Free-Radical Cyclizations

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It has long been known that free radicals may add to olefinic double bonds. The alkyl radical so formed may undergo further reactions such as abstraction of hydrogen or halogen. The "abnormal," peroxide-catalyzed addition of HBr to olefins is an early example of this type of phenomenon.

Radical addition to carbon–carbon double bonds can also occur *intramolecularly*. Such reactions lead to cyclization products and are of interest both in synthesis and for the mechanistic problems they pose.

In the earlier part of this Account, the question of the size of the ring (five or six membered) formed from a δ-unsaturated alkyl radical is discussed. A number of factors, thermodynamic or kinetic, have been recognized, the interplay of which leads to a variety of results. Knowledge of these factors allows the selection of experimental conditions favoring the formation of either cyclopentane or cyclohexane rings from the same precursor.

Later, a number of applications are presented. Carbon free radicals produced by the addition of benzoyloxy radicals to double bonds have been cyclized, leading to mono- or polycyclic compounds. This constitutes "oxidative cyclization" of the substrate. Cationic and free-radical cyclizations of the same compounds are compared, and the use of cyclization as a diagnostic tool in mechanistic studies is considered.
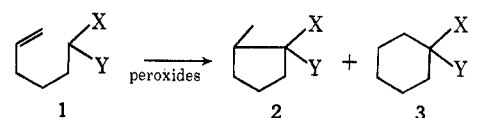
Formation of Cyclopentane or Cyclohexane Rings

When a free-radical center is generated in the δ position to a double bond, cyclization occurs very readily. Early examples describe the addition of carbon tetrachloride to aliphatic 1,6-diene systems leading to carbocyclic rings. In our early work[1] we generated free radicals by hydrogen abstraction from suitable unsaturated α-cyano esters and observed the formation of cyclohexane rings.

In the pyrolysis of 6-heptenoyl peroxide, however,[2] Lamb and his colleagues showed the main product to be methylcyclopentane. This result was surprising. On one hand, free-radical additions are well known to occur preferentially toward the unsubstituted end of a mono-substituted olefin; this is the "Kharasch" or "anti-Markovnikov" way of addition. On the other hand, cyclohexane ring formation is thermodynamically favored over cyclopentane ring formation. The formation of cyclohexane would therefore have been expected. In a number of other cases where primary δ-ethylenic carbon free radicals were produced by various

reactions, methylcyclopentane derivatives were also obtained almost exclusively (for a review see ref 3). Very recently, Kochi and Krusic[4] were able to observe at low temperature the epr spectrum of the primary hexenyl radical and its cyclization to the cyclopentylmethyl isomer.

The large difference in nature between primary alkyl radicals and tertiary resonance-stabilized ones made it necessary to investigate the behavior of a series of gradually substituted compounds. Table I shows the com-

Table I

Cyclization of 1-Substituted 5-Hexenyl Radicals

X	Y	2	3
H	H	100	0
H	CN	100	0
H	COCH$_3$	72	28
H	COOC$_2$H$_5$	56	44
COOC$_2$H$_5$	COOC$_2$H$_5$	70	30
COCH$_3$	COOC$_2$H$_5$	50	50
CN	COOC$_2$H$_5$	16	84
CN	COOC$_2$H$_5$ (ω-methyl substituted)	0	100

positions of the mixtures of isomers obtained when compounds of structure **1** were heated with benzoyl peroxide or di-*tert*-butyl peroxide in boiling cyclohexane.[5] As shown, as the free-radical carbon atom is gradually substituted, the mixture of products changes from pure cyclopentane to nearly pure cyclohexane derivatives. When the double bond was methyl substituted on the terminal carbon atom, no cyclopentane compound could be detected.

More information was obtained when the influence of temperature was investigated. In order to carry out the free-radical cyclization at a lower temperature, the reaction was initiated with a photoexcited ketone. From the cyano ester **1**, X = CN, Y = COOEt, the proportion of five-membered isomer formed was greater at the lower temperature.[6] The cyclopentylmethyl radical seems, however, to be less stable than its cyclohexyl isomer owing to ring strain and the eclipsing of substituents. Primary free radicals have been generally considered as less stable than secondary ones.[6a]

(1) M. Julia, *Rec. Chem. Progr.*, **25**, 1 (1964).
(2) R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Amer. Chem. Soc.*, **85**, 3483 (1963).

