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SOME PROPERTIES OF RADICAL REACTIONS IMPORTANT IN SYNTHESIS

CHEVES WALLING

Department of Chemistry, University of Utah
Salt Lake City, UT 84112, U.S.A.

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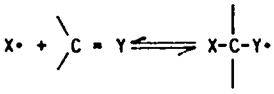
Properties of radical chain reactions are reviewed including propagating steps, lifetimes of chains, and choices of initiators. Structure and reactivity relations in chain-propagation steps and their effects on regio- and stereochemistry are discussed. The utility of redox chains involving transition metal ions is considered along with the importance of radical ions as reaction intermediates.

The current interest in the application of free radical reactions to the synthesis of complicated molecules which this Symposium in Print recognizes is most gratifying to old free radical chemists like myself. However, we can't help wondering why it has taken so long, since the reaction-steps used in todays elegant syntheses (or their close analogs) have been known for many years. While pioneers as D. H. R. Barton and M. Julia have employed them for a long time, most synthetic chemists have avoided radical reactions as messy, unpredictable, unpromising and essentially mysterious. I think there are several reasons for this lack of communication. Radical chemists do not generally study reactions under what might be called synthetic conditions. Radical chain reactions are different and their principles need to be understood if they are to be carried out successfully. In this paper I shall try to summarize some of these principles from a rather practical viewpoint. While what I say should be familiar to other authors in the symposium, (and radical chemists will recognize that I pass over many theoretical niceties) I hope it will be useful to other synthetic chemists who are hovering on the brink. The examples I have picked usually involve simple molecules and are often quite old. Space does not permit any comprehensive coverage of the literature, but for those wishing to pursue these matters further, the most recent comprehensive treatments are by Kochi (1973).[1] and Nonhebel, Tedder, and Walton (1979).[2] There have been numerous more specialized reviews, some of which are cited here and in other papers in this Symposium.

Properties of Chain Reactions. The majority of radical reactions of interest to synthetic chemists are chain processes in which radicals are generated by some initiation process, undergo a series of propagation steps generating fresh radicals, and finally disappear, usually by mutual coupling or disproportionation.

The types of propagation steps of interest in synthesis are really rather few. First, additions to multiple bonds, and their reverse, β-scission



$$X\cdot + \,{>}C=Y \rightleftharpoons X-\underset{|}{\overset{|}{C}}-Y\cdot \qquad (1)$$

Since π bonds are stronger when Y is O or N than when Y is carbon, β-scissions are particularly important in such systems. Second, radical displacements, usually on hydrogen or halogen (which again may be reversible).

$$\mathrm{X\bullet + H\text{-}R \rightleftharpoons X\text{-}H + R\bullet} \qquad (2)$$

Finally, there are "valence expansion" processes with higher row or electron deficient species (e.g. boron) leading to transient intermediates, e.g.[3]

$$\mathrm{RO\bullet + P(OBu)_3 \longleftarrow \overset{\bullet}{ROP}(OBu)_3 \longrightarrow OP(OBu)_3 + R\bullet} \qquad (3)$$

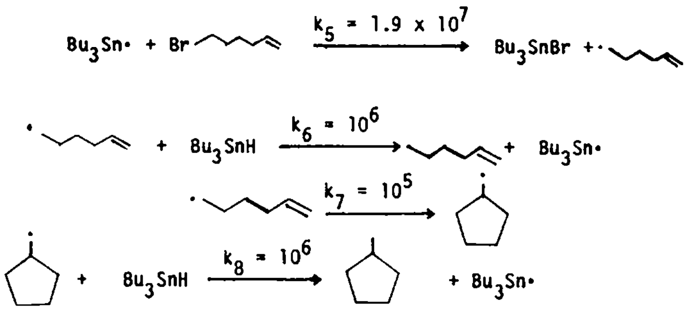
and many overall displacements on polyvalent atoms apparently fall in this class.[4]

The reaction 6-bromo-1-hexene with tributylstannane,[5] a prototype of many useful cyclizations, provides a convenient example of a typical chain process. Where In represents an initiator such as azobisisobutyronitrile (AIBN) which decomposes into initiator radicals, In•, we have

Initiation

$$\mathrm{In \xrightarrow{k_4} 2\ In\bullet \qquad In\bullet + Bu_3SnH \longrightarrow InH + Bu_3Sn\bullet} \qquad (4)$$

Propagation



(5)

(6)

(7)

(8)

Termination

$$\mathrm{2\ Bu_3Sn\bullet \xrightarrow{k_9 \sim 2 \times 10^9} X} \qquad (9)$$

$$\mathrm{Bu_3Sn\bullet + R\bullet \xrightarrow{k_{10} \sim 2 \times 10^9} Y} \qquad (10)$$

$$\mathrm{2\ R\bullet \xrightarrow{k_{11} \sim 2 \times 10^9} Z} \qquad (11)$$

The kinetic rate expression for such a sequence is easily derived.[6] At low stannane concentrations for example it takes the form

$$\mathrm{Rate} = k_8\,[\mathrm{Bu_3SnH}](k_4[\mathrm{In}]/k_{11})^{1/2} \qquad (12)$$

and tells us some useful things: rate is proportional to the square root of the rate of chain initiation, i.e., not very sensitive to initiater concentration. Similarly, the overall activation energy, $E_a = E_4/2 + E_8 - E_{11}/2$. Since E_8 and E_{11} are small, E_a depends chiefly on E_4, the activation energy for initiator decomposition. E_a is usally in the range of 12-18 kcal/mole, while photoinitiated reactions, for which $E_4 \sim 0$, are almost temperature independent in their behavior (there are important exceptions to this, see below). From the equations and rate constants we can further calculate that, for a reaction proceeding at a moderate rate and producing 1 M ℓ of products/hr the radical concentration is $\sim 2.8 \times 10^{-10}$ M. The kinetic chain-length is ~900,000 and the average chain life, from initiation to termination, 0.9 sec. Such a rate would be produced by the decomposition of 3×10^{-4} M AIBN at 40°. Such a calculation is rather hypothetical, since kinetic chains of this length are hard to observe except in a few systems with very pure reagents and carefully controlled conditions, and an actual laboratory reaction would probably be a bit slower. However, it makes three important points. First, the short lifetimes of kinetic chains require a steady supply of radicals. However, if propagation steps are fast, as here, very little initiator is required.

