

Kochi, Krusic and Eaton[73] have reported the esr spectra of the rearranged radical (25) and the un-rearranged radical (24) at very low temperatures. This rearrangement was found to be extremely fast and at temperatures above -100°C they were able to detect only the rearranged radical. At

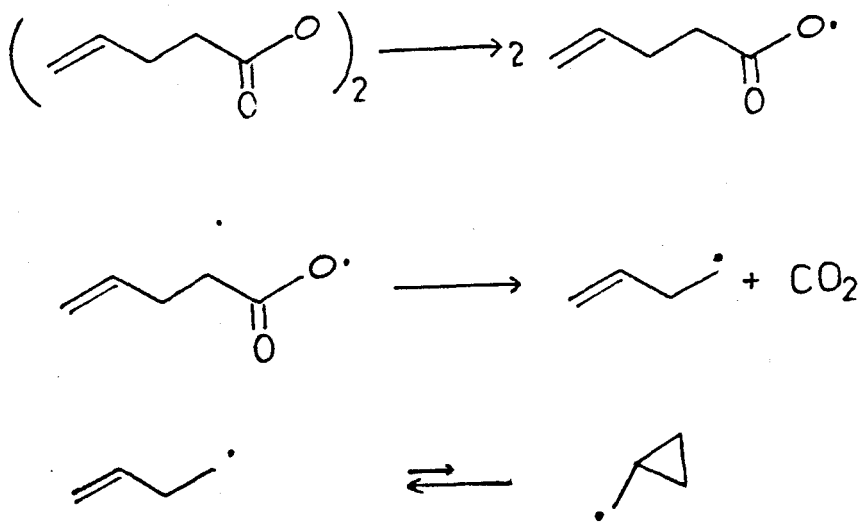
temperatures lower than -100°C, both the rearranged and unrearranged radicals could be observed.[74-76] The esr spectrum of cyclopropylcarbinyl radical differs from those of other β-substituted alkyl radicals. The hyperfine splitting constant (hfc) for the β-hydrogen in the cyclopropyl carbinyl radical is much smaller (2.55G) than is usual for a β-hydrogen in other alkyl radicals (20-25G). It has been inferred from these observations that the $-\dot{C}H_2$ group bisects the cyclopropane ring, since this configuration places the single hydrogen in the node of the p-orbital containing the unpaired electron[74] and hence the unusually low hfc. The equilibrium conformations are shown in eq. 22.



[22]

26 27

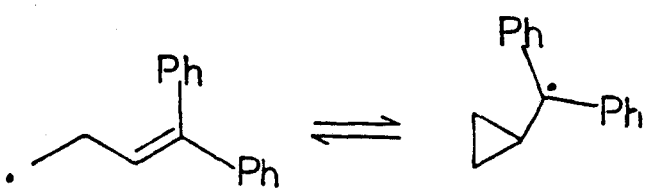
The reversibility of this rearrangement has been a topic of serious discussion and investigation for several research groups[77-79] in recent years. No evidence for the presence of cyclopropylcarbinyl radical (eq. 23) from the photolysis of allyl acetyl peroxide could be observed by the esr technique even at temperatures below -140°C.[75]



[23]

With the help of "labelling" studies Montgomery and Matt[77] have established the interconversion of allylcarbinyl and cyclopropylcarbinyl radicals. The reason for the failure of the esr technique to detect the intermediate cyclopropylcarbinyl radical could be due to the fact that the rearrangement is slow on the esr time scale.[75]

Two different lines of evidence exists for the cyclopropyl carbinyl radical in the rearangement of allylcarbinyl systems. The first one comes from the work of Roberts et. al.[78] Good yields of cyclopropyl products could be obtained from radical precursors leading to stabilized cyclopropylcarbinyl radicals. (eq. 24).

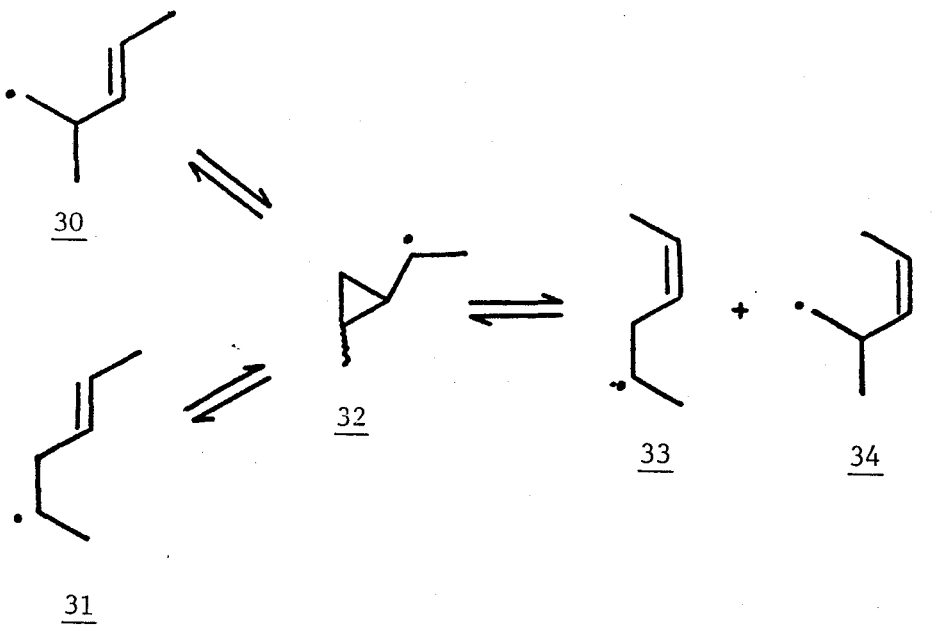


[24]

28 29

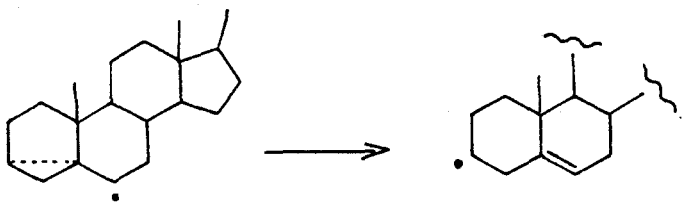
Another line of evidence is obtained from the decarbonylation studies of 2-methyl- and 3-methyl- trans-4-hexenal.[79] The products obtained from these two compounds were the same. These results could be explained on the basis of the cyclopropyl radical intermediate as shown in Scheme 1.

SCHEME 1



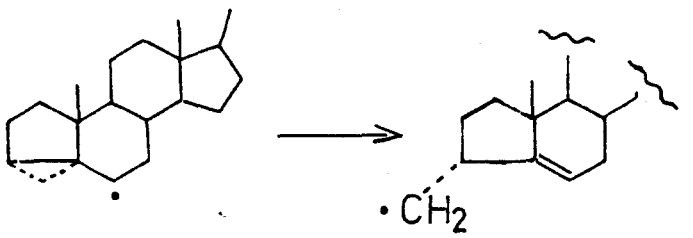
It was found that in both cases, products formed from all the four radical species 30, 31, 33 and 34 were obtained. This can only be possible through an intermediate radical 32 where the free rotation of the radical bearing group about the $\underline{c}\text{-}C_3H_5\text{-}\dot{C}HCH_3$ bond enables the formation of both cis- and trans-products as shown in Scheme 1.

The 'homoallylic' rearrangement is sensitive to stereoelectronic effects. The isomeric steroid radicals 35 and 37 rearrange specifically to give 36 and 38 respectively.[80] (eq. 25 and 26).



[25]

35 36



[26]

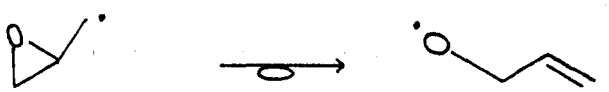
37 38

It is observed from eq. 26 that, of the two possible ring-opening modes, the less stable primary radical is formed in preference to the more stable secondary radical. A similar stereo-electronic effect has already been observed in the cyclization of the 5-hexenyl radical (Sec. 1.2.1), where the less stable primary radical is formed by the rearrangement.

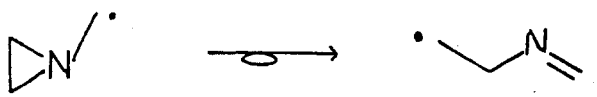
These results as well as results from other work[81-85] are consistent with the view that stereoelectronic effects are of overriding importance in determining the direction of the β-scission of cyclopropylcarbinyl and related radicals. The ring-opening will occur by the preferential fission of the β,γ bond which lies closest to the semioccupied p-orbital.

Because of the high rate constant for the isomerisation of the cyclopropylcarbinyl radical, (k_{25} = 2.1 x $10^8 s^{-1}$),[86] the products obtained by the reaction of cyclopropylcarbinyl radical (24) with other molecules consist only of the rearranged product, if the radical-molecule reaction is slow. Very few radical-molecule reactions are known to have rate constants comparable to the ring-opening rate constant of these radicals. Some examples of these reactions include bromine atom abstraction from $BrCCl_3$ and iodine atom abstraction from I_2 and $(CH_3)_2CHI$. The rate constants for the halogen abstractions from these compounds by phenyl radical are known to be near the diffusion-controlled limit.[87]

A number of radicals related to cyclopropylcarbinyl radical undergo similar ring-opening reactions. Some heterocyclic radicals like 39 and 41 rearrange to give 40 and 42 respectively.[88,89]

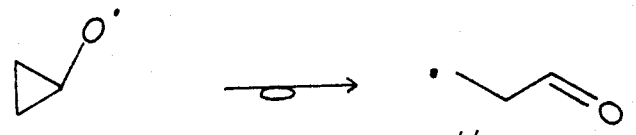


39 40 [27]

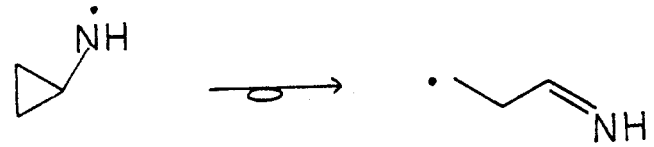


41 42 [28]

Some hetero-atom-centered radicals which rearrange in a similar manner are given below (eq. 29, 30).