(3) M. Julia, *Pure Appl. Chem.*, **15**, 167 (1967).
(4) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **91**, 3940 (1969).
(5) M. Julia and M. Maumy, *Bull. Soc. Chim. Fr.*, 2415 (1969).
(6) (a) M. Julia and M. Maumy, *ibid.*, 2427 (1969); (b) see, however, C. Ruechardt, *Angew. Chem.*, **21**, 845 (1970); *Angew. Chem. Int. Ed. Engl.*, **9**, 830 (1970).
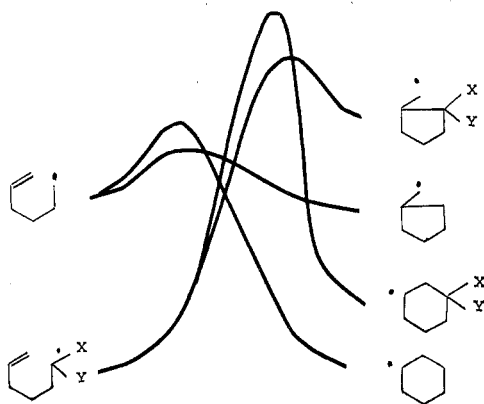
Figure 1. Suggested reaction paths for cyclization with stabilizing substituents X and Y.

With regard to the possibility of thermodynamic control, it had been shown[2] in the case of the primary hexenyl radical that the cyclization step is not reversible, but the situation might be different with substituted, resonance-stabilized radicals. In Figure 1, cyclized radicals are represented as of higher energy when they are substituted, whereas in the open-chain radicals the opposite is indicated. This suggests that the reverse reaction may be possible under the experimental conditions used. It has recently been shown that the addition of the ethyl cyanoacetate radical to cinnamonitrile is reversible at 160°.[7]

Indirect evidence was obtained by adding good hydrogen-donating solvents which might trap the rapidly formed cyclopentane radicals before equilibration to the more stable cyclohexane isomers. It was indeed found that addition of toluene or cumene increased the proportion of five-membered rings.
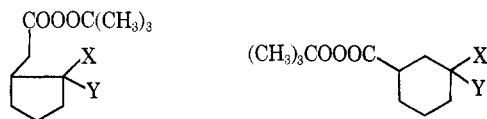
4, X = CN; Y = COOC_2H_5
6, XY = O

5, X = CN; Y = COOC_2H_5
7, XY = O

More direct evidence was obtained when isomeric pairs of substituted peresters (**4** and **5**, and **6** and **7**) were heated in boiling cyclohexane to generate the isomeric radicals in the same environment. The cyano carbethoxy peresters **4** and **5** gave clear-cut results (Table II), since both isomers gave almost exactly the same mixture of products and this mixture was identical with that obtained by cyclization. The isomerization of these radicals is therefore very easy indeed. The keto peresters **6** and **7** underwent only partial isomerization. The formation of six-membered rings from the compounds mentioned at the bottom of Table I can therefore be explained by equilibration of the more rapidly formed cyclopentane radical to the more stable cyclohexane isomer before the hydrogen-abstraction step. The results obtained with good hydrogen-donating solvents are readily explained by trapping of the cyclopentane radical.

(7) R. L. Huang, C. O. Ong, and S. H. Ong, *J. Chem. Soc. C*, 2217 (1968).

Table II
Products Obtained from Cyclization, and from Precursors 4, 5, 6, and 7

Precursor	8 Yield, %	9 Yield, %
4	20	80
5	15	85
Cyclization	16	84
6	30	70
7	0	100
Cyclization	0	100

It seems rather difficult to explain why the hexenyl radicals should add more rapidly to the substituted end of the double bond rather than to the other end, the "terminal one." It is clear that the stability of the radical that is formed in the addition step is not the deciding factor. It has been suggested[8] that more conformations are available for cyclopentane than for cyclohexane cyclization. This might contribute to the answer. A stereochemical reason might also be operative. Cyclohexane formation should be hindered by a bad interaction between a hydrogen atom on C-2 and the cis hydrogen on C-6 in the chair-form transition state leading to the cyclohexane ring.[9] This interaction might explain why dimethylation of C-2 prevents cyclization.

