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Radical Chemistry: Past, Present, and Future**

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Reactive free radicals were recognized as important intermediates in organic chemistry during the 1930's. By the early 1970's, most features of structure and reactivity were understood, and had even been placed on a reasonably secure quantitative foundation. It was, however, only slowly that this understanding was formulated by organic chemists into valuable synthetic methodology. In parallel with these more recent developments in chemical application, there has been recognition that radical intermediates are important both in aspects of human disease, and in vital enzyme-mediated biochemical transformations. Important future directions seem likely to include development of a deeper understanding of biologically relevant processes, and, in organic chemistry, of even greater control, notably stereocontrol, of synthetically useful reactions.

Key words: Free radicals

INTRODUCTION

Radicals in organic chemistry have provided my principal scientific interest ever since I started my doctoral research under the guidance of one of the pioneers of the subject, Donald Hey. Although I'm now fully retired, I've kept an active interest in the way organic chemists in particular are making use of radicals, and I'm currently preparing a short teaching text on the subject. Nevertheless, It's something of a challenge to attempt to give a balanced overview of radical chemistry, and of where it may be heading, in just a few pages. With the proviso that the emphasis will be on organic chemistry, I shall try!

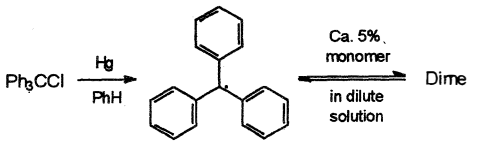
The term radical goes back to Lavoisier in the XVIIIth Century, and was then indicative of a fragment (or "root") of a molecule which remains unchanged during a chemical transformation – as for example ethyl in the sequence:

$$C_2H_5-OH \rightarrow C_2H_5-I \rightarrow C_2H_5-CN \rightarrow C_2H_5-CO_2H$$

For a short time around 1850, it was believed that the gas released from ethyl iodide by heating it with zinc was the free ethyl radical [1]. But it was, of course, a mixture of ethane, ethene, and butane.

$$C_2H_5—I \xrightarrow{Zn} ZnI_2 + \begin{cases} C_2H_6 \\ + \\ C_2H_4 \\ + \\ C_4H_{10} \end{cases}$$

Thereafter, it became the accepted wisdom that carbon was universally tetravalent, until, that is, the experiments of Moses Gomberg at the turn of the century [2]. Shaking a benzene solution of trityl chloride (chlorotriphenylmethane) with mercury in the absence of air gave a yellow solution, the colour of which Gomberg correctly deduced was due to the triphenylmethyl radical. (We now routinely represent the unpaired electron at trivalent carbon with a dot).



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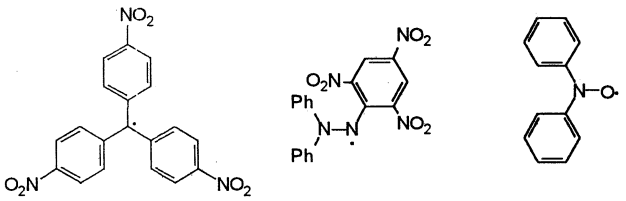
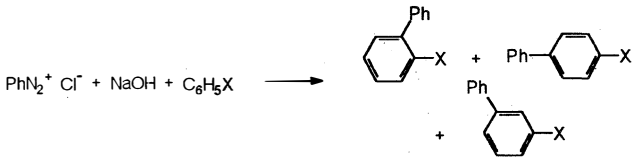
Although this free radical is in equilibrium with well over 90% of a colourless dimer, it was subsequently found possible to *isolate* some triarylmethyl radicals as monomeric crystalline solids, one example is the tris-*p*-nitro analogue. Furthermore, other compounds were isolated which formally contain divalent nitrogen or univalent oxygen:



Nevertheless, it was not until the early 1930's that it was first suggested in print that reactive, electrically neutral, trivalent carbon species (i.e. *reactive* free radicals) might be involved in chemical reactions [3, 4].

One line of evidence came from a study, by Donald Hey, working in Manchester, England, of the preparation of biphenyls, in which a heterogeneous mixture of an aqueous diazonium salt solution and an aromatic solvent is made alkaline whilst being vigorously stirred [3].