43 44 [29][90]



45 46 [30][89,91]

1.4.C Rate Constants for Free Radical Reactions in Solution

As has been mentioned in Sec. 1.0.0, free radical reactions fall into one of three general classes:

a) unimolecular reactions

b) radical-radical reactions

c) radical-molecule reactions.

A few examples of these different types of reactions and the experimental methods by which some of the rate constants of these reactions have been studied are discussed below

1.4.1 Rate Constant for Unimolecular Radical Reactions

The most important class of unimolecular radical reactions are the rearrangements mentioned in Section 1.1. The rate constants for a number of radical rearrangements have been measured directly by the technique of kinetic electron spin resonance spectroscopy, developed by Ingold and co-workers.[48,71,92-96]

The principle of this technique is very simple and straightforward. From a suitable radical source the unrearranged radical, U•, is generated in the cavity of an esr spectrometer, either photochemically or thermally. The spectrometer picks up signals from both the rearranged radical, R•, and the unrearranged radical, U•. The rate constant, k_r, for the rearrangement is calculated based on Scheme 2 of the radical reaction

Scheme 2

$$\text{Radical source} \xrightarrow[(\text{or } \Delta)]{h\nu} U\bullet \qquad [31]$$

$$U\bullet \xrightarrow{k_r} R\bullet \qquad [32]$$

$$U\bullet + U\bullet \xrightarrow{k_t^{U\bullet}} \qquad [33]$$

$$U\bullet + R\bullet \xrightarrow{k_t^{UR}} \text{Non radical products} \qquad [34]$$

$$R\bullet + R\bullet \xrightarrow{k_t^{R\bullet}} \qquad [35]$$

The steady-state treatment[97,98] yields the following expression:

$$\frac{1}{[R\bullet]} = \frac{2k_t^{R\bullet}[R\bullet]}{k_r\,[U\bullet]} + \frac{2k_t^{UR}}{k_r} \qquad [36]$$

A plot of $1/[R\bullet]$ vs. $[R\bullet]/[U\bullet]$ will give a straight line of slope $2k_t^{R\bullet}/k_r$. The rate-constant for rearrangement (k_r) is calculated from a knowledge of $2k_t^{R\bullet}$ (see Section 1.4.2 under the same experimental conditions by the usual kinetic esr technique.[99-102]

In certain cases, where the radical centers are of approximately the same structure and reactivity, $k_t^{R\bullet}$ can be taken as equal to k_t^{UR}, in which case eq. 19 can be simplified as eq. 20.

$$k_r = 2k_t^{R}\left[\frac{[R\bullet]^2}{[U\bullet]} + [R\bullet]\right] \qquad [37]$$

Only one measurement of the concentrations of the unrearranged and the rearranged radicals is enough to calculate the rate constant for the rearrangement reaction (k_r).

Using this technique Ingold and co-workers have determined the absolute rate constants and activation parameters for a number of radical rearrangements like the

5-hexenyl rearrangement and the cyclopropylcarbinyl rearrangement. Most of these rate constants have been used as free radical 'clocks'.[18] Table I of ref. 18 lists some of the kinetic parameters for a number of these radical 'clocks.'

The primary alkyl radical clocks listed in the above reference (18), with the exception of the 5-hexenyl cyclization, have been used only occasionally in quantitative kinetic studies of radical-molecule reactions. The reason could be that most of these rate constants have been calibrated only recently. The wide use of the 5-hexenyl 'clock' as a powerful mechanistic probe comes from the fact that its rate constant was known as early as 1968[48] and the Arrhenius parameters were determined by the steady-state epr method as early as 1974.[49] The present research aims at the calibration of such a powerful radical clock namely the cyclopropylcarbinyl radical rearrangement.[103]

1.4.2 Rate Constants for Radical-Radical Reactions

Among the bimolecular radical reactions, the rate constant for radical-radical reactions such as radical coupling (eg, $2R\bullet \rightarrow R-R$) is known to approach the diffusion controlled limit. When two species react with one another, a chemical change can take place only as fast as the reactants can diffuse together. Such a process is called a 'diffusion controlled' reaction. The second order rate constant for such

a reaction can be calculated from a combination of the laws of diffusion[104] and the modified form of the Stokes-Einstein equation.[105] The final expresion for the diffusion controlled rate constant is given[106] as

$$k_{diff} = 1/4\ (2 + d_1/d_2 + d_2/d_1)(8RT/3x10^3\eta)M^{-1}s^{-1} \quad [38]$$

where η is in poise.

In radical reactions where the radicals involved have the same radii ($d_1=d_2$, as for coupling of identical radicals), the diffusion controlled rate constant reduces to the form:

$$k_{diff} = 8RT/(3x10^3\eta)\ M^{-1}s^{-1} \quad [39]$$

For common solvents like cyclohexane, benzene, carbon tetrachloride, water, etc., the diffusion-controlled rate constant calculated using the above equation comes approximately to $10^{10}M^{-1}s^{-1}$.[106]

Rotating sector and kinetic electron spin resonance spectroscopy are the most commonly used techniques for the determination of the rate constant for the radical coupling reactions. A few examples of rate constants for some simple radical coupling reactions are given in Table 2.

Table 2: Some Radical-coupling Reactions and their Rate Constants for Carbon-centered and Tin-centered Radicals at 25°C.

	Radical	Method	Solvent	Rate Constant $2k_t \times 10^{-9}$ ($M^{-1}s^{-1}$)	Ref.
1.	$CH_3\bullet$	RS	cyclohexane	8.9	10
		KESR	t-Bu-O-O-tBu	$11.0^{(-17°C)}$	100
2.	$CH_3-CH_2-CH_2\bullet$	RS	cyclohexane	3.4	107
3.	$CH_3-(CH_2)_3-CH_2\bullet$	RS	cyclohexane	2.2	10
4.	$(CH_3)_3C-CH_2\bullet$	KESR	t-Bu-O-O-tBu	4.0	100
5.	$c\text{-}C_6H_{11}\bullet$	RS	cyclohexane	2.7	10
		KESR	cyclohexane	$2.5^{(+10°C)}$	108
		KAS		2.5	11
6.	$(CH_3)_3C\bullet$	RS	cyclohexane	2.1	10

Table 2: continued

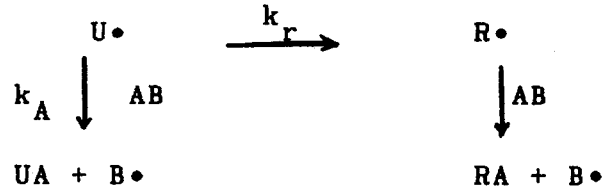
7.	$(CH_3)_3C\bullet$	KESR	t-Bu-O-O-tBu	8.1	100
8.	$C_6H_5-CH_2\bullet$	RS	cyclohexane	4.0	107
9.	$(CH_3)_3C-CH_2$	KESR	cyclohexane	4.0	100
10.	$(CH_3)_3Sn\bullet$	RS	cyclohexane	3.1	10
	$(CH_3)_3Sn\bullet$	KESR	cyclohexane	5.5	100
11.	$n\text{-}Bu_3Sn\bullet$	RS	cyclohexane	1.4	10
12.	$Cl_3C\bullet$	KESR	cyclohexane	5.8(27°C)	109
13.	$CH_3\overset{\bullet}{C}H-OH$	RS	water	2.0	110
14.	$(CH_3)_2\overset{\bullet}{C}-CN$	SSESR	cyclohexane	8.0	101

1.4.3 Rate Constants for Radical-Molecule Reactions

As has been mentioned in the beginning of this chapter, there is no simple method for the determination of the absolute rate constant for a radical-molecule reaction. One of the well-understood radical-molecule reactions is the hydrogen-abstraction reaction from a variety of trialkyltin hydrides by a number of alkyl radicals.[10,113] The absolute values for many of these reactions have been determined by the kinetic esr techniques.

Another approach for the determination of rate constants for radical-molecule reactions makes use of radical 'clocks'. The successful determination of a rate constant for a radical-molecule reaction depends on the proper selection of a calibrated 'clock' reaction. The experimental procedure is simple. A radical which undergoes unimolecular rearrangement (for example) is generated in the medium containing the molecular substrate. The unrearranged radicals (U•) and the rearranged radicals (R•) then react with the substrate (AB) forming products. From the ratio of products formed from the unrearranged and the rearranged radicals, the rate constant for the reaction can be calculated from Scheme 3 of the radical reactions.