Second, this short lifetime requires that all propagation-steps be fast (with rates > 10^2 M/l/sec) low-activation energy (usually exothermic) processes. Fortunately extensive data are now available not only on bond dissociation energies (from which minimum activation energies may be estimated) but also on actual rate constants of classes of radical reactions, along with activation energies and A factors.

Finally, the actual products in this reaction depends upon the competition between steps (8) and (4). If methylcyclopentane is the desired product, the stannane concentration must be low, either by working at high dilution, or (probably better) by slow addition of Bu_3SnH during the reaction. In complex systems involving large molecules and several chain propagation steps, such competitons are common, but can often be shifted in a desired direction by proper experimental design.

Initiators. Although many radical chain processes occur spontaneously at moderate temperatures, due to adventitious initiators, laboratory light, or ill-defined redox processes, it is usually desirable to facilitate chain initiation by deliberately adding initiators or other means. A large number of species are known which decompose thermally to generate free radicals a bit above room temperature, and some very complex systems are used in technology, e.g. vinyl polymerization. However, in laboratory syntheses it is desirable to stick wth a few which are easily available and well understood and match them to the temperature at which the reaction is to be carried out. Fig. 1 shows a plot of half-life of a number of common initiators vs. temperature. For efficiency, each is best used at a temperature such that it's half-life is comparable to reaction-time, e.g. 120-140° for di-t-butyl peroxide and 60-100° for AIBN or benzoyl peroxide, this insuring an adequate and steady supply of initiating radicals during reaction. If for some reason one wishes to use a relatively low-temperature initiator at a higher temperature, this can be done conveniently by slow addition of a solution of the intitiator over the whole reaction time.

In many ways AIBN (and related azo compounds) are ideal initiators. They are safe, easily handled, give good radical yields (20-80%, the balance being lost by cage recombination) and have almost solvent independent decomposition rates. AIBN's only drawback is that the 2-cyano-2-propyl radicals which it produces are relatively unreactive. For chains to be initiated a reactive double bond or a weak reactive bond (e.g. S-H or Sn-H) must be present in the system since C-H bonds are usually not attacked.

Peroxides yield more reactive radicals: methyl radicals from acetyl peroxide, benzoyloxy- and phenyl radicals from benzoyl peroxide, and t-butoxy radicals (plus $CH_3\cdot$) from di-t-butyl peroxide. Their drawback is that their chemistry is more complicated.[7] Thus, benzoyl peroxide undergoes an induced decomposition in the presence of alcohols and ethers, is reduced by stannanes, and reacts rapidly with phenols and amines. While the amine reactions give low yields of radicals (and have been used as a room-temperature initiation system for polymerization) they are messy and unattractive for synthetic work.

If reactions must be carried out near or below room temperature, thermal initiators are simply not very practical for synthetic work. Initiators such as di-t-butyl peroxyoxalate are difficult to prepare and dangerous to work with, and many other unstable peroxides, e.g. phenylacetyl peroxide, ($t_{1/2}$ 3-4 min at 40°) decompose largely by non-radical paths. Redox systems, e.g. Fe^{2+}-t-BuOOH, may be employed, but the method of choice is usually photoinitiation.

Many reaction mixtures, particularly if they contain carbonyl groups or higher row elements have end absorption in the near UV transmitted by ordinary laboratory glassware, and undergo photoreactions leading to radical generation. However, when in doubt, or if no