X	% *o*-	% *m*-	% *p*-
Methyl	64	20	16
Nitro	63	10	27

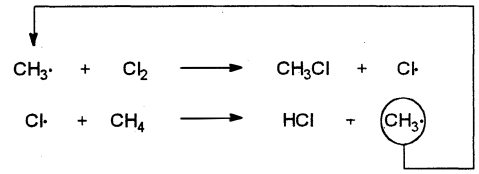
When the solvent was a substituted benzene, it was found that, irrespective of the electronic character of the substituent, substitution occurs at the *ortho* and *para* positions. (In fact, we *now* know that a significant proportion of *meta* product is always formed as well; see Table). This was interpreted to mean that the attacking species must be the electrically neutral phenyl free radical, although, in order to pass a highly sceptical refereeing system, the title of the paper was a cautious one:

397. *Amphoteric Aromatic Substitution. Part I. Reactions of Sodium Benzenediazoate and Nitrosoacetanilide*
By William S. Grieve and Donald H. Hey.

At about the same time, in Chicago, Morris Kharasch concluded that free radicals must be involved in some anomalous addition reactions of hydrogen bromide to alkenes [4]. Very soon, numerous other organic transformations were interpreted in terms of these electrically neutral intermediates [5].

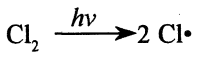
One of the examples most familiar to the student of organic chemistry is halogenation, for example the chlorination of methane, with which the important concept of the free radical-chain reaction is commonly introduced.

In modern terminology, a reactive carbon-centred radical such as methyl (represented as $H_3C\cdot$) possesses an odd number of electrons. Therefore, when it reacts with an even-electron species the result must include another odd-electron molecule C i.e. another free radical. A "chain" of similar events ensues. The repeating steps are the so-called "propagating" steps of a "radical chain reaction" – which in this case produces chloromethane.

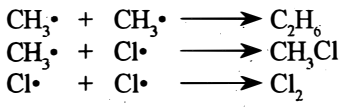


The reaction steps may repeat many hundreds of times, converting many hundreds of molecules before a chance encounter between two radicals brings about "termination" of the kinetic chain. Of course, some special event must also occur to "initiate" the chain, and in this case this might be the absorption of a quantum of light by a chlorine molecule.

Initiation:

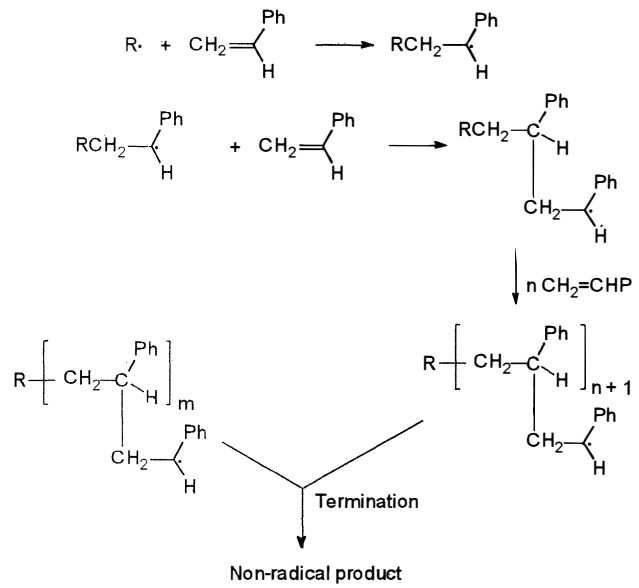


Termination:

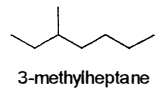


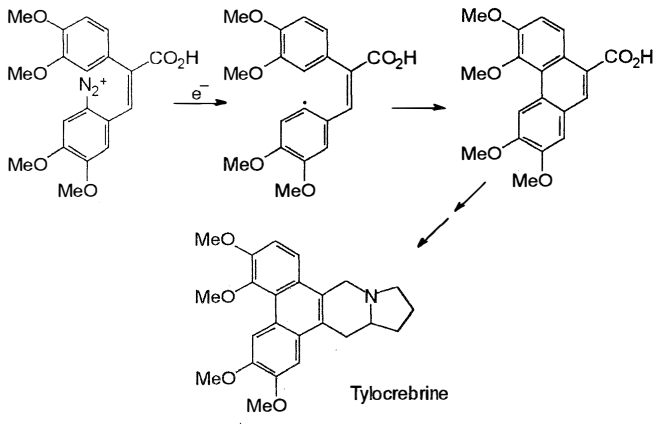
Methane chlorination takes place in the gas-phase, but exactly the same types of reaction steps would be involved in liquid-phase chlorination of e.g. cyclohexane. Photochemical initiation is also possible here, but in many liquid-phase reactions thermal initiation is employed, using a peroxide or azo-compound which spontaneously decomposes into radicals at a conveniently low temperature.