Scheme 3



The rates of formation of UA and RA are given by eq. 40 and 41 respectively

$$\frac{d[UA]}{dt} = k_A[U\bullet][AB] \qquad [40]$$

$$\frac{d[RA]}{dt} = k_r[U\bullet] \qquad [41]$$

If the concentration of AB remains approximately constant, the product ratio [UA]/[RA] can be expressed as:

$$\frac{[UA]}{[RA]} = \frac{k_A[U\bullet][AB]}{k_r[U\bullet]} \qquad [42]$$

$$k_A = k_r \frac{[UA]}{[RA][AB]} \qquad [43]$$

1.5.0 Generation of Radicals in Solution:

a) Direct Methods:

There are several convenient ways of generating radicals in solution. The direct ways of generating radicals involve the thermal or photochemical scission of bonds. Due to the

high bond energy of C-C bonds (~90 kcal/mole), carbon-centered radicals are very difficult to form by the homolysis of C-C bonds at or near room temperature. Compounds containing azo (-N=N-) groups or peroxy (-O-O-) groups decompose thermally and also photochemically producing radicals.

For example t-butyl peroxide decomposes thermally above room temperature and photochemically at low temperature producing t-butoxy radical (eq. 44) as the primary decomposition product.

$$t\text{-}BuOOBu\text{-}t \xrightarrow[\Delta]{h\nu \text{ or}} 2t\text{-}BuO\bullet \qquad [44]$$

Similarly, acetyl peroxide and benzoyl peroxide also decompose thermally to form methyl and phenyl radicals respectively according to the following equations.

$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \xrightarrow{\Delta} 2\,CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\bullet \longrightarrow 2CH_3^{\bullet} + 2CO_2 \qquad [45]$$

$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}O\text{-}\overset{O}{\overset{\|}{C}}C_6H_5 \xrightarrow{\Delta} 2C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\bullet \longrightarrow 2C_6H_5\bullet + 2CO_2 \qquad [46]$$

47

Peracids and peresters also decompose in a similar manner by the homolysis at the -O-O- bond giving alkyl and alkoxy radicals. Peracetic acid on thermolysis gives methyl radicals (eq. 47).

$$CH_3-\overset{O}{\overset{\|}{C}}-O-OH \xrightarrow{\Delta} CH_3\bullet + CO_2 + \cdot OH \qquad [47]$$

t-Butyl peracetate and t-butyl perbenzoate are known to give the t-butoxy radical.

$$t\text{-}Bu-O-O-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{\Delta} t\text{-}BuO\bullet + \bullet O-\overset{O}{\overset{\|}{C}}-CH_3 \qquad [48]$$

$$\bullet O-\overset{O}{\overset{\|}{C}}-CH_3 \longrightarrow CO_2 + \bullet CH_3$$

$$t\text{-}Bu-O-O-\overset{O}{\overset{\|}{C}}-C_6H_5 \xrightarrow{\Delta} t\text{-}BuO\bullet + CO_2 + C_6H_5\bullet \qquad [49]$$

Alkyl radicals are also produced conveniently from azo compounds by the usual homolytic processes.

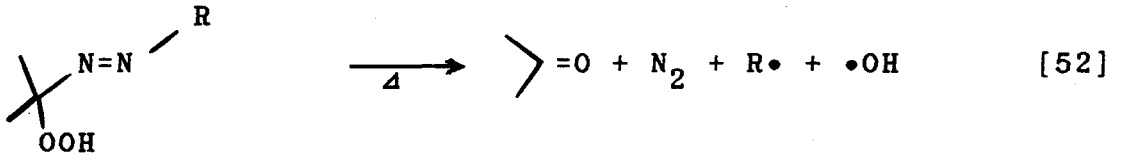
$$R-N=N-R \xrightarrow{h\nu/\Delta} 2R\bullet + N_2 \qquad [50]$$

An example of this is the decomposition of azobis isobutyronitrile (AIBN), eq. 51. Its convenient thermolysis rate at 50-80°C makes it one of the best free radical initiators.

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{CN}{\overset{|}{C}}}-N=N-\underset{\underset{CH_3}{|}}{\overset{CN}{\overset{|}{C}}}-CH_3 \xrightarrow{\Delta} 2CH_3-\underset{\underset{CH_3}{|}}{\overset{CN}{\overset{|}{C}}}\bullet + N_2 \qquad [51]$$

<u>48</u>

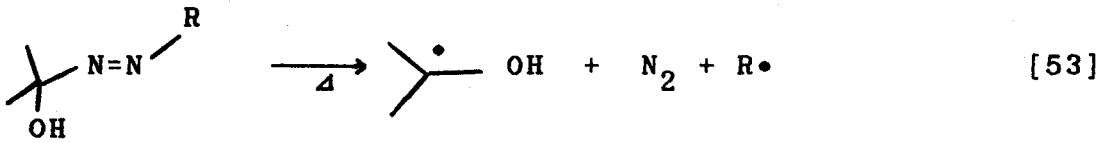
Another class of azo compounds which decompose thermally to produce alkyl radicals are the α-hydroperoxydiazenes.[114] The general decomposition pattern is given in eq. 52.



[52]

49

Azo carbinols[115] also decompose in a similar manner (eq. 53).



[53]

50

b) Indirect Methods

Radicals can also be produced as part of a chain propagating step in a free radical chain reaction. For example, alkyl radicals are produced in the radical-chain reduction of an alkyl halide by organotin hydrides in the presence of radical initiators. The following are the various reaction steps.

Initiation:

$$In \rightarrow In\bullet \qquad [54]$$

$$In\bullet + R^{1}_{3}SnH \rightarrow InH + R^{1}_{3}Sn\bullet \qquad [55]$$

Propagation:

$$R_3^{\prime}Sn\bullet + R\text{-}X \rightarrow R_3^{\prime}SnX + R\bullet \quad [56]$$

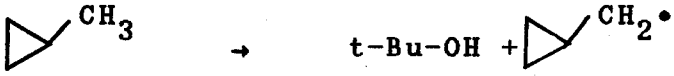
$$R\bullet + R_3^{\prime}SnH \rightarrow RH + R_3^{\prime}Sn\bullet \quad [57]$$

Termination:

$$\left.\begin{array}{l} R\bullet + R\bullet \rightarrow \\ R\bullet + R_3^{\prime}Sn\bullet \rightarrow \\ R_3^{\prime}Sn\bullet + R_3^{\prime}Sn\bullet \rightarrow \end{array}\right\} \text{non-radical products}$$

Another indirect way of making radicals in solution is by the attack of alkoxy radicals on hydrocarbns. For example cyclopropyl carbinyl radical is produced by the photolysis of di-t-butyl peroxide in the presence of methylcyclopropane at low temperatures.[116]

$$t\text{-}Bu\text{-}O\text{-}O\text{-}Bu \xrightarrow{h\nu} 2t\text{-}BuO\bullet \quad [58]$$



[59]

OBJECTIVE, RESULTS, AND DISCUSSION

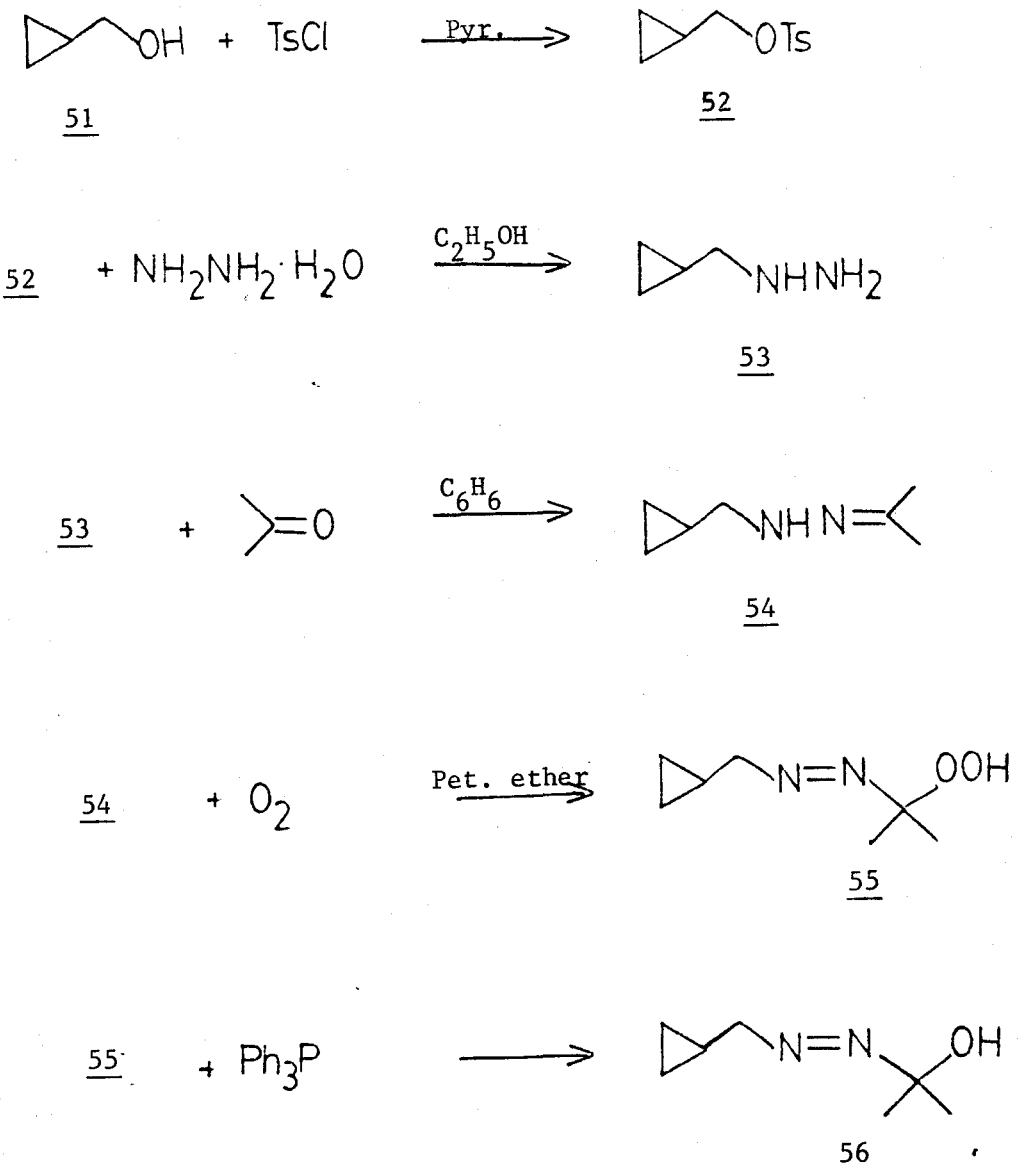
We wanted to determine the absolute rate constants for some fast radical processes such as bromine atom abstraction from bromotrichloromethane and iodine abstraction from iodoform and isopropyl iodide by primary alkyl radicals at room temperature. A search of the literature showed that the best available radical 'clock' from such a fast (near diffusion controlled) process is the cyclopropylcarbinyl rearrangement. Ingold and coworkers[71] had calibrated this 'clock' at temperatures very far below room temperature, 125-153K. The use of such a radical clock at ambient or higher temperatures involves considerable extrapolation by means of Arrhenius parameters, assuming that the Arrhenius relationship is linear over a range of temperatures very much larger than that over which those parameters were determined. In order to use this 'clock' for our purposes it was necessary to calibrate the clock at and above room temperature.