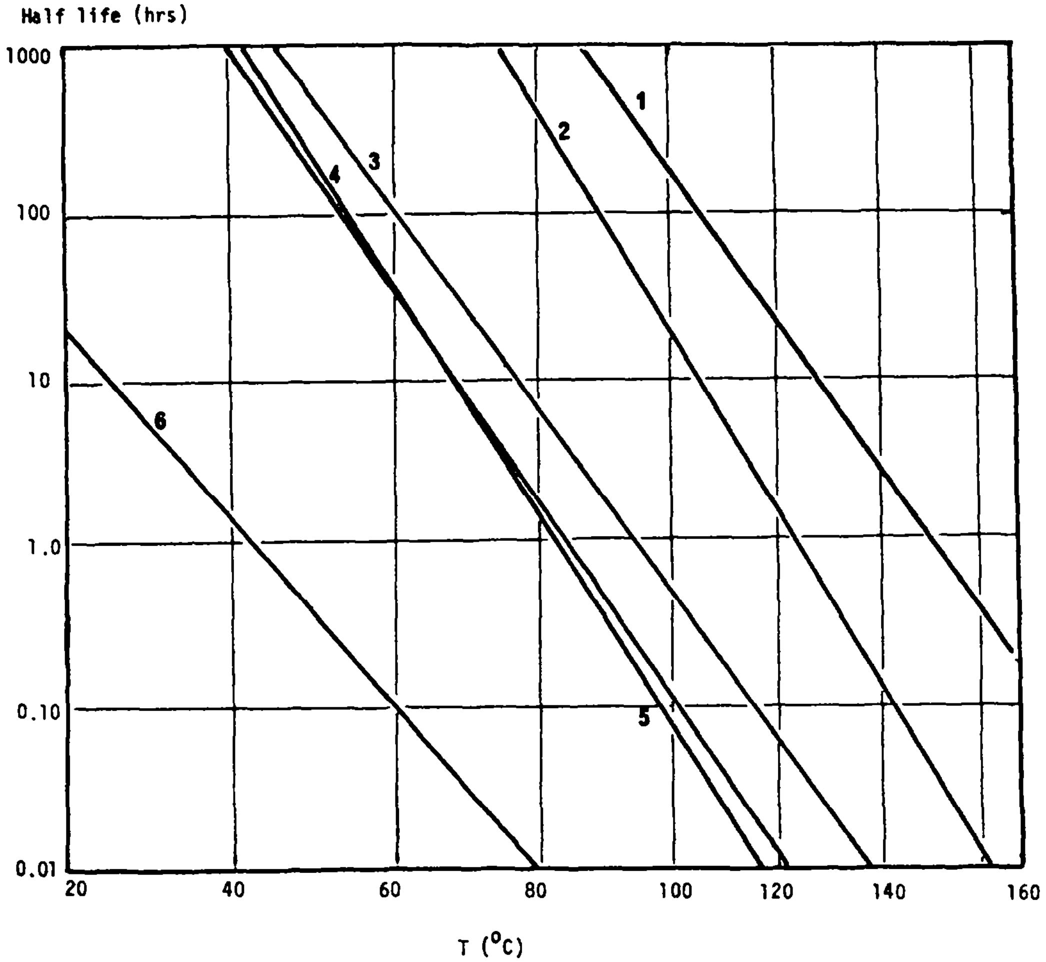


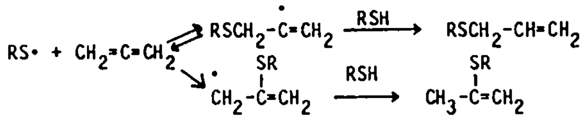
Fig. 1. Half-lives for decomposition of typical thermal initiators (values are approximate, since rates may vary with solvent).

(1) Di-t-butyl peroxide; (2) t-butyl peroxybenzoate; (3) Benzoyl peroxide; (4) $S_2O_8^{=}$ (5) Azobisisobutyronitrile (AIBN); (6) di-t-butyl peroxyoxalate

reaction occurs, photoinitiators may be added. AIBN and its analogs are particularly convenient, since they absorb strongly in the near UV (λ_{max} 345 nm, $\varepsilon = 14.9$) and have a high quantum yield for dissociation.[8] Benzoyl peroxide also has significant end-absorption, and also dissociates by energy transfer from other photoexcited species, e.g. aromatics and carbonyl compounds. Other peroxides behave similarly and it is worth knowing that many acyl peroxides which decompose thermally by non-radical paths, give good radical yields on photolysis (presumably because they decompose via their triplet states). Their photolysis thus provides a way of reliably producing radicals of known structure.[9]

Although they have received less study for the purpose, some ketones are effective as photoinitiators, benzoin, for example being a good photoinitiator of vinyl polymerization. The chemistry involved is complex and depends strongly on structure. Dibenzyl ketone dissociates to benzyl radicals and CO, benzophenone undergoes photoreduction by attacking RH bonds to yield R• radicals and benzhydrol radicals, while ketones with γ-C-H bonds undergo intramolecular H transfer to yield diradicals which have such short lives that they do not efficiently induce radical chains.

Since the propagation steps of radical chain reactions are necessarily fast processes with low activation energies, they can usually be run successfully over a wide temperature range providing suitable initiation systems are chosen. The most notable exceptions are reactions involving a β-elimination step in which a higher activation energy is offset by a large A factor. This may lead to a significant change in products with temperature. As examples in simple systems, thiyl radical addition to allenes give predominantly allyl thioethers at low temperatures and vinyl thioethers at higher temperatures (or low thiol concentration)



$$RS\cdot + CH_2{=}C{=}CH_2 \rightleftarrows RSCH_2\text{-}\dot{C}{=}CH_2 \xrightarrow{RSH} RSCH_2\text{-}CH{=}CH_2$$
$$RS\cdot + CH_2{=}C{=}CH_2 \rightarrow \dot{C}H_2\text{-}\underset{SR}{C}{=}CH_2 \xrightarrow{RSH} CH_3\text{-}\underset{SR}{C}{=}CH_2 \qquad (13)$$

addition to the terminal CH_2 is more rapid, but more easily reversed. Similarly, the distribution between 5- and 6-membered ring products from some substituted 5-hexenyl radicals is quite temperature-dependent. Cyclization to a 5-membered ring is kinetically favored but reversible, so 6-membered ring products are favored at higher temperatures.[10]

Solvents. The common impression that radical reactions are best carried out in non-polar media reflects chiefly the fact that such media repress possible competing ionic reactions since, as a matter of fact, rates of the chain-propagating steps of radical chains are usually quite solvent independent. A much more important criteria is that the solvent be inert towards the chain propagating radicals involved. For most of the sequences which have been developed for synthesis, this presents no problem since the common functional groups of solvents--carbonyl groups, aromatic rings and aliphatic C-H and C-Cl bonds--are unreactive. However, there are some exceptions. Obviously, halogenated solvents should be avoided in processes involving Sn, Si and probably P centered radicals with which they react rapidly. Again, alkyl radicals will add to benzene, and this is a possible complication in aromatic solvents, particularly for reactions run at high dilution. With polynuclear aromatics and protonated aromatic nitrogen bases, such additions are very fast and the synthetic use of such reactions has been examined by Minisci.[11] Sometimes solvents which react readily with one radical but not another can be used to suppress unwanted side reactions in chain processes. E.g. competing halogen atom chains can be reduced in alkyl hypohalite and N-haloimide reactions by the addition of di-or trichlorethylene (or other olefins lacking allylic hydrogens) as halogen and halogen atom traps.[12]

Finally, a few cases are known where solvents do have a significant effect on the rates and selectivity of chain-propagation effects. The best-known and striking example is in chlorine atom reactions, where selectivity is markedly increased by aromatic solvents, CS_2 and SO_2.[13] Evidently the chlorine atom complexes with the solvent, decreasing the exothermicity of its subsequent reaction, but whether π or σ complexes are involved is still a matter of debate. Similar smaller effects have been observed in Br• reactions. In the reactions of t-butoxy radicals the competition between β-scission and H-abstraction from, e.g., cyclohexane has been shown to be quite solvent dependent, with β-scission favored by π-electron systems (e.g. aromatics and chloroolefins) and hydrogen-bonding solvents.[14] The effects are smaller with larger alkoxy radicals where more stable groups are split off in the β-scission, but still should be considered when this competition is of importance.