A special impetus was given to one of the other familiar aspects of radical chemistry by the events of World War II, when access to supplies of natural rubber for the Western Allies was disrupted by the fighting. Alternatives became essential, and enormous effort was devoted to the chemistry and technology of synthetic high polymers. In the radical polymerisation of e.g. styrene, the propagating steps involve radical addition to the double bond. Termination now occurs when two growing polymer chains meet.



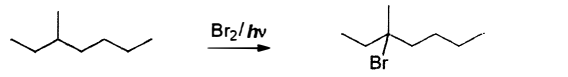
Despite their obvious commercial importance, these two examples – chlorination and polymer production – afforded the basis of one of the problems which seem to have hampered the progress of organic free-radical chemistry. Organic chemists traditionally liked easily purified products – crystalline solids or stable, readily distilled liquids. Not polymeric glasses! On the other hand, a moment's reflection would show that the conversion of styrene monomer into polymer approaches 100%; this is astonishingly efficient compared with most synthetic transformations. The problem with chlorination is quite different. It is that the process is so unselective. Monochlorination of, for example, 3-methylheptane would produce significant proportions of all eight positional isomers (with stereoisomers a further complicating factor). So reactions involving radicals were generally perceived to be hopelessly unselective.


3-methylheptane



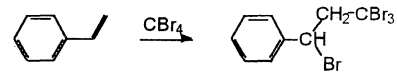
The Gomberg phenylation reaction, in which mixtures of *ortho*, *meta*, and *para* isomers are formed, appeared to provide a further example of this, (although intramolecular analogues did afford moderately successful routes to some structurally fairly simple alkaloids, as illustrated here [6]).

With hindsight, however, it is clear that the wrong precedents were generally being emphasized, and that these provided a completely false impression of the potential value of radical reactions. Thus, radical-chain mono*bromination* of 3-methylheptane gives a mixture which is more than 70% one isomer:



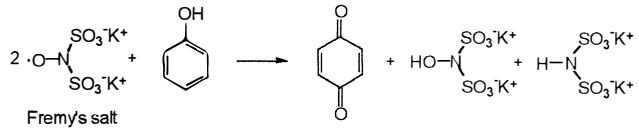
(ca. 70%, admixed with other isomers

The efficiency of styrene conversion has been mentioned; but more appealing to the synthetic chemist might be the fact that in the presence of sufficient quantities of carbon tetrabromide, styrene does not polymerise but gives, in excellent yield, the 1:1 adduct:



Clearly then, under properly chosen conditions, free-radical reactions can be adjusted to give good to excellent yields of simple products. Nevertheless, with the exception of a few specialist reagents such as *N*-bromosuccinimide which brings about allylic bromination, and Fremy's salt which oxidizes monohydric phenols to (usually *para*) quinones, it was not really until the last 20 years or so that organic chemists have perceived the enormous potential for radical chemistry in organic synthesis.

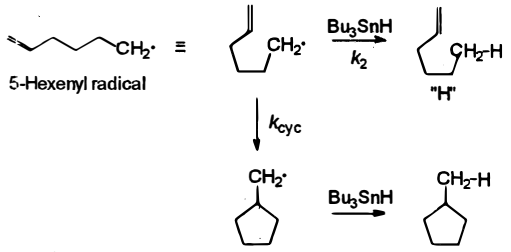

N-bromosuccinimide


Fremy's salt

In great part, this has come not just from a better qualitative understanding of radical reactions but from the accumulation of quantitative data on their rates, and I should like to say a little about some aspects of this. Development of a variety of methods, such as the techniques kinetic spectroscopy used in conjunction with flash photolysis and pulse radiolysis, for monitoring rapid reactions has made direct measurement

of kinetic data possible, but even now the majority of rate constants are actually determined indirectly, by comparison with existing data.

An early example relates to the important cyclization of the 5-hexenyl radical into cyclopentylmethyl, the rate of which was first estimated by competition with the reaction of the uncyclized radical with tributyltin hydride. The rate constant, k_2, for interception of a primary alkyl radical by this reagent was known, and analysis of the mixture of hexene (H) and methylcyclopentane (MP) then allows determination of the rate constant, k_c, for cyclization [7].