Cyclopropylmethyl (1-hydroxy-1-methylethyl)diazene was chosen as the source of the cyclopropylcarbinyl radical because of its convenient thermolysis at and above room temperature. Another advantage of using such a radical source is that azo carbinols decompose by a radical chain process. Radical pair chemistry is therefore largely avoided and the problem of product analysis is simplified.

Synthesis and Properties of Cyclopropylmethyl (1-hydroxy-1-methyl ethyl) diazene.

The source of the cyclopropylcarbinyl radical was cyclopropylmethyl(1-hydroxy-1-methylethyl)diazene (56) which was prepared according to Scheme 4.

Scheme 4

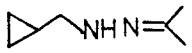
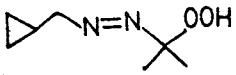
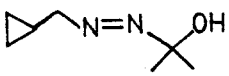


The conversion of the alcohol to the tosylate is straightforward, but the yield varied from 60-96%. It was observed that traces of moisture in the solvent could appreciably decrease the yield of the product. The unpurified tosylate was slowly converted to unidentified products above 0°C. A suspension of the impure tosylate in petroleum ether was found to crystallise slowly as colourless crystals over a period of one week, when the solution was put in the freezer at -30°C.

The hydroperoxydiazene and hydroxydiazene are known to decompose at an appreciable rate even at room temperature. Therefore, the solutions were always kept in the freezer at ca. -30°C and were taken out only when needed.

The spectral data of the hydrazone 54, α-hydroperoxydiazene (55), and α-hydroxydiazene (56) are given in Table 3. Oxidation of the hydrazone to the hydroperoxydiazene using molecular oxygen was done either in petroleum ether or in benzene at 0-5°C. A gas burette fitted with a mercury manometer was used to measure the volume of oxygen taken up. The completion of the reaction was inferred from the steady oxygen level in the burette for more than two hours, and was confirmed by taking the NMR spectrum of the solvent free material, which gave a singlet peak of the gem-dimethyl group of 56 in place of the two separate methyl singlets for the hydrazone. The purity of the hydroperoxy diazene was estimated by iodometric titration.

Table 3: Spectral data of compounds 54, 55 and 56.

Compound	Yield	^{1}H NMR ($CDCl_3$) δ(ppm)	^{13}C NMR ($CDCl_3$) δ(ppm)	UV(hexane) λ (ε)	IR (neat)
	28%	0.08--.63 (m, 4H) 0.77-1.27(m,1H) 1.75(s,3H) 1.93(s,3H) 3.01(d,2H) 3.80-4.70(s,br,1H)	2.80 10.26 15.21 24.81 55.88 145.36	290(16.1) 358(2.7)	3420 3240 3080 2992 2904 2842 1660 (weak)
	98%	0.17-0.77(m,4H) 1.03-1.40(m,1H) 1.47(s,6H) 3.67(d,2H) 9.47(s,br,1H)	3.51 9.20 21.84 73.60 102.89	292(10.2) 358(21.9)	3320 3080 2988 2936 1680 1179 847
	67%	0.07-0.63(m,4H) 0.97-1.33(m,1H) 1.34(s,6H) 3.68(d,2H) 4.73(s,1H)	3.30 9.01 26.90 71.39 93.60	290(9.8) 338(19.2)	3410 3080 2982 2933 1685 1215

The compounds described in Table 3 were characterised by ^{1}H NMR spectroscopy. The cyclopropylmethylhydrazone of acetone (54) has two singlet methyl groups at δ1.75 and 1.93 ppm and a doublet due to the $\underline{c}\text{-}C_3H_5\text{-}\underline{CH_2}$ group, as expected.

The difference between the NMR spectra of the hydroperoxy-and hydroxydiazene is mainly in the chemical shift for the gem dimethyl region (δ1.47 and 1.34 ppm, respectively) and also for the -O-OH (δ9.47) and -OH (δ4.73) groups.

The $n\text{-}\pi^*$ transitions for the azo function in the UV spectrum are also different. For the hydroperoxydiazene, λ_{max}=358 nm, whereas for the hydroxy diazene λ_{max}= 338 nm. Another feature by which the two compounds can be distinguished is the characteristic O-O stretching frequency at 847 cm^{-1} in the ir spectrum of the hydroperoxide, which is absent in that of the azocarbinol.

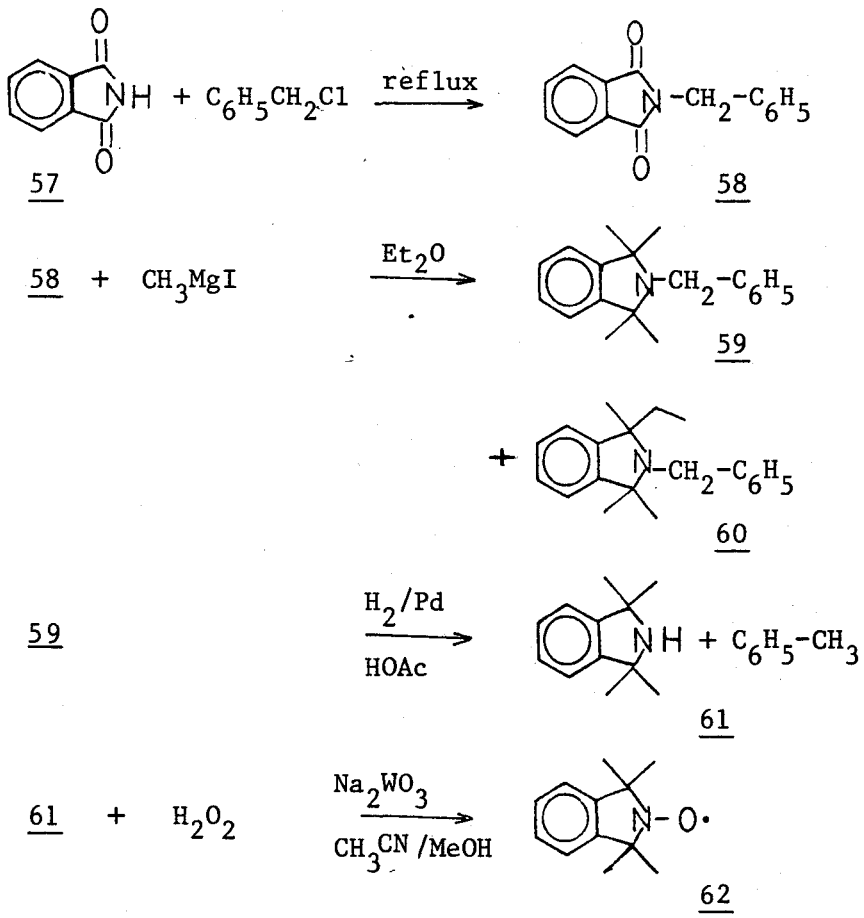
The use of Ph_3P as the reducing agent for converting hydroperoxy diazene to the azocarbinol has the following advantages:

1) The reaction is very fast even at low temperatures (0°C)
2) The product Ph_3PO and the reagent (Ph_3P) are both non-volatile solids which made the work up simple.
3) The reaction is almost quantitative.

2.2 Synthesis of 1,1,3,3-Tetramethylisoindolin-2-yloxyl

This powerful radical scavenger had been synthesised and extensively used by Solomon and coworkers[114], who modified the procedure reported by Heidenbluth et al.[115] Solomon and coworkers[114] used N-benzyl phthalimide in the place of N-methyl phthalimide as the precursor for its synthesis. Their procedure, summarized in Scheme 5 was followed for the synthesis of the title compound.