It has also been suggested[10] that interaction of the unpaired electron with the lowest unoccupied orbital of the unsaturated system is the important factor in free-radical addition reactions. Bond formation should therefore occur at that end of the double bond more readily approached vertically by the attacking radical.

Now, the reversibility of the cyclization step should be favored by the stabilization of the aliphatic radical and the destabilization of the cyclized ones. It would be interesting to know more about the relative importance of these two factors. Free radicals are known to be stabilized by ketone, carboxylate, or cyano groups. The "stabilization energy" has been estimated to be less than 4 kcal/mole for a free radical α to a carbonyl group.[11] The cyano group is much more efficient.[12] Other groups such as phenyl or vinyl are known to stabilize adjacent free radicals; although estimates of their resonance energies have been going down steadily during the last few years, they still are of the order of 10 kcal/mole.[13]

In order to check on this, another series of isomeric radicals, in which the ethylenic isomer is stabilized by

(8) B. Capon and C. W. Rees, *Annu. Rep. Progr. Chem.*, **61**, 261 (1964).

(9) M. Julia and M. Maumy, *Bull. Soc. Chim. Fr.*, 1603 (1968).

(10) D. L. Struble, A. L. J. Beckwith, and G. E. Gream, *Tetrahedron Lett.*, 3701 (1968).

(11) S. W. Benson, K. W. Egger, and D. M. Golden, *J. Amer. Chem. Soc.*, **87**, 468 (1965).

(12) M. Hunt, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 5074 (1965).

(13) S. W. Benson, D. M. Golden, and A. S. Rodgers, *J. Amer. Chem. Soc.*, **88**, 656, 3196, 4725 (1966).

Table III
Products from Pyrolysis Reactions

Substrate	Solvent	Temp, °C	14 (Et)	15 (CPt)	16 (CPc)	17 (CH)
14a	Cyclohexane[a]	80	26	10	4	60[c]
	Cyclohexane[b]	140	1	6	3	90
	Decalin[b]	140	2	11	3	84
Peresters						
14b	Decalin	140	40[d]	3	2	55
15b	Decalin	140	5	59	2	34
16b	Decalin	140	7	1.5	0.5	91
17b	Decalin	140	3	3	3	91
15b	Benzene	80 (140)	35 (51)	9 (9)	4 (3)	52 (38)
16b			26 (84)	6 (6)	3	65 (10)
17b			15 (58)	1 (2)	(2)	84 (38)

[a] Benzoyl peroxide catalyst. [b] Di-*tert*-butyl peroxide catalyst. [c] Total yield 50–60%. [d] The perester used contained some hydrocarbon **14a** formed by ready decarboxylation of the parent acid.

a phenyl group, was investigated. The experimental approach was to treat the ethylenic hydrocarbon **10a** with peroxides and alternatively to pyrolyze the appropriate isomeric *tert*-butyl peresters **10b**, **11tb**, **11cb**, and **12b** under the same conditions and analyze the mixture for the isomeric hydrocarbons: phenylcyclohexane (**12a**), *trans*- and *cis*-1-methyl-2-phenylcyclopentane (**11ta** and **11ca**, respectively), and **13**.[14]
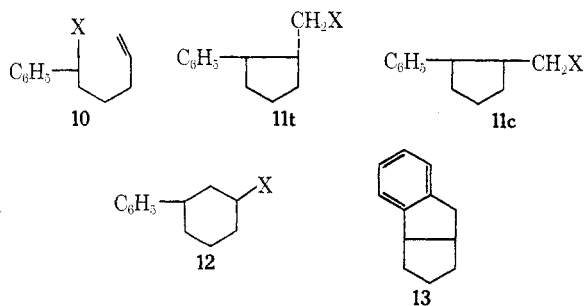
a, X = H; b, X = COOO-*tert*-C₄H₉

With the ethylenic hydrocarbon, cyclopentane formation is favored by a factor of 10 over cyclohexane, in agreement with previous results.[15]

The pyrolysis of the isomeric peresters was carried out in two different solvents, cyclohexane and benzene, differing widely in their hydrogen-donating abilities, and at two temperatures: 80 and 140°. The cyclohexyl radical does not rearrange. The *cis*-2-phenylcyclopentylmethyl radical rearranges much more extensively than the trans isomer and both rearrange more extensively in benzene than in cyclohexane. The results are, however, obscured by the formation of large amounts of tricyclic compound **13** that obviously arises by efficient intramolecular aromatic alkylation in the *cis*-2-phenylcyclopentyl radical.