If any conclusions can be drawn from the above, it is that strong solvent effects on propagation steps in radical chains are rare because radical centers are generally quite non-polar, and any weak association of the center with solvent must be broken for a bimolecular reaction to occur (halogen atoms, which can react on the "back-side" would be an exception). On the other hand, a unimolecular reaction converting a radical to a more polar species (as in the cleavage of t-butoxy to acetone) can, in some cases be facilitated by hydrogen-bonding in the transition-state.

Finally, although 1,2-hydrogen shifts are rare in free-radical chemistry, primary and secondary alkoxy radicals are rapidly converted to hydroxyalkyl radicals in water (and perhaps other strongly polar media).[15] A plausible explanation is that the reaction occurs through the common radical-anion

$$R_2CH\text{-}O\bullet \rightleftharpoons R_2\overset{\bullet\,-}{C}\text{-}O + \overset{+}{H} \rightleftharpoons R_2\dot{C}\text{-}OH \qquad (14)$$

The $R_2\dot{C}\text{-}OH$ radical is known to be a weak acid, and, since the equilibrium above lies far to the right, the alkoxy radical must be even more acidic. As a result, reactions of 1° and 2° alkoxy radicals may be difficult to achieve in such media.

Structure and Reactivity. The first comprehensive data on the relation between structure and reactivity came from copolymerization studies in the 1940's,[16] and these have been subsequently extended to a great variety of other systems, e.g. the recent detailed studies of relative reactivities of a wide variety of olefins towards alkyl radicals by Giese.[17] Determination of the relative reactivities of different substrates towards a given radical is a simple matter of generating the radical and determining the products (or consumption of reactants) in a competitive reaction, and only becomes complicated when reversible steps are involved. Accordingly, most of the data involve such substrate comparisons. Determining the relative rates of reaction of two radicals towards a given substrate is much more difficult and usually requires determining the actual rate constants of the steps involved. Data here are a good deal scantier.

Fortunately, all these data fall into a relatively simple pattern, and can be discussed qualitatively in terms of three major factors. The first of these has often been called "resonance stabilization", and is simply the old principle that rates of similar reations tend to parallel overall energetics: reactions yielding resonance stabilized radicals are faster than those giving radicals lacking such stabilization. For endothermic reactions, e.g. Br• reactions with alphatic hydrocarbons, these differences may be large, with differences in RTlnk equal to differences in ΔH. With exothermic reactions (the usual case in long chain reactions) they are much smaller. Thus, in radical addition reactions, styrene is typically 50-100 times as reactive as propylene, although the difference in resonance stabilization of the resulting radicals is approximately 9 kcal/mole. (I've neglected some niceties--the addition loses the resonance-stabilization of styrene-- ~1.5 kcal--but such differences in substrate stability are usually small.) The notable exception is radical addition to perfluoroolefins which are rapid because the olefin π bond is relatively weak, although there is little stabilization of the resulting radical. Conversely, radicals which are themselves resonance-stabilized react more slowly with the same substrate than those which are not. Thus, fast radical chains may be observed between reactive unstabilized radicals and unreactive substrates, and unreactive, resonance-stabilized radicals and reactive substrates yielding resonance stabilized prodcuts, but attempting to cross the two sorts of systems often fail. This can be very important, and is basically the explanation of action of most inhibitors of radical chains.

When the reactions compared involve radicals with the odd electron at the nuclei of other elements, the situation becomes more complicated. Hydrogen abstraction by $CH_3\cdot$, t-BuO• and Cl• all have very similar energetics but their relative reaction rates with the same substrate are approximately $1:3 \times 10^4:4 \times 10^7$. If there is any generalization, it seems to be that radical reactions involving the formation of C-C bonds or transfer of H or halogen between carbons are relatively slow compared to reactions in which the odd electron of the radical is on a heteroatom (typically halogen, O, N, S etc). The exceptions to this are peroxy radicals, $RO_2\cdot$, which react very slowly (k's often > 1) even in exothermic processes. This, of course, explains why traces of O_2 usually inhibit radical chains. On the other hand, autoxidations carried out in oxygen saturated systems can be very fast indeed. The apparent contradiction arises because, under these conditions, peroxy radicals are almost the only radical species present, and their bimolecular termination reactions are complex and slow. With only traces of O_2, both $RO_2\cdot$ and R• radicals are present, and they undergo cross-termination at diffusion-controlled rates.

Since radical displacement reactions (e.g. transfers of -H or halogen) occur at the periphery of molecules, they usually show little sensitivity to steric effects. The only notable examples involve very bulky radicals and well-buried atoms to be transferred, e.g. the reaction of phosphorus radicals with dialkyldisulfides[18]. On the other hand, steric effects in radical additions to multiple bonds can be very large and important in determining the success of radical chains. Substitution at the point of radical addition to a double bond substantially decreases reactivity. Even towards methyl radicals cis- and trans-2-butene are only 1/10 and 1/5 as reactive as ethylene or isobutylene, and stilbene 1/8 as reactive as styrene. Many similar examples are known for other radicals and substituents and steric retardations are often even larger with bulkier radicals.