SCHEME 5

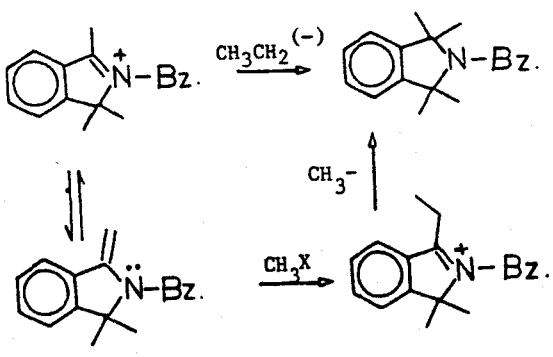


57 → 58 → 59 + 60 → 61 → 62

In our hands Solomon's procedure[114] for the Grignard reaction in Step 2 (Scheme 5) gave a yield of only 10%, which is less than half of the reported yield for 59 (37%). However, reducing the volume of the solvent and increasing the reaction time (see Experimental Section), increased the yield to 42%, which was considerably greater than that reported. The only major difference observed was in the ratio of the products 59 and 60 formed in the Grignard reaction. Product 60 was obtained in a relative yield of 18.5% in the unrecrystallized product, whereas the authors reported the contaminant 60 to be 2-3% in their unrecrystallized product.

The formation of the ethyl substituted isoindolin derivative (60) could be explained[114] by the attack of a nucleophilic ethylating agent on the starting material or on the intermediate iminium ion or by the attack of an electrophilic methylating agent on the enamine (Scheme 6).

SCHEME 6



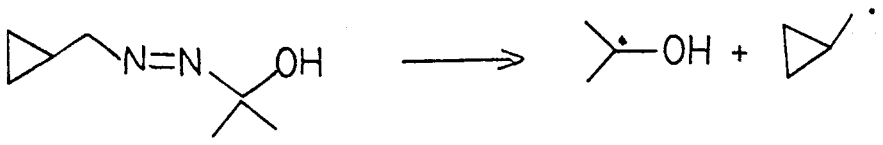
More research is needed for the full understanding of this very interesting mechanistic problem.

2.3 Rate Constant for Isomerization of the Cyclopropylcarbinyl Radical

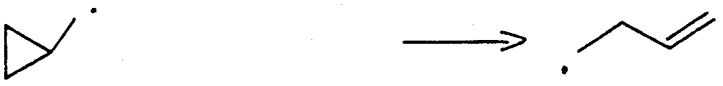
Method:

The cyclopropylcarbinyl radical (R•) is produced conveniently by the thermolysis of 56 in hexafluorobenzene. Thermolysis of 56 in the presence of an excess of the radical scavenger 62 was a very clean process, yielding only the products in Scheme 7. The radical (R•) rearranges to the allylcarbinyl radical (R'•). The aim of this project was to determine the rate constant (k_i) for this isomerization. This was achieved by clocking the isomerization reaction with the radical-radical reaction between 62 and R•. The rate constant for the bimolecular radical encounter (k_c) can be easily estimated from the diffusion controlled rate constant (k_d). Scheme 7 summarizes the reactions upon which the whole principle is based.

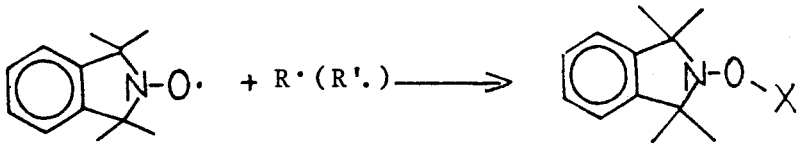
SCHEME 7



56

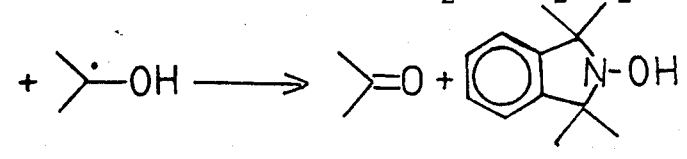


(R·) (R·')



62 63 a) X=c-$C_3H_5CH_2$·

b) X=CH_2=CH-CH_2-CH_2·



62 65

The rate constant, k_i, is calculated from eq. 60.

$$k_i = k_c \frac{[\underset{\sim\sim}{63}b][\underset{\sim\sim}{62}]}{[\underset{\sim\sim}{63}a]} \qquad [60]$$

The radical trap $\underset{\sim\sim}{62}$ was always taken to be more than 10-fold in stoichiometric excess to the azocarbinol ($\underset{\sim\sim}{56}$). The final concentration of $\underset{\sim\sim}{62}$, relative to the sum of the concentrations of the products was checked independently for each run, from the gc counts for the remaining radical trap and

the products of reaction. The term [$\underset{\sim}{\underset{\sim}{62}}$], in eq. 60, was taken as the average of the initial and final concentration of $\underset{\sim}{\underset{\sim}{62}}$. Usually $[\underset{\sim}{\underset{\sim}{62}}]_{ave}$=0.92 to 0.94$[\underset{\sim}{\underset{\sim}{62}}]_{initial}$. This small correction for the concentration change for $\underset{\sim}{\underset{\sim}{62}}$ with time was applied in each case to minimize the error that would have occurred if it had been assumed that the concentration of $\underset{\sim}{\underset{\sim}{62}}$ remains constant during the reaction.

The rate constants for coupling of R• or R'• with $\underset{\sim}{\underset{\sim}{62}}$ (k_c in eq. 60) were obtained by dividing the diffusion controlled rate constants, k_d, calculated from the viscosities of the solvent at various temperatures (see next section), by five, i.e., $k_c=0.2k_d$. The rationale for this correction, which is a consequence of the numerous estimates of rate constants for bimolecular radical-radical reactions published in the literature, is discussed below.

The rate constant for radical dimerization reactions ($2R\bullet \xrightarrow{2kt}$ R-R) of a wide range of carbon-centered and tin-centered radicals (discussed in detail in the Introduction Section) range from near difffusion controlled ($\sim 10^{10} M^{-1}s^{-1}$) to values which are smaller by a factor of ten or even more. The average value of these rate constants comes to about $2X10^{9} M^{-1}S^{-1}$, which is a factor of approximately five less than the diffusion limit.

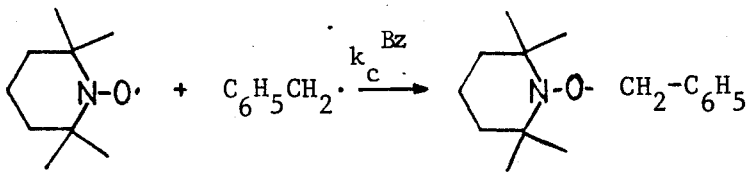
In a recent review by Ingold[116] the absolute rate constants for a number of radical-radical reactions, including the coupling of 1°-alkyl radicals with stable nitroxyls (>N-O•+R• $\xrightarrow{k_c'}$ >N-O-R)

have been discussed. Pulse radiolysis is the most commonly used technique for the determination of such rate constants. Kinetic electron spin resonance spectroscopy, kinetic absorption spectroscopy, and steady state electron spin resonance spectroscopy have also been used in some cases.

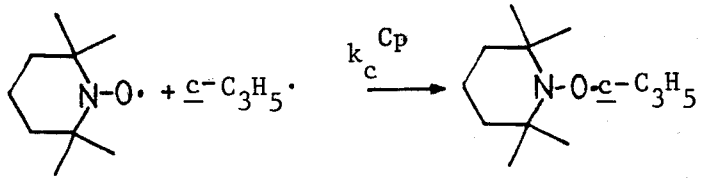
The rate constants for coupling of alkyl radicals with stable nitroxyl radicals range from the diffusion-controlled limit to values about ten times smaller.[116] The majority of these rate constants have been reported using pulse-radiolysis studies in aqueous solutions, in which the H-bonded nitroxyl radicals could posssibly be less reactive than in aprotic solvents, such as hexafluorobenzene, where H-bonding effects are absent.

Even though there is no direct evidence for a systematic variation in these rate constants with the structure of the radicals, the general trend indicates that radical coupling rate constants are, in fact, about 4-6 times smaller than those calculated for the diffusion controlled limit (Section 1.4.2).

A recent measurement of k_c for the coupling of $\underset{\sim}{\underset{\sim}{62}}$ with alkyl radicals suggest a value at 60°C of $1 \times 10^{9} M^{-1} s^{-1}$.[117] Very recently, Ingold and coworkers[118,119] have determined the rate constants for the coupling of benzyl and cyclopropyl radicals with a similar radical scavenger, tetramethyl piperidinooxy (TEMPO). The following equations give the reactions and their rate constants.



$$k_c^{Bz} = 4.9 \times 10^8\ M^{-1}s^{-1} \quad \text{at } 23°C$$



$$k_c^{Cp} = 1.2 \times 10^9\ M^{-1}s^{-1} \quad \text{at } 25°C$$

It can be concluded from the above data, that the coupling of $\underset{\sim}{62}$ with R• is not quite diffusion controlled. A value of $k_c = 0.2k_d$ is justified because a factor of about 5 is indicated from the general trend outlined above.

The attenuation factor of five was also indicated from estimates of the rate constant (k_i) derived from data published in the literature. Bergman and coworkers[120] studied the radical chain reduction of cyclopropylmethyl bromide with tri-n-butyltin hydride. When the concentration of the Bu_3SnH was 0.74M, they obtained a product ratio of 90:1 for 1-butene to methylcyclopropane at 25°C. Using the most recent values for the rate constant for H-abstraction from Bu_3SnH by primary alkyl radicals ($k_H^{25°C}=2.4\times10^6 M^{-1}s^{-1}$)[111], the above data gives $k_i^{25°C}=1.6\times10^8 s^{-1}$.