With the phenyl cyano derivatives shown in Table III, the same experiments as before were carried out. The peroxide-initiated cyclization gives a ratio of cyclopentane over cyclohexane derivatives [(**15a** + **16a**): **17a**] of 1:4 at 80° and 1:6 to 1:10 at 140°. Whereas the trans cyclopentane perester **15b** rearranges to the
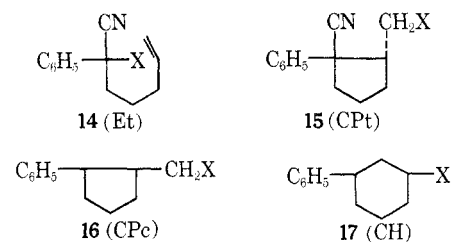
a, X = H; b, X = COOO-*tert*-C₄H₉

extent of 40% in decalin, the cis isomer **16b** does so almost entirely, and even the cyclohexane isomer **17b** rearranges to the extent of roughly 10%.

In benzene the remarkable feature is the formation of large amounts of ethylenic derivative **14a**; in fact, more of this than of the cyclohexyl isomer. At 140°, therefore, the presence of the cyano group changes the result from no isomerization to 60% opening.

Small differences in the reaction mixtures had been found when initiating the cyclization with ketone triplets. This had been investigated in greater detail with the same substituted benzyl cyanide **14a** (Table IV).[14] A variety of ketones have been used. Fair to good yields of cyclized products have been obtained only at higher temperatures, so the comparisons were made at 140° in decalin. Without any ketone present the irradiation with unfiltered light did lead to cyclization with a CP/CH ratio of 0.3. A Pyrex filter prevented this cyclization, so a filter was used to compare the excited ketones.

It is at first sight evident that the ketones used have a marked influence on the ratio of products formed, which varies from 0.14 to 2.9. Therefore, from a preparative point of view this is a third method (together with temperature and solvent) to guide the cyclization toward five- or six-membered-ring formation.

The results of the cyclization with the ketones and the unfiltered light are given in Table IV in parentheses. Remarkably enough, it appears that this is not a superposition of the photoreaction and the ketone-triplet-initiated one since the results lie outside the interval of the first two values. It is not easy to explain these results. Several hypotheses are being investigated.

(14) R. Perrey, Thesis, University of Paris, 1969.
(15) H. Pines, W. C. Sih, and D. B. Rosenfeld, *J. Org. Chem.*, **31**, 2255 (1966).

Table IV
Cyclization of 2-Phenyl-6-heptenenitrile (14a) Initiated by Photoexcited Ketones[a]

Initiator	Pyrex filter	14a	15a	16a	17a	(15a + 16a)/17a	Triplet energy[b]
		42	10	4	44	0.32	
	+	100	0	0	0		
2-Octanone	+ (−)	86 (32)	2 (10)	1 (3)	11 (55)	0.27 (0.23)	74
Propiophenone	+ (−)	18 (12)	35 (58)	5 (4)	42 (26)	0.95 (2.4)	74.6
p-Methoxyacetophenone	+ (−)	22 (12)	26 (45)	4 (3)	48 (40)	0.62 (1.2)	71.5
2-Acetonaphthone	+ (−)	74 (75)	1 (4)	1 (1)	14 (20)	0.14 (0.25)	59.3
Benzophenone	+ (−)	32 (30)	31 (40)	(3)	37 (27)	0.84 (1.6)	69.2
Xanthone	+ (−)	42 (29)	40 (62)	3 (2)	15 (7)	2.9 (9.1)	74.2

[a] Conditions: decalin solvent; 140°; mercury high-pressure lamp, Hanau Q 81.   [b] Kilocalories per mole.