The third factor, also originally noted in copolymerization studies is the so-called "polar effect", the tendency of radicals with electron withdrawing groups to react preferentially with electron-rich substrates and vice versa. Thus radicals can be thought of as electron acceptors or donors or as having electrophilic or nucleophilic properties. A convenient way of thinking of the phenomenon is in terms of a lowering of transition-state energy through the contributions of ionic resonance-structures, e.g. for addition to a double bond,[19]

$$X\cdot\ CH_2{=}CHR \longleftrightarrow X^-\ CH_2^+{-}\dot{C}HR \longleftrightarrow X{-}CH_2{-}\dot{C}HR \qquad (15)$$

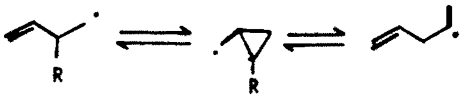
although the matter can also be discussed in molecular orbital terms. Interestingly, this concept has recently come full circle with the recognition of the possible role of electron transfer in a variety of polar, 2-electron processes leading to similar transition state formulations.[20]

In endothermic reactions overall energetics usually dominate, but in exothermic steps any factor may be dominant. Compared to the enormous range in rates with structure observed in polar reactions such as solvolyses, the total effect on substrate reactivities in radical chains which actually run well is rather small--rarely over a factor of a few hundred, but it is clearly enough to have a profound effect on regioselectivity as discussed in the next section.

Regio- and Stereospecificty. In intermolecular radical reactions, regiospecificity is determined by the reactivity factors just discussed. In double bond addition, both energetic and steric factors direct addition quite clearly to the least substituted carbon (anti-Markovnikov addition) with only traces of the other product. In fact, with aliphatic olefins, the steric factor is probably most important,[16] The only conspicuous exception is in radical additions to fluoroolefins. Fluorine atoms are small and contribute little resonance stabilization to the resulting radical. As a result, mixed products are obtained.[21] Additions to non-terminal, olefins, R_1-CH=CH-R_2 also give both regioisomers unless there are large differences in the resonance stabilizing effects of the substituents.

Achieving regiospecificity in intermolecular radical displacements, particularly hydrogen abstractions, is difficult in large molecules. Weak C-H bonds, e.g. benzyl and allyl, are preferentially attacked, as are electron rich sites, adjacent to O- and N when electrophilic radicals such as halogen or alkoxy are involved. However, in large molecules with a variety of C-H bonds, differences in reactivity are small enough that mixed products usually result.

Regiospecificity in radical reactions can be greatly enhanced by making them intramolecular, since now they are controlled by molecular geometry. In favorable cases, a large increase in rate is observed as an additional bonus. Since an excellent review of this topic is available,[22] I shall only summarize it briefly. Intramolecular additions occur most readily in 3-butenyl- and 5-hexenyl radical systems. The first case has not found much synthetic use, since the addition is highly reversible, leading to regeneration of the original radical or to a 1,2-vinyl migration



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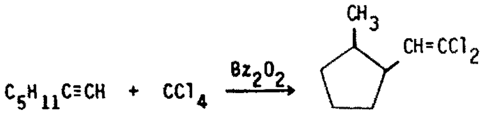
Only in systems with particularly favorable geometry (e.g. in the norbornyl ring system) can the intermediate cyclopropylcarbinyl radical be trapped in significant yield.

Cyclizations involving the 5-hexenyl radical have proved more useful and have been studied in greater detail. The most interesting feature is the preferred formation of a 5-membered ring except where this presents steric difficulties, or where a highly resonance-stabilized radical is involved. Even in the latter case, the five-membered ring may be the kinetically preferred product, but it reopens and closes to the more stable six-ring, so that product distribution depends upon the life-time of the quasi-equilibrating radical. Among others, the 1-phenyl-5-hexenyl radical provides a clear example of this behavior.[23]

The ring closure of the 5-hexenyl radical has been useful in identifying radical processes. Its rate has been measured over a wide temperature range and provides a useful "radical clock."[24] At room temperature $k = 10^5$. For comparison, the biomolecular rate constant for addition of $C_2H_5\cdot$ to 1-heptene is $\sim 10^3$ so one might say that the "effective" concentration of 5-hexenyl bonds is roughly 100 M. Similar cyclizations involving odd electrons on heteroatoms, or additions to multiple bonds involving heteroatoms, e.g.-CN, are also known and usually behave similarly. In contrast, cyclizations of 4-pentenyl and 6-hexenyl radicals have been difficult to observe. They are clearly much slower, and show little synthetic promise.

Most of the data on intramolecular radical displacements involve hydrogen abstraction. In flexible chain molecules the regiochemistry is clear: 1,5-hydrogen transfers are strongly preferred.[22] With similar hydrogens 1,6-transfers occur about 1/10 as readily, although they can be more important if the C6-H bond is weak or C-5 hydrogens are lacking. Most of the useful examples involve H transfer from C to -O· or =N· radicals, but transfers between carbon atoms can be fast enough to participate in chains with weak C-H bonds and particularly reactive radicals, e.g. vinyl. Here an interesting example is the reaction of 1-heptyne with CCl_4 reported by Heiba and Dessau[25]



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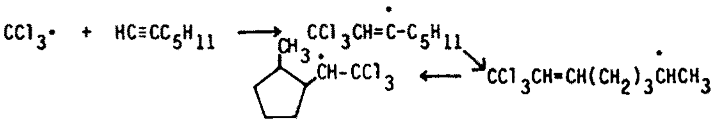
which evidently involves two intramolecular steps, hydrogen abstraction and cyclization.



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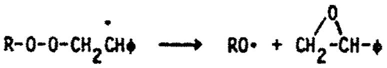
Again in these systems there is a large accelleration in rate over the corresponding intermolecular reaction. The yield of intramolecular product from 2-methyl-2-hexyloxy radicals is scarcely decreased when the reaction is carried out in cyclohexane, the CH_2 group on C-5 acting as though it were several hundred molar.[26] In more rigid molecules, regiospecific hydrogen abstraction from more remote sites have been observed. The most spectacular cases are those of Breslow[27] in steroid molecules where radicals at the far end of rigid aromatic groups, attached by ester linkages at C-3 quite specifically attack C-H bonds at C-9, C-14 and C-17 depending on the size of the aromatic structures.

Data on preferred ring-sizes for other intramolecular radical displacements are much scantier. Best known is the facile formation of epoxides from β-peroxy radicals,[28] e.g.