Cristol and Barbour[121] used triphenyltin hydride for the radical chain reduction of 6β-chloro-3α,5α-cyclocholestane (cyclocholestanyl chloride). The cyclocholestanyl radical (35) rearranges to the cholesteryl radical (36) and the corresponding hydrocarbons were formed by reaction of these radicals with Ph_3SnH. The ratio of 5-cholestene to 3α, 5α-cyclocholestane was found to be 6.25:1, when 4M triphenyltin hydride was used. Carlsson and Ingold[10] have obtained a five-fold greater reactivity for Ph_3SnH, compared with Bu_3SnH. This fact, together with the recent estimates of the rate constant for H-abstraction from Bu_3SnH by cyclohexyl radical ($k_H^{30°C}=2.2\times10^6$ $M^{-1}s^{-1}$)[122], gives a value for the isomerization rate constant for cyclocholesteryl radical as $k_i = 2.5 \times 10^8 s^{-1}$ at 30°C.

In order to bring our rate constant into alignment with these independent rate constants, one for cyclopropylmethyl-radical itself and another for Cristol and Barbour's model, a factor of five was necessary. The use of $k_c=0.2k_d$ brings our value for the rate constant to $k_i^{25°C}=2.1\times10^8 s^{-1}$.

2.4 Viscosities of Hexafluorobenzene at Various Temperatures

Table 3 lists the viscosities of hexafluorobenzene at various temperatures (see Experimental Section for details). The viscosities of benzene were taken from the literature[123] and the viscosity of hexafluorobenzene were calculated from

measurements of the time taken for benzene (t_B) and hexafluorobenzene (t_H), to drain through the viscometer.

Table 4

Viscosity of C_6F_6 as a Function of Temperature

Temp. T,K	t_B (s)	t_H (s)	η_B (cp)	$\eta_H = \frac{\eta_B t_H d_H}{t_B d_B}$ [a]
298.5	252.1	204.6	0.595	0.886
307.0	232.2	186.5	0.541	0.797
318.8	203.6	162.8	0.468	0.686
340.8	161.7	125.3	0.362	0.514
355.0	145.3	115.0	0.320	0.465

[a] d_H/d_B was assumed to be independent of temperature and was obtained by dividing their respective densities at 20°C; viz, $d_H/d_B = 1.612/0.879 = 1.834$.

2.5 Calculation of Diffusion-Controlled Rate Constants

The values of diffusion-contolled rate constants (k_d) were calculated from the measured viscosities of the solvent (C_6F_6) by means of the following equation,[106]

$$k_d = 1/4(2 + \frac{d_1}{d_2} + \frac{d_2}{d_1}) \frac{8RT}{30\eta}$$

where η is in cp, R is in erg. $deg.^{-1}mol^{-1}$, T in K, and k_d is in $M^{-1}s^{-1}$. The ratio of the diameters of the reacting radicals (d_1/d_2) was estimated from molecular models of R• and 62 to be 1/2. Table 5 gives the diffusion-controlled rate constants for bimolecular reactions in hexafluorobenzene at various temperatues.

Table 5

Diffusion Controlled Rate Constants at Various Temperatures:

T,K	η_H[a](cp)	k_d[b] $M^{-1}s^{-1}$
303	0.836	9.00×10^{9}
323	0.647	1.24×10^{10}
343	0.517	1.66×10^{10}
362	0.427	2.12×10^{10}

a) obtained from Table 4.

b) $k_d = 1/4(2 + d_1/d_2 + d_2/d_1)\times\frac{8RT}{30\eta}$, $d_1/d_2 = 1/2$

$k_d = 1.125 \times \frac{8RT}{30\eta}$, $R = 8.3\times10^{7}$ erg deg^{-1} mol^{-1}

2.6 Identification of 63a and 63b

In addition to the solvent peak and the peak from excess 62 there were only two other peaks observed in the gas chromatogram of the reaction mixture (see Experimental Section). Experiments specially designed to see the effect of concentration of the spin

trap on the ratio of the two products (assigned tentatively as 63b and 63a based on the order of elution), showed that the relative amount of the component eluting second to last decreased with increasing concentration of the radical trap. This is what is expected for the ring-opened radical adduct 63b.

Analysis of the thermolysis reaction mixture by gc/ms gave, for both adducts: m/z 245 (m^+), 230 (100%), 190, 176, 160, 158, 145, 551, 55. The relative intensity of the signal at m/z = 55 was greater for the adduct assigned structure 63a. This is expected because of the inherent stability of the cyclopropylmethyl cation.

Another piece of evidence for the assignment of 63b and 63a came from bromination studies - a very common test for unsaturation. Incremental addition of Br_2 in CCl_4 to the reaction products, and gc analysis after each increment, showed that the component eluting just after the 62 was being consumed while the ratio of the other product (63a) to that of the excess 62 remained constant. Table 6 lists the ratio of the products 63a and 63b relative to 62 after the addition of different volumes of Br_2 in CCl_4 (~ 0.2 M).

Table 6

Change in Concentration of 63b with Increasing Amounts of Br_2

Vol. of Br_2 in CCl_4(~.2M)	[62]	Relative Concentrations [63b]/[62]	[63a/[62]
0	1.0	1.1	0.25
20μL	1.0	0.99	0.26
50μL	1.0	0.82	0.27
150μL	1.0	0.15	0.26

2.7 Calculation of Arrhenius Expression

The rate constant for isomerization, k_i, was calculated from eq. 60 using the experimentally determined product ratios (63b/63a) and the corrected concentration of the radical scavenger, $[62]_{ave}$. The experiments were done in triplicate at each temperature and the products were analysed by gc. The product ratios for each of these experiments were taken from the averages of at least three injections. Table 7 lists the values obtained for k_i at various temperatures ranging from 303K to 362K.

Taking our data alone, the least squares treatment yields the Arrhenius expression:

$$\log (k_i/s^{-1}) = (14.6 \pm 0.1) - \left(\frac{8.6 \pm 0.1}{\theta}\right)$$

where $\theta = 2.3\ RT$ kcal mol^{-1}

This yields $k_i^{25°C} = 2.1 \times 10^8 s^{-1}$

Table 7: Product Ratios and Isomerization Rate Constants

T(k)[a]	[62]$_{avc}$[b] (M)	[56]$_{init}$[c] (M)	[63b]/[63a][d]	Mean[e]	$k_c=0.2k_d$[f] ($\times 10^{-9}$)	k_i, s^{-1} [g]
303	0.153	0.0113	0.940 0.990 1.01	0.980±0.036	1.80	2.70×10^{8}
323	0.149	0.0113	1.69 1.77 1.76	1.74±0.04	2.48	6.43×10^{8}
343	0.145	0.00915	2.75 2.97 2.91	2.88±0.11	3.32	1.42×10^{9}
362	0.145	0.00915	4.37 4.59 4.47	4.48±0.11	4.24	2.75×10^{9}

a) ± 0.2°.
b) Calculated from the initial concentration, assuming that one mole of 56 leads to consumption of two moles of 62. Corrected for solvent expansion.
c) $[56]_{final}=0$.
d) Ratio determined by gas chromatography. Each number represents a separate run and is the average value for at least three injections. The detector responses for the isomers was assumed to be equal.
e) Errors are standard deviations.
f) Diffusion controlled rate constants are taken from Table 5.
g) k_i is calculated using eq. 60.

At this point it is very important to recall the low temperature epr data by Ingold *et al.*[71] The reported Arrhenius expression for the isomerization rate constant was

$$\log (k_i/s^{-1}) = (12.48 \pm 0.85) - (\frac{5.94 \pm 0.57}{\theta})$$

That equation is incorrect because of an arithmetic error. Recalculation of the rate constants from the original experimental data gave the corrected Arrhenius expression as,

$$\log (k_i/s^{-1}) = 11.34 - \frac{5.94}{\theta}$$

A correlation coefficient of 0.85 for this low temperature Arrhenius expression is not unexpected for the inherently difficult esr experiment.

The rate constant calculated from the above expression is $k_i^{25°C} = 9.2 \times 10^6 s^{-1}$. This value is about 20 times less than our own. It implies that the extrapolation from the low temperature results to room temperature leads to large errors.

As has been pointed out at the beginning of this section, it is not only important to determine the rate constant for this very useful radical 'clock' at or near room temperature, but also to establish an Arrhenius expression including experimental values for k_i over a wider range of temperatures. One way of getting around this is to use Ingold's experimental values[71] for the low temperatures (128-153K) and our new rate constant values for the higher temperatures (303-362K). This creates a problem

as to which equation is to be used at temperatures between 153 and 303K. A very reasonable and satisfactory solution is to derive a new Arrhenius expression, making use of all the experimental data from the low temperature esr work (Table 8) and our own data at higher temperatures (Table 7).

The least squares treatment of the combined data gives

$$\log (ki/s^{-1}) = (13.93 \pm 0.37) - \left(\frac{7.59 \pm 0.12}{\theta}\right)$$

The increased error in the log A term reflects the uncertainty in adjusting measured k_d values to k_c. Although a factor of 5 was used ($k_c=0.2k_d$), the range of factors was estimated to be 5 ± 2 and the error in log A is therefore log 7 - log 3 = 0.37. Considering also the experimental errors, it is meaningless to emphasize more significant figures. Therefore, the new Arrhenius expression for the rate constant for isomerization of cyclopropylcarbinyl radical can be expressed as

$$\log (k_i/s^{-1}) = (13.9 \pm 0.4) - (7.6 \pm .1)/\theta$$

The rate constant at room temperature comes to $k_i^{25°C} = 2.1 \times 10^8 s^{-1}$.