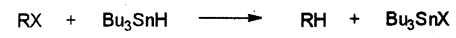


$$\frac{[H]}{[MP]} = \frac{k_2 \times [Bu_3SnH]}{k_{cyc}}$$

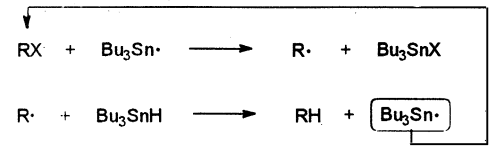
whence:

$$k_{cyc} = \frac{k_2 \times [Bu_3SnH] \times [MP]}{[H]}$$

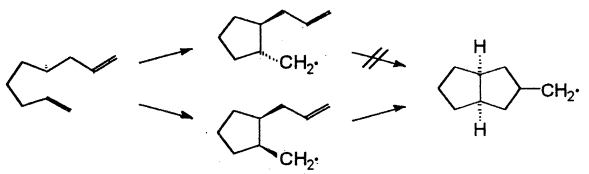
The reagent tributyltin hydride has played a major role in a variety of recent synthetic strategies, but it was initially important simply for the dehalogenation of alkyl halides (especially bromides and iodides) by the chain sequence shown:



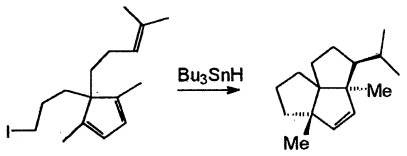
Propagating chain:



Under preparative conditions, the hexenyl cyclization reaction is best carried out in the presence of low concentrations of reagent, which can be maintained by slow addition, usually admixed with catalytic quantities of initiator, and often controlled by use of a syringe pump. In this way, essentially quantitative cyclization occurs. The procedure has been utilized in syntheses of a variety of important cyclopentanoid molecules. At first, initial progress towards the more interesting targets was slow. For example, the early bicyclization shown here was inefficient because the initial stage is not stereoselective, and one isomer of the monocyclic radical is unable to cyclize further.

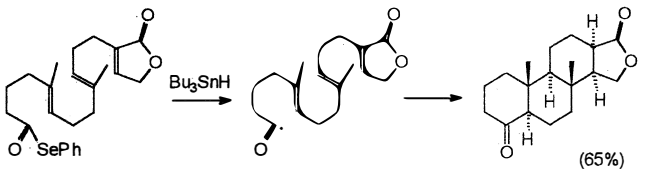


A solution to this problem is to construct a precursor for which only the desired cyclization geometry is possible. A nice example is the synthesis of the angular triquinane shown [8]. This constituted a model for a projected synthesis of a tetracyclic antibiotic, crinipellin A.

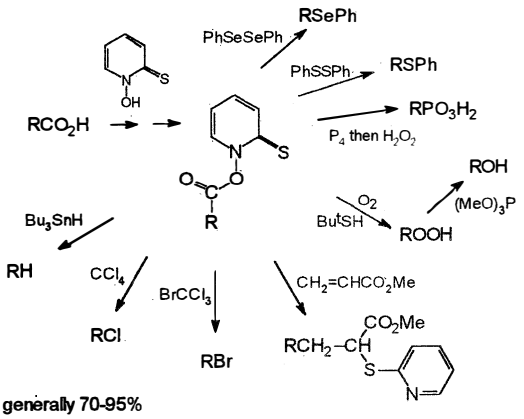


ca. 70% (together with ca. 15% of a stereoisomer)

This double or "tandem" cyclization is illustrative of the more general concept of "cascade" reactions in which two or more intramolecular steps occur on the way to product. Another example is the synthesis of a tetracyclic precursor to the marine diterpene spongianone [9]:

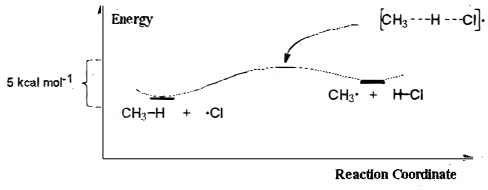


There is also interest in new functional group interconversions. The best known of these are Barton's transformations of carboxylic acids via *N*-acyloxypyridinethiones. Without any mechanistic detail, the versatility of this procedure is hinted at below [10]. Often one of the advantages of these processes is that it is unnecessary to protect e.g. hydroxyl groups which might be sensitive to the conditions of ionic reactions.



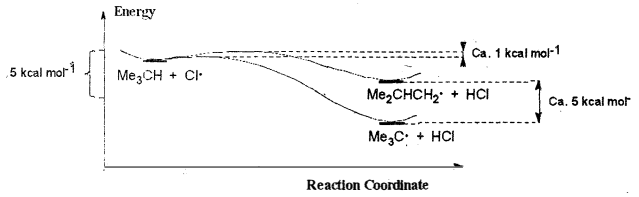
Yields generally 70-95%

Returning for a moment to simpler chemistry, a feature of the abstraction of hydrogen from methane by the chlorine atom is the extraordinary compensation between bond-breaking and bond-making which occurs as the reaction proceeds.