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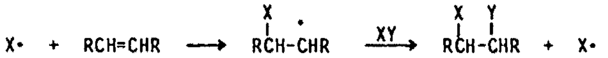
but it appears that similar displacements can occur through larger rings, since 4- and higher membered ring ethers have been observed in some hydrocarbon autoxidations.

The stereoselectivity of radical reactions has been studied chiefly with small molecules. In double bond additions where neither radical nor substrate contains a chiral center, the matter of interest is the relative stereochemistry at the two carbons which formerly provided the double bond.



$$X\cdot + RCH{=}CHR \longrightarrow R\overset{X}{C}H-\overset{\cdot}{C}HR \xrightarrow{XY} R\overset{X}{C}H-\overset{Y}{C}HR + X\cdot \qquad (20)$$

In most radical chains, the intermediate radical has a lifetime of microseconds or longer, ample to come to conformational equilibrium by rotation about single bonds and inversion at the radical center if it is not strictly planar. As a result, cis-and trans-olefins usually give the same mixture of threo- and erythro-products, often near 50:50, although, where the difference is significant the more stable product may be favored. The only notable exception to this are reactions involving higher-row elements. If these are sufficiently rapid, weak bridging is thought to retain the orginal stereochemistry of the adduct, and anti-addition occurs.

Most of the data involve Br• additions,[29] but there is evidence for this effect with S and other elements as well.

If radical or substrate has a nearby chiral center, or the radical center itself is prochiral, the situation is more complicated since diastereomers are created in the initial radical addition. This circumstance is notable in ring closures. 1-Substituted-5-hexenyl radicals usually give chiefly trans-1,2-disubstituted cyclopentanes, and closures generating fused rings usually give trans stereochemistry at the ring junctions, but there are exceptions (and some contradictions) in the literature so the stereoelectronic factors involved are not yet entirely clear.[22]

In radical displacement reactions generating a carbon-centered radical, the situation is the same as in the second step of a radical addition. The intermediate carbon radical is usually in conformational equilibrium, and, if it is prochiral, may show a preference for reaction on its less-hindered face. Again there is evidence for weak bridging by neighboring atoms such as Br, e.g. the 1,2-dibromocycloalkanes obtained by bromination of bromocycloalkanes are chiefly the trans-isomers, particularly when the Br has a preferred axial conformation.[29]

Finally there is some interesting regio- and stereochemistry connected with allyl radicals. Since the odd electron is delocalized they can react at either end and usually do. Generally reaction at the least-hindered end is preferred by a small factor. E.g. allylic halogenation of terminal olefins give chiefly 1-halo-2-olefins.

The stereochemistry is more complex, since an allylic radical may be trans,trans, trans,cis, or cis,cis and the barrier to inversion is appreciable, 10-20 kcal/mole depending on structure. When an allylic radical is produced, e.g. by abstraction of an allylic hydrogen, the configuration of the original double bond is conserved, while the configuration of the "new" partial double bond is determined by the conformational distribution of the original allylic substrate and the energies of the transition-states associated with them. In open chain systems the new partial double bond tends to be trans, e.g. cis olefins give chiefly cis,trans radicals. If these react before inversion, products formed with the double bond in its original position will be cis, while their allylic isomers will be chiefly trans. These relations were first worked out in t-butyl hypochlorite chlorinations of simple olefins.[30] Here the reaction of the allylic radical with hypochlorite if relatively rapid and original cis stereochemistry is only lost when the cis configuration is highly strained. In slower reactions, more loss of original stereochemistry may be observed.[22]

Redox Chains. An important and useful extension of radical chain reactions is to sequences involving the oxidation-reduction of transition-metal ions (most commonly Fe or Cu). A simple example is the addition of CCl_4 to olefins, a reaction which, in the usual peroxide initiated process, is complicated by the formation of telomers $CCl_3(CH_2CHR)_nCH_2CHClR$. However, as first shown by Assher and Vofsi,[31] in the presence of $FeCl_3$ or $CuCl_2$ good yields of 1:1 products are obtained, presumably via a sequence such as

$$FeCl_2 + CCl_4 \longrightarrow FeCl_3 + \cdot CCl_3 \qquad (21)$$

$$CCl_3\cdot + CH_2{=}CHR \longrightarrow CCl_3CH_2\dot{C}HR \qquad (22)$$

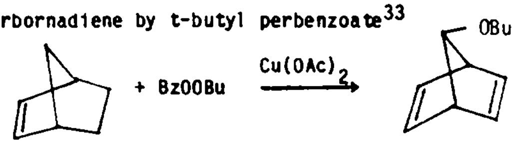
$$CCl_3CH_2\dot{C}HR + FeCl_3 \longrightarrow CCl_3CH_2CHClR + FeCl_2 \qquad (23)$$

Here the success of the reaction depends upon the high rate of (23) compared with the usual step (24)

$$CCl_3CH_2\dot{C}HR + CCl_4 \longrightarrow CCl_3CH_2CHClR + CCl_3^{\cdot} \qquad (24)$$

Although such reactions work with several other polyhalides, they have had only limited study and probably deserve more. They are known to be quite sensitive to solvent and reaction conditions, and may well involve other metal halide ion complexes than those indicated.