Fig. 1 gives a plot of 1/T vs. $\log(ki/s^{-1})$ at various temperatures. The line which is the best fit for both the low temperature data (Table 8) and the high temperature data (Table 7) are given. Another line which fits the low temperature data alone is also given for comparison, in this figure.

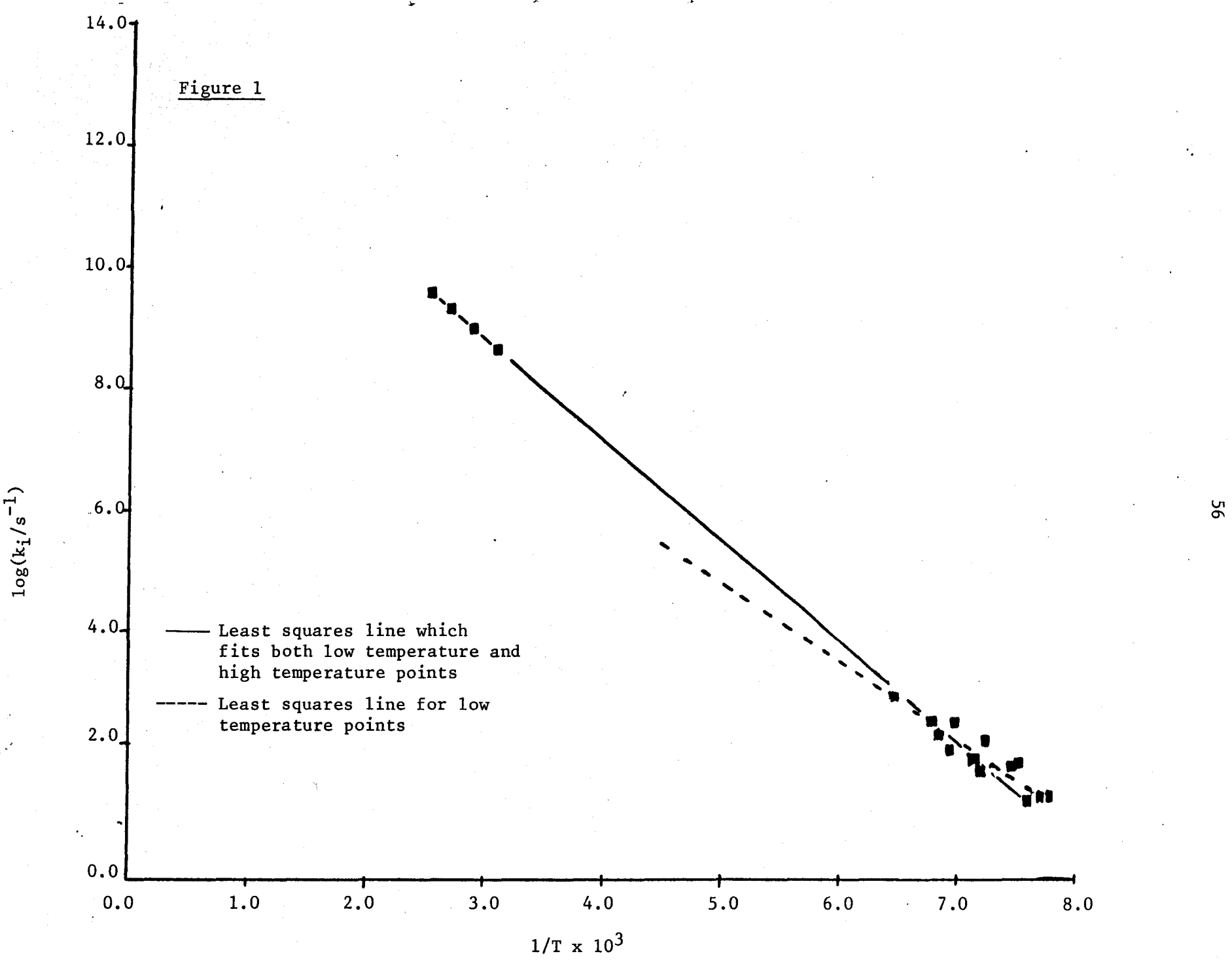


Figure 1
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
log(k_i/s^-1)
1/T x 10^3
Least squares line which fits both low temperature and high temperature points
Least squares line for low temperature points

Table 8: Low Temp. esr data[a]

T(k)	$k_i/2k_t$[b] x 10^7	$2k_t$[c] x 10^{-8}	k_i (s^{-1})
153	18.6	4.89	909
146	9.33	3.43	320
145	5.60	3.26	182
143	3.68	2.92	107
142	11.0	2.76	304
139	3.06	2.33	71.2
138	2.21	2.19	48.5
137	6.70	2.07	130
136	2.30	1.94	44.0
133	2.94	1.61	47.0
132	3.73	1.51	56.3
131	0.90	1.41	12.7
129	1.17	1.24	14.5
128	1.23	1.15	14.2

a) Taken from data given in Table I and II of Ref. 71.

b) Column 4, Table I of Ref. 71.

c) The least squares teatment of data in Table II of ref.71 gives the Arrhenius expression as $\log(2k_t/M^{-1}s^{-1})=11.91-2.25/\sigma$ where $\sigma=2.3RT$. The $2k_t$ values at various temperatures are calculated using this expression.

EXPERIMENTAL SECTION

3.1 General

Proton magnetic resonance (^1H nmr) spectra were recorded on either a Varian EM-390, a Bruker WP-80, or a Bruker WM-250 spectrometer. Tetramethylsilane (TMS) was used as the internal reference in all cases. The solvents used were either hexafluorobenzene or deuterochloroform ($CDCl_3$).

The carbon-13 nmr spectra were recorded either on the Bruker WP-80 instrument or a Bruker WM-250 spectrometer. $CDCl_3$ was used as the solvent in each case.

The mass spectra (high and low resolution) were recorded on a VG7070 mass spectrometer.

The melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

The UV spectra were recorded on a Hewlett Packard 8451A diode array spectrophotometer.

The gas chromatographic analysis were done on a Varian VISTA 6000 instrument equipped with an off-column flash injector and a flame ionization detector (FID). The detector temperature was usually set at 300°C.

Chemicals were purchased from Aldrich Chemical Co., (Milwaukee, Wisconsin) and chromatographic materials were obtained from Chromatographic Specialities (Brockville, Ontario).

The chemicals were used without purification, unless otherwise noted. Solvents were mostly glass-distilled and stored, in some cases, over molecular sieves 4Å.

3.2 Synthesis

i) Cyclopropylmethyl tosylate (52)

To 14.5 g (0.20 mol) of cyclopropyl methanol was added 42 g (0.22 mol) of p-toluene sulfonyl chloride, with ice-cooling and in an atmosphere of dry N_2. To the cold and well-stirred solution was added dry pyridine (48g, 0.6 mol) over a period of one hr. and the resulting solution was kept at 0-5°C for two hr. After overnight storage in the freezer at about -10°C, the reaction mixture was acidified with ice-cold, 10% HCl and extracted three times with ether (50 mL). The combined ether fraction was washed once with 10 mL of saturated NaCl solution in ice-water. The ether layer was then dried over anhydrous magnesium sulfate and the solvent was evaporated to yield crude cyclopropylmethyl tosylate (31 g, 68.5%).

ii) Cyclopropylmethyl hydrazine (53)

Cyclopropylmethyl tosylate (11.3 g, 0.05 mol) was added during one hr. to a stirring, ice-cold solution of hydrazine hydrate (50 g, 1 mol) in ethanol (25 mL). The temperature was then allowed to rise to 20° where it was kept for two hr. before it was raised to 40° and kept at that temperature for two hours. The solution was allowed to stand overnight at room temperature before the bulk of the ethanol was taken off with a rotary evaporator. Continuous extraction of the residual liquid with ether for three days, drying of the ether extract with $MgSO_4$, and evaporation of the solvent yielded crude cyclopropylmethyl hydrazine (4.0 g, 92%) as a syrupy liquid which was used directly for the next step.

iii) Cyclopropylmethyl hydrazone of acetone (54)

To crude cyclopropylmethyl hydrazine (4.0g, 0.046 mol) in anhydrous benzene (20 g) was added, dropwise and with stirring, 10 g of acetone in 15 min. The resulting mixture was shaken at room temperature in an atmosphere of N_2 for one hr. before the temperature was raised to the reflux temperature for another hour. The mixture was cooled and dried over $MgSO_4$. It was filtered, the drying agent was washed with benzene, and the combined benzene filtrate was dried again over $MgSO_4$. Further filtration and evaporation of the solvent left crude hydrazone (2.2 g) as a colourless viscous liquid which was fractionally distilled. Acetone cyclopropylmethyl hydrazone (1.6 g, 28%) boiling at 42-43°C (0.5 Torr) was collected in a small round bottomed flask and was kept glass-stoppered in the fridge, after the air had been flushed out with nitrogen. Spectral data are given in Table 3.

iv) Cyclopropylmethyl[1-hydroperoxy-1-methylethyl]diazene (55)