Another problem was to explain why a *trans*-decalin derivative, **20**, had been isolated in the double cyclization of ethyl 2-cyano-6,10-undecadienoate (**18**),[16] whereas in the formation of the second ring no substituents are present on the free radical **19**, and at first sight this should have given a hydrindan derivative. The only peculiar feature of this radical is that it is a cyclohexyl one. Examination of models shows that axial attack on the double bond is hindered by interaction with the axial substituent (if any) on C-4 and C-6, whereas equatorial attack will be hindered by torsional strain when the hydrogen on C-2 has to pass the equatorial substituent on C-1. A difference with simple hexenyl radicals, however, lies in the rotation of the radical carbon C-2 around the C-1–C-2 bond being now prevented by the cyclohexane ring. This should make the cyclopentane ring formation more difficult since it should demand more coplanarity than the cyclohexane cyclization.

The desired starting material could be prepared easily, thanks to free-radical chemistry. Decalin hydroperoxide **21** on treatment with copper salts led to 2-butenylcyclohexanone (**22**) which was reduced with borohydride to a mixture of alcohols **23**. It has been shown in several cases that cyclohexyl radicals "epimerize" very rapidly, so the mixture of bromides **24** was used. Treatment with tin hydride[17] indeed gave *trans*-decalin, together with 1-methylhydrindan.[18]

The substitution pattern on the double bond also influences the size of the ring. With the cyano carbethoxy radical **25a** a methyl group on the ethylenic carbon atom C-5 leads to formation of the cyclohexane isomer.[4] This can be ascribed to the eclipsing of substituents in the transition state leading to cyclopentane formation, or in the cyclopentylmethyl radical itself. With two methyl groups cis to each other (**25b**) cyclohexane formation again prevails, with the two methyl groups 50% cis and 50% trans in the cyclized cyano ester.[18]

The primary radicals formed in the tin hydride[17] reduction of the corresponding bromides behaved differently: with a monomethylated double bond (**25c**) a mixture of hydrocarbons was obtained in which the ratio of methylcyclohexane:1,1-dimethylcyclopentane was
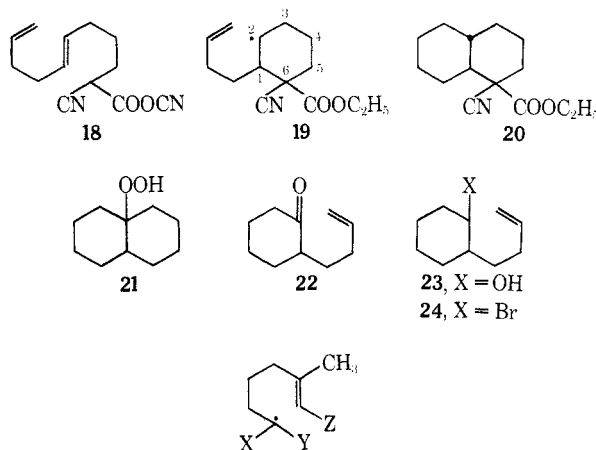
25a, X = COOC₂H₅; Y = CN; Z = H
b, X = COOC₂H₅; Y = CN; Z = CH₃
c, X = Y = H; Z = H
d, XY = H; Z = CH₃
e, XY = CH₃; Z = CH₂OCOCH₃
or isoprenologous radical

about 1.7, whereas the unsubstituted 5-hexenyl radical gave mainly methylcyclopentane;[19a] with the dimethylated double bond (**25d**) this C6:C5 ratio was about 8.[19b] When the double bond is engaged in a cyclohexene ring, reduction of the primary bromide led to a mixture of spiro-C₅ (55%) and decalin ring systems (45%).[10] Tertiary alkyl radicals **25e** with trisubstituted double bonds also led to cyclohexane rings (see below).

Applications, Oxidative Cyclizations, and Mechanistic Studies

Some examples of synthesis of mono- or polycyclic compounds through free-radical cyclization can be found in published reviews.[1,3] Our interest has concentrated lately on oxidative cyclizations.