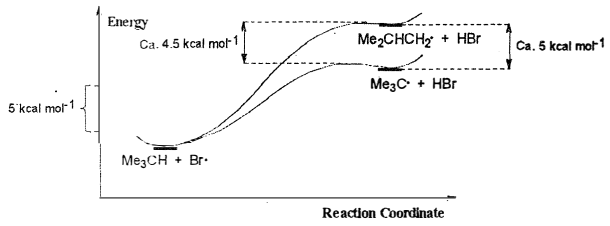


This hydrogen transfer is very slightly endothermic, but the activation barrier is only marginally greater than is the endothermicity, and it is so low that the rate in solution is close to the diffusion-controlled limit, at which every collision results in chemical reaction.

C–H bonds in other alkanes are a little weaker, and it is interesting that a slight skewing of the picture for methane rather accurately reflects what happens with, for example, isobutane, which incorporates both tertiary and primary hydrogens. The former is less strongly held. The reactions are now almost activationless, but a small difference in barrier height is reflected in a roughly six-fold greater rate for attack by chlorine at the tertiary than at one of the primary hydrogens.



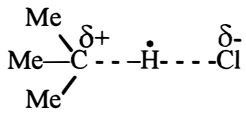
The situation for attack by the much less reactive bromine atom is reversed. The bond in H–Br is much weaker than that in H–Cl; both reactions are now endothermic, and the reaction profiles are skewed in the opposite sense. The barrier difference is now almost as great as the difference in strength between the primary and tertiary C–H bonds. This manifests itself in the result, noted earlier, that bromination is very much more selective than is chlorination. In this case the proportion of tertiary bromide is greater than 99%!



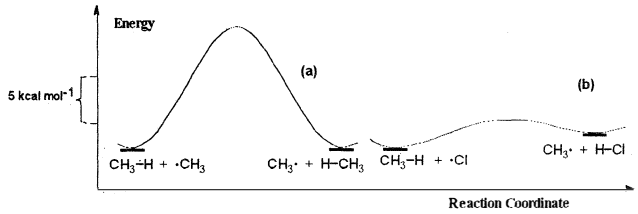
The parallels between these reactions led to an early attempt at a simple empirical relationship between reaction rate and heat of reaction, the Evans-Polanyi Equation [11]:

$$E_a = E_o + \alpha\Delta H$$

But this works only for closely related reactions, and a special feature of the reactions which we have considered is that the transition state for hydrogen abstraction by halogen enjoys an appreciable measure of dipolar stabilisation, e.g.:



It is arguably important that this is so. It is interesting to compare the reaction profiles for the Cl· + methane reaction with that for CH_3· + methane (which must, of course, be thermoneutral). The latter reaction turns out to have a fairly substantial barrier. Were this not the case, any radical reaction involving alkanes might be expected to b e accompanied by rapid scrambling of the alkyl radicals by hydrogen-transfer (R^1· + R^2–H⟹ R^1–H + R^2·), so that complex product mixtures would invariably be formed. Fortunately, this is usually not the case!



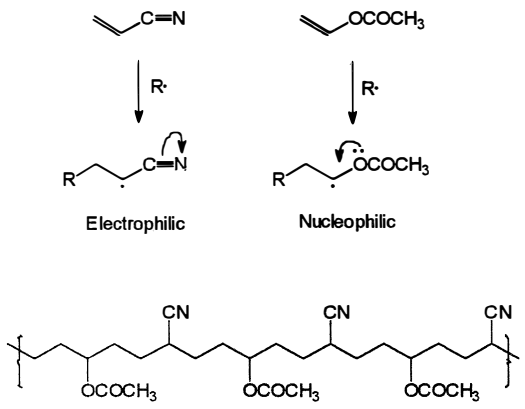
A more general empirical relationship has been advanced recently [12], which looks frighteningly complicated, but which contains various terms that may easily be related to familiar structural concepts relevant to the reaction A· + H–B → A–H + B·:

$$E_a = Ef + \alpha\Delta H(1 - d) + (\beta\Delta\chi)^2 + \gamma(s_A + s_B)$$

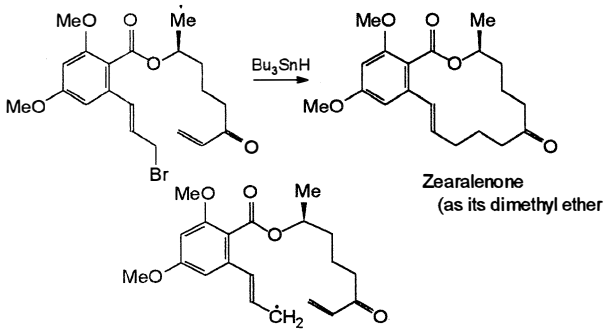
For example, $\Delta\chi$ is the difference between the Mulliken electronegativities of A and B; the s terms allow for changes in geometry as A and B approach the transition state, and, in a similar way, d values allow for changes in conjugation. The equation accurately correlates data on more than sixty intermolecular hydrogen-atom transfer reactions. Importantly, for all of these there is no difficulty in achieving the optimum *co-linear* geometry for the transition state:

A- - - - -H- - - - -B

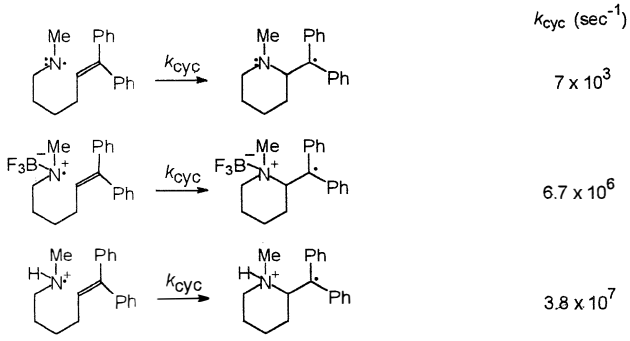
The practical importance of polar effects is especially evident in addition reactions. The copolymerization of vinyl acetate and acrylonitrile constitutes a good example:



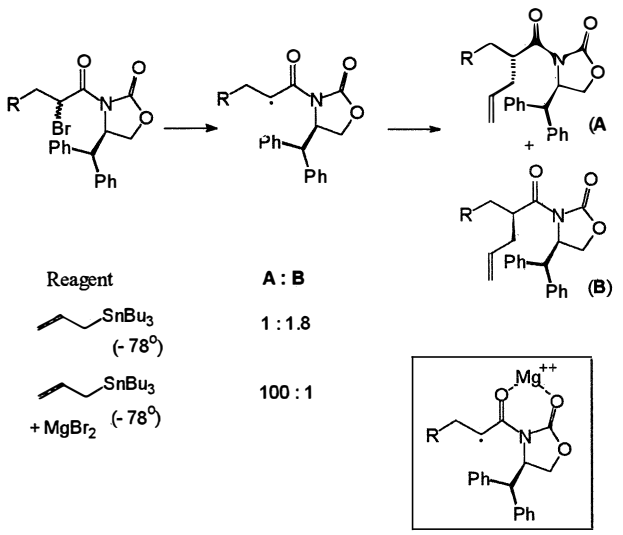
But control of polar effects has been extended into some very useful synthetic strategies for smaller targets molecules. The synthesis of the macrocyclic mycotoxin zearalenone (as its bismethyl ether) is a good example [13]. The point here is that alkyl radicals, with the exception of methyl itself, behave as if they are weakly nucleophilic. A parallel attempt to effect cyclization of the structure lacking the ketone carbonyl was completely unsuccessful. The success of this reaction is perhaps even more surprising when it is noted that the intermediate radical has allylic stabilization, and hence is, in general terms, relatively unreactive.



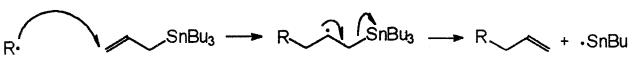
Extreme polar effects are evident in reactions promoted by Lewis acids. Aminyl radicals RNH· are generally rather unreactive, but protonation or complexation with BF_3 affords much more reactive species as illustrated here [14]:



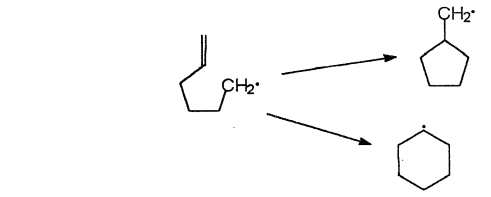
Complexation with Lewis acids is an area of active current interest. In particular, complexation effects have recently been brought to bear on the developing field of stereoselective radical reactions. Shown below is an example in which the acyl group is held in a single conformation allowing pronounced stereocontrol of the allylation reaction [15].