Acetone cyclopropylmethyl hydrazone (0.5 g, 4.0 mmol) in dry petroleum ether (20 mL, b.p. 40-60°C), cooled in ice and stirred, was exposed to oxygen in a gas system fitted with a gas burette and a mercury manometer. When the uptake of oxygen ceased, the completion of reaction was checked by taking the NMR spectrum of an aliquot, freed from solvent. The two methyl singlets for the hydrazone had completely disappeared. The entire solution was stored in the freezer at -30°C. The purity of the sample, checked by iodometric titration, was 99.9%. Spectral data are given in Table 3.

v) Cyclopropylmethyl[1-hydroxy-1-methylethyl]diazene (56)

An aliquot containing 2.4 mmol of the above azohydroperoxide (55) in petroleum ether was added slowly to a solution of triphenyl phosphine (0.70 g, 2.7 mmol) in 12 mL of petroleum ether, cooled to 0-5°C in ice-water. The flask was then kept at ca -5°C overnight, and the precipitated Ph_3PO was filtered off. The filtrate was evaporated at 10-15°C with a rotary evaporator and the crude residue was subjected to bulb-to-bulb distillation under high vacuum, from a bulb at room temperature to a receiver in liquid nitrogen. The first fraction was the petroleum ether. The second fraction distilling at 10^{-2} torr was collected as a colourless oil (0.23 g, 67%). The spectral data are given in Table 3.

vi) N-Benzylphthalimide (58)

A method similar to that given in the literature[124] was used for the synthesis of 58.

Phthalimide (147 g, 1.0 mol) and anhydrous K_2CO_3 (88 g, 0.6 mol) were ground well in a mortar and the mixture was added to benzyl chloride (253 g, 2 mol) in a 2 litre round bottom flask. The mixture was refluxed for four hours in an oil bath at 190-200°C, after which the excess benzyl chloride was removed by steam distillation. On cooling, the whole solution solidified. The solid was broken into pieces, filtered, washed several times with water until free from carbonate, washed with 200 mL of 60% ethanol and dried. The crude product weighed 180 g (75%), m.p.

100-105°C. About 100 g of this material was used for recrystallization from glacial acetic acid, which gave 70 g. of white crystalline solid m.p. 108-111°C. A second recrystallization from the same solvent yielded 52 g. of the N-benzylphthalimide which was dried under high vacuum (0.2 torr) at 40°C. The melting point of this material was 114-115°C (lit.[124] 116°C).

vii) N-Benzyl-1,1,3,3-tetramethylisoindoline (59)

A slight modification of a procedure reported by Solomon et. al.[114] was used.

A solution of methyl Grignard reagent was prepared from methyl iodide (170 g, 1.2 mol) and magnesium turnings (30.5 g, 1.25 mol) in dry ether (600 mL), under N_2 atmosphere. The solution was concentrated by slow distillation of ether under N_2, until the internal temperature rose to 80°C. About 400 mL of ether had been distilled out. The solution was cooled to 60°C, and 200 mL of toluene was added to it. With vigorous stirring, a solution of N-benzyl phthalimide (47.5 gm, 0.2 mol) in 300 mL of toluene was added to the solution at such a rate as to maintain a temperature of 60-65°C. When the addition was complete, the solvent was distilled slowly from the mixture until the temperature reached 108-111°C. The solution was kept refluxing at this temperature for 14 hrs. It was then concentrated to about 200 mL by further solvent distillation, 300 mL of light petroleum ether was added, and the resulting slurry was filtered through

Celite. The residue was washed with petroleum ether (4 x 100 mL). The combined filtrate, initially yellow in colour, was left open in a wide mouthed filter flask and kept stirring for 2 hr. During this time the solution turned purple in colour and a fluffy purple-coloured material was precipitated. It was kept stirring for one more hour and the solution was filtered through Celite again, when a pale yellow solution was obtained. The solution was concentrated on a rotary evaporator, during which time the solution turned purple-brown and finally a thick, brown liquid was obtained (30 g). The residue was dissolved in a minimum quantity of petroleum ether and transferred onto a short column (6") of basic alumina (60 gm) of activity 1, and the column was eluted with petroleum ether. The very pale yellow solution obtained on evaporation gave 22 g (42%) of a pale yellow solid, which on analysis by gc gave two peaks, one at retention time 17.9 min (81.5%) and another at 19.1 min (18.5%), which were later identified as 59 and 60, respectively. Recrystallisation of this sample once from methanol gave a white crystalline solid, which by gc analysis was found to contain ca 3% of 60 and ca 97% of 59. A second recrystallisation from methanol gave 59 (6.2 g, m.p. 62-62.5°C), which was found to be 99.8% pure by gc analysis. Concentration of the mother liquor gave another crop of white crystals (5.1 g), which was found to be 99% pure by gc analysis. The spectral data matched with those reported[114].

viii) 1,1,3,3-Tetramethylisoindoline (61)

A solution of N-benzyl isoindoline 59 (5 g, 18.9 mmol) in glacial acetic acid (100 mL) was taken in a hydrogenation bottle, 1 g of Pd/C was added to it and the solution was kept for hydrogenation at 30 lb/in^2, for four hours. The solution was filtered and the solvents were distilled off under reduced pressure, at about 30-40°C. About 4 g of a pale yellow liquid was left behind. Crystallization, induced by blowing N_2 gas onto the surface while cooling, gave colorless flaky crystals of 61 (crude). The crystals were dissolved in 20 ml of water and the solution was made alkaline (pH 9) with 10% NaOH. The organic materials were extracted with ether (3 x 50 ml). The combined organic layer was dried over anhydrous $MgSO_4$ (2 hr.), filtered and the filtrate was evaporated to give 61 as colourless crystals (3.1 g, 94%). Gc analysis showed that it was 99% pure; m.p. 35-37°C, (lit.[114] 36-38°C from MeOH).

ix) 1,1,3,3-Tetramethylisoindolin-2-yloxyl (62)

A solution of 1,1,3,3-tetramethylisoindoline (3 g, 17.1 mmol) was prepared in methanol (30 mL) and acetonitrile (2.4 mL). Sodium bicarbonate (1.2 g, 14.8 mmol), sodium tungstate (0.18 g, 0.55 mmol), and 30% aqueous hydrogen peroxide (7 ml, 62 mmol) were added to it. The resulting mixture was kept stirring at room temperature and progress of the reaction was monitored by gc. The

solution, stirred for 36 hr. was found to contain the final product 62 in more than 99% yield by gc analysis. The reaction mixture was diluted with 20 mL of distilled water and the organic materials were extracted with light petroleum ether (3 x 75 ml). The combined extract was dried over $MgSO_4$ (5g, 6 hrs.), it was then filtered and the solvent was evaporated. Product 62 was obtained as yellow, spongy, needle-shaped crystals (3.2g, 97%). Recrystallisation from light petroleum ether gave long needle-shaped crystals,m.p. 127-128°C. The compound was found to be 99.8% pure by gc analysis. The spectral data were identical with those reported.[114]

3.3 Iodometric Titration

The purity of α-hydroperoxy diazene (55) was determined by iodometric titration.

A sample of 55 was freed from petroleum ether (solvent) by blowing N_2 through the solution at 0-5°C. A small amount of 55 (14.45 mg, 9.15×10^{-5} mol) was accurately weighed into an iodine-flask. Cold methanol (5 ml) was added into it followed by a small piece of Dry Ice, to expel oxygen. Freshly prepared saturated KI solution (2 mL) and glacial acetic acid (10 mL) containing $FeCl_3$ (ca 0.003%) were added, and the flask was kept stoppered, in the dark, for 10 min. The iodine liberated was diluted with 25mL of water and was titrated using 0.01 M $Na_2S_2O_3$ solution to the starch end point. From the volume of $Na_2S_2O_3$ used (18.2 ml - 18.3 ml), the purity of the hydroperoxide was calculated (>99%).

3.4 Thermolysis of 56 in presence of 62

Stock solutions of each of 56 and 62 were prepared in volumetric flasks at room temperature. Aliquots of these stock solutions were measured, using calibrated syringes, into short tubes which were then sealed after three freeze-pump-thaw cycles under vacuum. Thermolyses were carried out by immersing the tubes in oil baths thermostated to ± 0.2°C and the temperatures were measured with calibrated thermometers. At 30°C, complete decomposition of 56 took about 30 days. Tubes kept at 89°C were left for 3 days. These reaction times, determined by running parallel reactions with much lower concentrations of 62 in nmr tubes, with periodic monitoring, were more than sufficient for total decomposition of 56.

3.5 Analysis of Thermolysis Products

The products were analyzed on a glass column (8' x 1/8") packed with OV-17 (3%) on Chromosorb P-AW, 100/120 mesh). The column temperature was held at 35°C for 15 min. before it was programmed at 5°/min. to a maximum temperature of 220°C, for those analysis which included the assay for acetone (quantitative). The order of elution and retention times of the products of reaction, when the carrier gas (N_2) flow was 10 mL/min, were acetone (3.3 min), solvent (C_6F_6, 5.6 min), 62 (38.4 min), 63b (43.1 min.), 63a (45.4 min.). The data in Table 7 were obtained using a different temperature programme - the initial column temperature (100°C) was

held for 2 min. before it was programmed to 220°C at the rate of 5°C/min. At a flow rate of 10 mL/min for the carrier gas, the order of elution (retention times) was: acetone and hexafluorobenzene (2 min.), 62 (14.5 min.), 63b (17.1 min.), and 63a (18.7 min.).

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