The problem of oxidative cyclizations of polyolefins, particularly polyisoprenoids, has received considerable attention in the recent past; this culminated in the biosynthesis of lanosterol from squalene being elucidated; the natural process involves epoxidation of a terminal double bond in squalene followed by quasi-acid catalyzed cyclization of the epoxide. Studies such as the
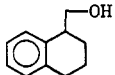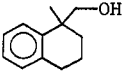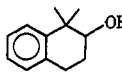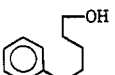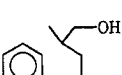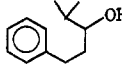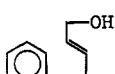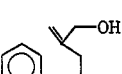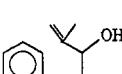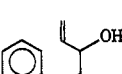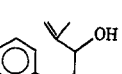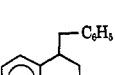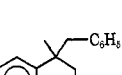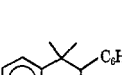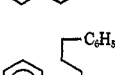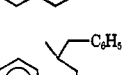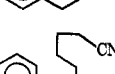
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(17) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968); *Synthesis*, **2**, 499 (1970).

(18) B. Jacquet, unpublished results.

(19) (a) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *J. Amer. Chem. Soc.*, **88**, 5361 (1966); (b) C. Descoins and D. Uguen, unpublished results.

Table V
Reactions of Benzoyl Peroxide in Acetonitrile with γ- or β-Phenylalkenes

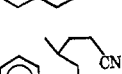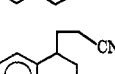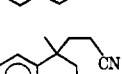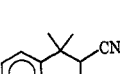| Product (γ-phenylalkene)	Yield, $\%^{a,b}$	Product (β-methyl)	Yield, $\%^{a,b}$	Product (trisubstituted)	Yield, $\%^{a,b}$	Yield, $\%^{a,c}$
1-hydroxytetralin deriv.	22 (7)		42 (34)		70	51 (48)
hydroxy deriv.	6 (<1)		4 (<1)		4	1.5 (<1)
hydroxy deriv.	2 (20)		<2 (18)		1	≅1 (4.5)
hydroxy deriv.	12 (12)		4 (4)			
C_6H_5 deriv.	22		16		1.5	1.5
C_6H_5 deriv.	7.5		6			
CN deriv.	2		1.5			
CN deriv.	6		4		2	16
Total yield of identified compounds, %	**79.5**		**77.5**		**78.5**	

^{a} Yield of each product obtained (if necessary after saponification). In parentheses are the yields of the same reactions performed in the presence of copper salts. ^{b} Solvent:olefin:peroxide = 80:10:1. ^{c} Solvent:olefin:peroxide = 80:1:1.

cyclization of the dienic cyanoester **18**[16] or the reaction of squalene with Fenton's reagent[20] were initiated at least in part to investigate the possibilities of free-radical processes in this respect.

It has recently become increasingly clear[21] that acyloxy radicals are prone to addition to double bond. Indeed the rate of addition of $C_6H_5COO\cdot$ on terminal double bonds has been found to be four to five times that of α-hydrogen abstraction. This appeared interesting since it was a means of linking an oxygen atom to the end carbon atom of a terminal double bond, and anti-Markovnikov hydration is an interesting and important problem. Another reason is that, after addition of C_6H_5-$COO\cdot$ on a double bond, the second carbon atom becomes a free radical and can attack suitably situated double bonds or aromatic rings.

We shall first be concerned with its attack on an aromatic ring. It is now recognized that arylbutyl radicals cyclize easily to tetralin derivatives. Table V shows some results obtained with benzoyl peroxide

and phenylpentenes or -butenes in acetonitrile.[22]

Oxidative cyclization takes place and the yield of hydroxytetralin derivatives increases markedly with substitution of the double bond. This might be a preparative way of synthesis (see below). The increased efficiency of the benzoyloxy radical's addition on the more substituted double bond is confirmed by the ratio of products derived from $C_6H_5COO\cdot$ addition to products derived from $C_6H_5\cdot$ addition, decarboxylation of C_6H_5-$COO\cdot$ competing with its addition. The ratio of benzoyloxy to phenyl addition is roughly 1 for terminal olefins, 2.5 for 2-substituted terminal olefins, and 50 for the trisubstituted one.