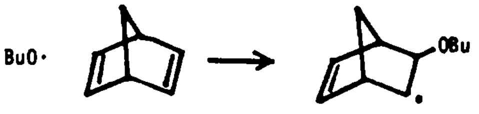
The largest and most useful group of redox chains involve stoichiometric reactions between peroxides and substrates in which the metal ion is alternately oxidized by the peroxide yielding a radical, and reduced by the product of reaction of the radical with the substrate. A great variety of such reactions are known, and many have been reviewed by Sheldon and Kochi,[32] but typical are the Cu catalyzed reactions of peroxides first examined by Kharasch in the 1950's. An example is the conversion of norbornadiene to 7-t-butoxynorbornadiene by t-butyl perbenzoate[33]



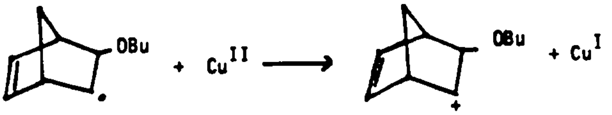
(25)

via a sequence which may be written as

$$BzOOBu + Cu^{I} \dashrightarrow BzO\cdot + BzO^{-} + Cu^{II} \qquad (26)$$



(27)



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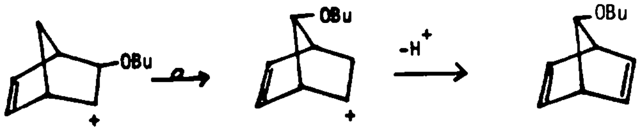


(29)

Reaction (29) is a typical carbonium ion rearrangement in this series (deuterium labeling has shown almost complete "scrambling" of the carbon skeleton), but (28) needs further attention. There is now convincing evidence that such Cu^{II} oxidation of a radical R· involves the formation of a transient R-Cu^{III} species, usually with a lifetime measured in milliseconds, which can decompose by several paths, depending on the structure of R: solvolysis to a carbocation when R$^+$ is relatively stable as here (often with characteristic carbocation rearrangements), loss of a β-proton, when available, to give olefin; or transfer of another ligand on the Cu to copper (e.g. with Cu(OAc)$_2$, to give an acetate). If R contains a suitably located nucleophilic group it may act as the ligand, leading to cyclic products. Thus β-hydroxyalkyl radicals can give expoxides, and γ-carboxy alkyl radicals γ-lactones. Finally, with some Cu species such as CuX$_n^{(n-2)-}$, the oxidation may involve a simple displacement on X (analogous to the reaction of R· with CCl$_4$) rather than formation of R-Cu^{III}.

Essentially all C-centered radicals (except possibly those with very strong electron-withdrawing groups) are rapidly oxidized by Cu^{II}. Rate constants are of the order of 10^6-10^8, so that the oxidations compete with other possible reactions, even at low Cu^{II} concentrations. Reactions are conveniently carried out in acetic acid or acetonitrile which are adequate solvents for both metal ions and substrates and relatively inert to radical attack.

In contrast, radical oxidations by Fe^{III} appear to be outer sphere electron transfer processes

$$Fe^{III} + R\cdot \longrightarrow Fe^{II} + R^{+} \qquad (30)$$

and occur readily only when R$^+$ is relatively stable, although here rate constants can approach 10^9. In some systems mixtures of Fe and Cu have been employed, Fe^{II} reducing the peroxide, and Cu^{II} oxidizing the resulting radicals.

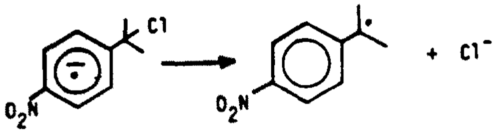
Other metal ions which can exist in two or more oxidation states have received less study, but offer promise of extending the variety of redox chains of synthetic interest. In some cases, their higher oxidation states are able to oxidize substrates to radicals directly. Thus Mn^{III} oxidizes carbonyl compounds to carbonyl-conjugated radicals.[34]

$$CH_3COR + Mn^{III} \longrightarrow \dot{C}H_2COR + Mn^{II} \qquad (31)$$

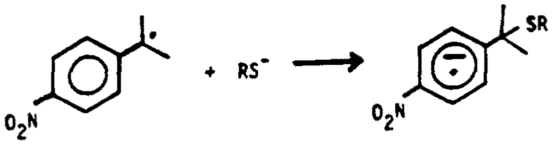
probably via the corresponding enol, and Ag^{II}, conveniently generated by $S_2O_8^{=}$ oxidation of Ag^+, oxidizes alcohols to alkoxy radicals and acids to acyloxy radicals which then lose CO_2.[35]

$$RCOOH + Ag^{II} \longrightarrow Ag^+ + RCO_2\cdot \longrightarrow R\cdot + CO_2 \qquad (32)$$

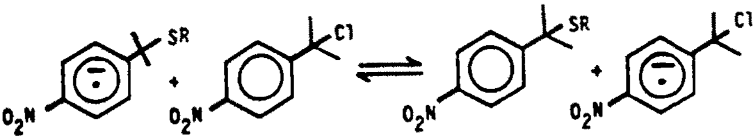
Radical Ions. Finally, one of the newest and promising areas of synthetic free radical chemistry is that involving aromatic radical ions as reaction intermediates. Radical anions have been recognized for some time as intermediates in $S_{RN}1$ reactions, which look like nucleophilic displacements, but actually involve radical chains,[36] e.g.



(33)



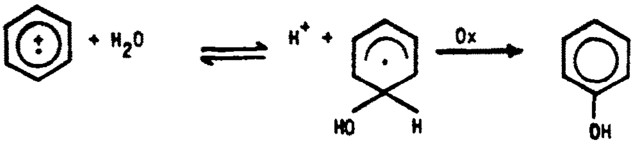
(34)



(35)

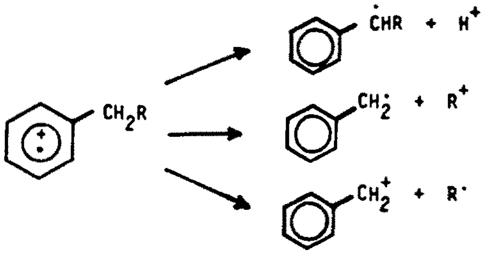
Radical anions now seem to be involved in many reactions of carbanions as well including such familiar processes as Grignard reactions.