The acceleration of the addition of electrophilic free radicals on double bonds by alkyl substituents has been studied previously.[23] The remarkable behavior of various olefins with acetoxy radicals has been discussed.[24]

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Table VI
Reactions of Acyl Peroxides with Cyclohexene and 1-Methylcyclohexene

Reactants		Products	
$(C_6H_5COO)_2$ 1 mole 1 mole	Cyclohexene 7.5 moles 10 moles + toluene (10 moles)	Cyclohexyl benzoate 70% 82%	2-Cyclohexenyl benzoate 13% 12.5%
$(CH_3COO)_2$[24]	Cyclohexene	Cyclohexyl acetate 29%	2-Cyclohexenyl acetate 5%
$(C_6H_5COO)_2$ 1	Cyclohexene + 1-methyl-cyclohexene 5 moles + 5 moles + toluene (10 moles)	Cyclohexyl benzoate 29%	2-Methylcyclohexyl benzoate 59%

The results of Table V show that benzoyloxy radicals efficiently react with trisubstituted double bonds of the isoprenoid type, although substituted double bonds are generally considered rather inert to free-radical addition. With heteroatom radicals, however, polar effects should be expected to be important.

Since the presence of benzene rings has been shown to influence the addition of radicals on double bonds,[25] isolated double bonds were investigated (Table VI). In the presence of good hydrogen donors such as excess olefin the reaction of benzoyl peroxide with cyclohexene gives a good yield of cyclohexyl benzoate together with some unsaturated ester. For comparison are included the results of a related reaction with acetyl peroxide.[24] The competitive experiment with cyclohexene and 1-methylcyclohexene shows that the methyl-substituted olefin is roughly twice as reactive as the unsubstituted one and that this technique amounts to a fair non-Markovnikov hydration.

Remarkable reactions of benzoyl peroxide with trisubstituted double bonds have been described by Breslow[26,27] and his colleagues. Using benzoyl peroxide and copper salts as recommended by Kochi,[28] they were able to bring about oxidative cyclization of geranyl acetate[28] and farnesyl acetate.[27] In the second case stereoselective formation of a *trans*-decalin ring system was observed. The relative yield of acyclic products increased with increasing cupric salt concentration, indicating that oxidation of the radical competes with cyclization. Since copper salts were involved in these reactions and they notoriously influence the course of free-radical reactions (see, for instance, the review by Kochi[29]), we investigated the reaction of benzoyl peroxide alone with the unsymmetrical 1,5-diolefin **30**. The formation of 2,2,3-trimethylcyclopentyl benzoate (**31**) again shows ready reaction of the benzoyloxy radical with the trisubstituted double bond.[30] It also shows the usual
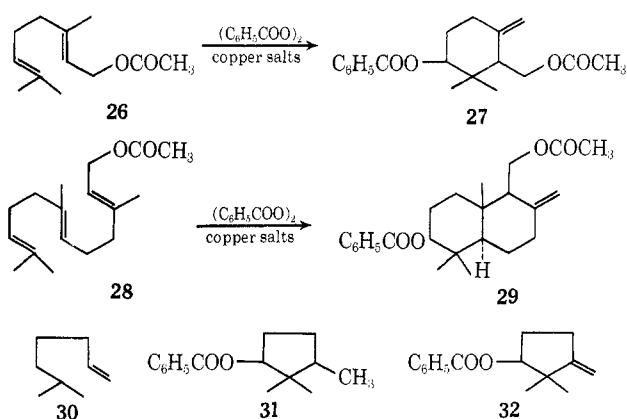
preference for cyclopentane formation displayed by δ-unsaturated alkyl radicals.

In the presence of copper salts, the unsaturated benzoate **32** was obtained. The formation of a five-membered ring is in agreement with the conclusion reached by Breslow: the cyclizing species is a free radical; oxidation by the cupric species occurring only after the cyclization. Formation of six-membered rings from geranyl or farnesyl acetate has therefore nothing to do with the cupric species and will have to be explained, together with the behavior of radicals such as **25d**.

Oxidative cyclization through free-radical reactions could be used in a simple synthesis of oxygenated tricyclic compounds of the diterpene type. Wittig condensation of methylheptenone with phenylpropyl bromide led to isomeric olefins which were separately treated with benzoyl peroxide. Copper salts were excluded since it had been shown[31] that cupric salt oxidation of aliphatic free radicals to olefins efficiently competes with attack of benzene rings[31] (see also Table V).

The trans isomer **33** led to moderate yields of the epimeric (on C-3) tricyclic benzoates of the alcohols **35** and **36** with trans stereochemistry of the decalin system. The tricyclic compounds were easily separated from the other components of the reaction mixture by column chromatography. The cis olefin gave very low yields of the same isomers (Table VII). The stereochemistry was assigned by comparison with reference samples prepared from 1-methyl-2-tetralone.

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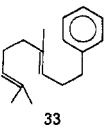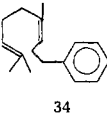(26) R. Breslow, J. T. Groves, and S. S. Olin, *Tetrahedron Lett.*, 4717 (1966).

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Table VII
Oxidative Cyclization of 4,8-Dimethyl-1-phenyl-3,7-nonadiene with Benzoyl Peroxide

Starting material					Nontricyclic alcohols
	35	36			
33	18	2–3	<1	<1	15
34	3	<1	<1	<1	20

Oxidative cyclization of 1,5-dienes has been performed in a completely different manner. It had been shown that the acetoxy-mercuration product **37** of biallyl gave on acid treatment 3-cyclohexenyl acetate (**38**).[32] Using the free-radical technique of mercury–iodine exchange of Winstein and Traylor,[33] we could transform the organomercurial **37** into 3-iodomethylcyclopentyl acetate (**39**) in high yield.[34] 5-Hexenyl carbonium ions are of course well known to give cyclohexane compounds.[35]

The two modes of cyclization, cationic, leading to cyclohexane derivatives, and free radical, leading to the cyclopentane isomers, were again found in the simple 5-hexenylmercuric derivative **40**, which gave cyclohexyl acetate (**41**) in acetic–perchloric acid and iodomethylcyclopentane (**42**) by treatment with iodine in dioxane. This duality of reaction pathways is another means to cyclize an open-chain compound at will into a cyclohexane or cyclopentane derivative.

Similarly lead tetracetate treatment of biallyl gives a mixture of 1,4-diacetoxycyclohexane (**43**) and 3-acetoxymethylcyclopentyl acetate (**44**).[36] This might have been the result of a competition between a free-radical cyclization leading to cyclopentane compounds and a cationic cyclization leading to the cyclohexane product: addition of boron trifluoride to the reaction mixture suppressed the formation of the cyclopentane glycol and led to a mixture of 1,4-diacetoxycyclohexane (**43**) and 3-cyclohexenyl acetate (**38**).[34]

The last application of free-radical cyclization is in the way of using it as a tool in mechanistic studies. So many examples of cyclization of primary 5-hexenyl radicals to cyclopentylmethyl derivatives are now known that this can be used as a means of detecting radicals of this kind as intermediates in organic reactions. This has been done for the reaction of alkyl halides with so-

dium naphthalene,[37] in the reduction of alkyl halides with chromium II salts,[38] or in the oxidation of Grignard derivatives.[39]
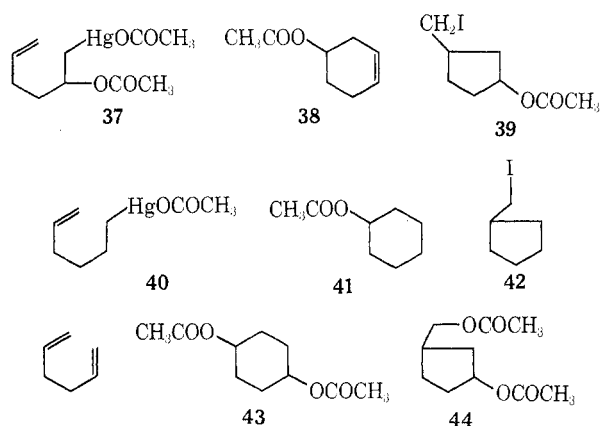
These studies could be made quantitative after Carlsson and Ingold[40] had measured the absolute rate constants of the tin hydride reduction of alkyl halides. Comparison of the rates of formation of open-chain and cyclized reduction products enabled them to determine the rate constants for cyclization of primary hexenyl radicals. They found a value of 10^5 sec^{-1}.

Knowledge of this rate constant allowed, in turn, by a similar competition method determination of the rate constant of the reduction of the primary hexenyl radical by sodium naphthalene.[37a] Many more applications in mechanistic studies can be, now, envisioned.

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