Radical cations, particularly aromatic radical cations, have become of importance more recently. They can react with nucleophiles to give eventually ring substitution. As an example, the benzene radical cation in water is in equilibrium with the hydroxycyclohexadienyl radical.[37]



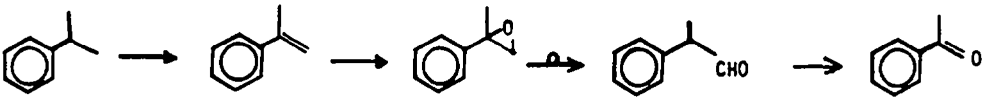
(36)

Of more synthetic interest, they undergo facile side-chain cleavage by several possible paths



(37)

We have recently reviewed the factors determining which path is followed,[38] and they are largely the relative stabilities of the possible fragments. Such cleavages may be important in many side-chain oxidations, and can lead to a remarkable variety of products. Thus, the principle path for oxidation of cumene by $S_2O_8^{=}$ - Cu^{II} in acetonitrile[38] appears to involve formation of a series of radical cations, their conversion to radicals, and oxidation in turn of these by Cu^{II} to yield the product sequence.



(38)

References

1. J. K. Kochi Free Radicals John Wiley and Sons, N.Y., 1973.
2. D. C. Nonhebel, J. M. Tedder and J. C. Walton Radicals, Cambridge University Press, Cambridge, 1979.
3. C. Walling and R. Rabinowitz J. Am. Chem. Soc. **81**, 1243 (1959). For recent comprehensive reviews cf. W. G. Bentrude Reactive Intermediates 3, 199 (1983); Accnts Chem. Res. **15**, 117 (1982).
4. K. U. Ingold and B. P. Roberts Free Radical Substitution Reactions, Wiley-Interscience, N.Y. 1971, see also Ch. 10 of Ref (1).
5. C. Walling, J. H. Cooley, A. R. Ponaras and E. J. Racah J. Am. Chem. Soc. **88**, 5361 (1966).
6. The kinetics of chain processes are treated in many texts, e.g. J. W. Moore and R. G. Pearson Kinetics and Mechanism, John Wiley and Sons, N.Y. 1981, Ch. 10.
7. D. Swern Organic Peroxides, Wiley-Interscience, N.Y. 1970. See also Ch. 3 of Ref (1).
8. The photolysis of azoalkanes is actually a bit complicated. Many undergo principally photoisomerication to the cis-structure. Cf. P. S. Engel Chem. Revs. **80**, 99 (1980).
9. C. Walling and M. J. Gibian J. Am. Chem. Soc. **87**, 3413 (1965); R. A. Sheldon and J. K. Kochi ibid **92**, 4395 (1970).
10. M. Julia Accnts. Chem. Res. **4**, 386 (1971).
11. F. Minisci Topics in Current Chemistry 62, 1 (1976).
12. C. Walling and J. A. McGuinness J. Am. Chem. Soc. **91**, 2053 (1969); P. S. Skell and J. C. Day Accnts. Chem. Res. **11**, 381 (1978).
13. G. A. Russell, J. Am. Chem. Soc. **80**, 4987, 4997 (1958). Cf. Ch. 15 of Ref. (1).
14. C. Walling and P. J. Wagner J. Am. Chem. Soc. **86**, 3368 (1964).
15. B. C. Gilbert, R. G. G. Holmes, H. A. H. Laue and R. O. C. Norman J. Chem. Soc. Perkin Trans. **2**, 1047 (1976).
16. F. R. Mayo and C. Walling Chem. Revs. **46**, 191 (1950).
17. B. Giese and W. Zwick Angew. Chem. **90**, 62 (1978) and subsequent papers.
18. W. G. Bentrude, private communication.
19. C. Walling and F. R. Mayo Disc. Faraday Soc. **2**, 295 (1947).
20. Cf. e.g. C. Walling and C. Zhao Tetrahedron **38**, 1105 (1982).
21. J. M. Tedder and J. C. Walton Accnts. Chem. Res. **9**, 183 (1976).
22. A. L. J. Beckwith and K. U. Ingold Free Radical Rearrangements in Rearrangements in Ground and Excited States, Vol. 1, p. 161. Academic Press Inc., N.Y. (1980). This is a comprehensive review of intramolecular radical reactions in general.
23. C. Walling and A. Cioffari J. Am. Chem. Soc. **94**, 6064 (1972).
24. D. Griller and K. U. Ingold Accnts Chem. Res. **9**, 13 (1976).
25. E. I. Heiba and R. M. Dessau J. Am. Chem. Soc. **89**, 3772 (1967).
26. C. Walling and A. Padwa ibid **85**, 1597 (1963).
27. R. Breslow, R. C. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna and R. Kaleya ibid **99**, 905 (1977).
28. F. R. Mayo Accnts. Chem. Res. **1**, 193 (1968).

29. P. S. Skell and J. G. Traynham *ibid* **17**, 160 (1984).

30. C. Walling and W. Thaler *J. Am. Chem. Soc.* **83**, 3877 (1961).

31. M. Assher and D. Vofsi *J. Chem. Soc.* 2261 (1961); 1887, 3921 (1963).

32. R. A. Sheldon and J. K. Kochi *Metal Catalyzed Oxidations of Organic Compounds*, Academic Press, N. Y. 1981. Cf. also Ch. 11 of Ref. (1).

33. P. R. Story *J. Am. Chem. Soc.* **82**, 2085 (1960); *Tetrahedron Lett.* 414 (1962).

34. J. B. Bush, Jr. and H. Finkbeiner *J. Am. Chem. Soc.* **90**, 5903 (1968): E. I. Heiba, R. M. Dessau and W. J. Koehl, Jr. *ibid* 5905; W. F. Fristad and J. R. Peterson *J. Org. Chem.* **50**, 10 (1985).

35. C. Walling and D. M. Camaioni *ibid* **43**, 3266 (1978); J. M. Anderson and J. K. Kochi *J. Am. Chem. Soc.* **92**, 1651 (1970).

36. N. Kornblum *Angew. Chem. Int. Ed.* **14**, 734 (1975).

37. C. Walling *Accnts. Chem. Res.* **8**, 125 (1975).

38. C. Walling, G. M. El-Taliawi and K. Amarnath *J. Am. Chem. Soc.* **106**, 7573 (1984).(38)