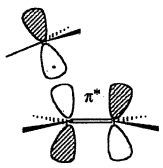


The mechanism of allylation in this reaction is as follows:

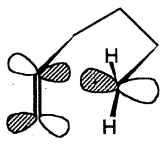


The cyclization of hexenyl and related radicals to give five-membered rings is important in synthesis, but it also exemplifies several other significant aspects of reaction mechanism. In the first place, it might have been expected that the cyclization would afford cyclohexyl, since secondary radicals are thermodynamically more stable than primary, and the six-membered ring is favoured over five. However, the geometry of radical approach to a double bond is dictated by an electronic interaction between the unpaired electron,





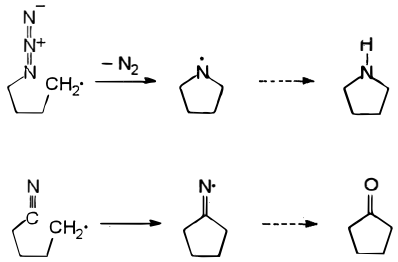
Approach of (planar) methyl radical to ethene



Chair-like transition state for cyclization of hexenyl radical to cyclopentylmethyl. (A boat-like geometry is also accessible).

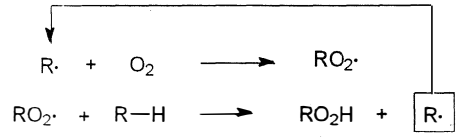
shown here for the (planar) methyl radical, and the π^* antibonding orbital on the alkene. For hexenyl cyclization, this transition state geometry is appreciably less strained for cyclopentylmethyl formation than for cyclohexyl formation. Clearly, for this cyclization reaction at least, any relationship between activation barrier and heat of reaction breaks down completely.

A second aspect of these cyclizations is also worth noting. They are extremely fast. If we attempt a comparison with model intermolecular processes, we find that the alkene would have had to be quite impossibly concentrated – ca. 10^5 M – in order for *inter*molecular depletion of radical to occur at a comparable rate to the *intra*molecular process. This has been likened to the chelate effect in inorganic chemistry. It is also pertinent to the efficiency of intracomplex reactions in enzyme chemistry. One consequence in radical chemistry is that synthetically valuable intramolecular reactions have been reported for which there is no recorded intermolecular counterpart, e.g. [16]:

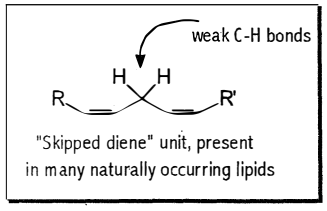


I have emphasised organic chemistry, and I am sure that there are numerous synthetic applications, perhaps with Lewis-acid catalysis, perhaps showing dramatic improvements in stereo-control, waiting to be discovered. But as yet I have said nothing about the explosion of interest in the biomedical and biochemical communities.

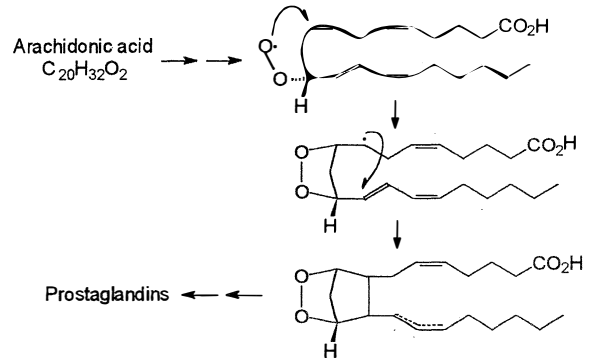
Oxygen is a free radical. Actually, it is a biradical. It reacts at, or close to, the diffusion-limited rate with many carbon-centred radicals, even the resonance-stabilized ones like triphenylmethyl. And it is involved in "autoxidation," characterized by the chain-propagating sequence:



Propagating steps for autoxidation



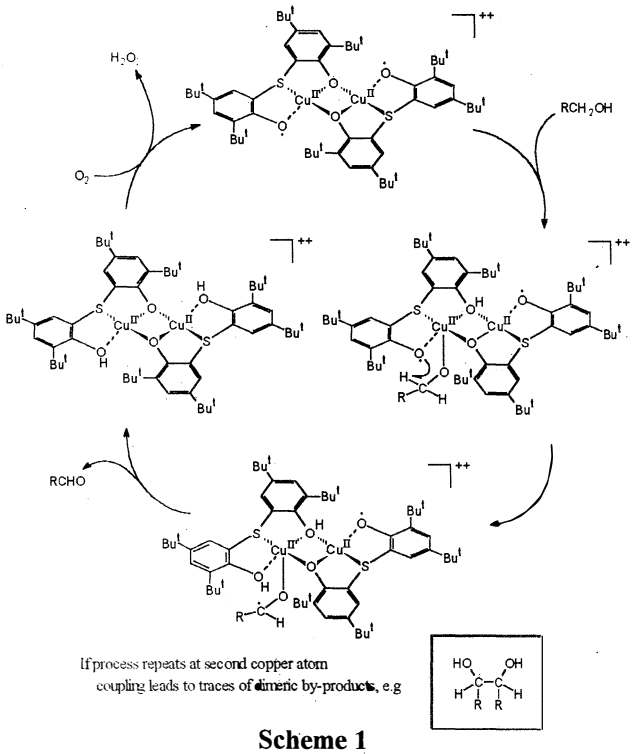
The reaction is particularly rapid when the C-H bond in the substrate is very weak, as it is in certain naturally occurring lipids containing the skipped diene unit. Occurrence of this type of oxidation in living tissue can be damaging, and is tentatively associated with several of the degenerative diseases of the nervous system. In healthy tissues, nature's antioxidant vitamins, especially E and C, are instrumental in intercepting the peroxyl radicals and breaking the kinetic chain, although more recently, evidence has been accumulating to show that these vitamins may, under extreme circumstances, actually promote oxidative damage. Yet again, autoxidation may be beneficial; for example it is crucial to the biosynthesis of the prostaglandins and related hormones. It is noteworthy that the biosynthetic pathway to the prostaglandins incorporates nature's contribution to a tandem hexenyl radical cyclization:



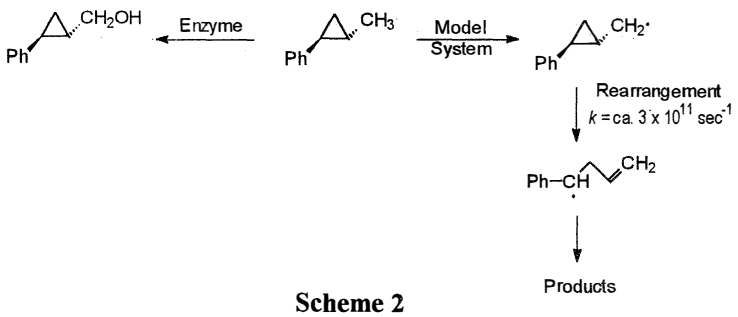
A much more damaging oxygen species than the peroxyl radicals is hydroxyl. This is less readily formed, and the body has in-built defense mechanisms to prevent its occurrence, but these appear to be overcome in a variety of disease conditions. Hydroxyl is so reactive that it reacts on encounter with almost any organic molecule. So-called hydroxyl-radical scavengers *must* therefore be largely ineffective other than at very high concentrations!

Whilst many aspects of the chemistry of these oxidizing radicals has been worked out, it is clear that much remains to be accomplished if our understanding of radical-related diseases is to progress.

And, perhaps even more fundamental, is the understanding of enzyme-catalysed processes which incorporate radical (or radical-like) behaviour. It is now clear that there is radical character in aspects of the mechanism of action of ribonucleotide reductase, pyruvate formate lyase (which is involved in bacterial fermentation of glucose), and of several other enzymes. One fascinating example of an apparently successful *modelling* of radical-based enzyme activity was reported recently. This relates to the copper-containing enzyme, galactose oxidase. The natural enzyme catalyses oxidation of the primary alcohol group of the sugar into aldehyde. Critical to its mode of action is the abstraction of



Scheme 1



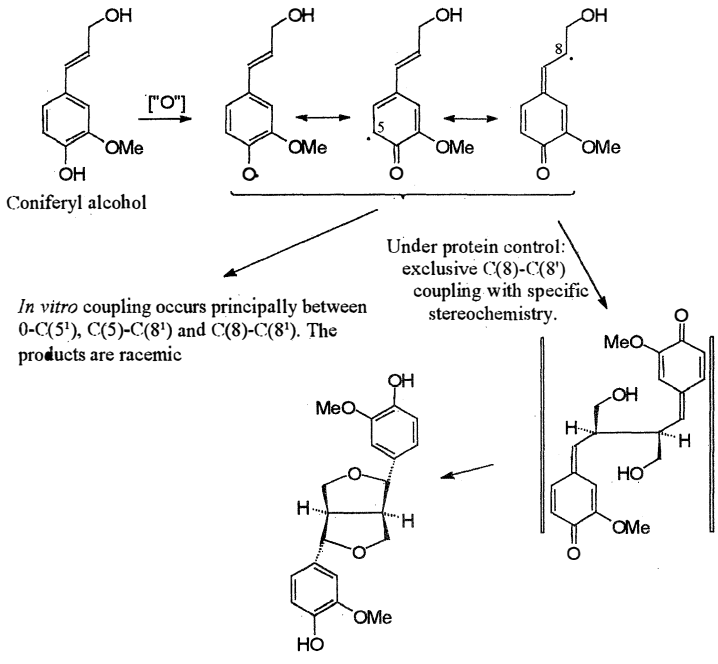
Scheme 2

hydrogen by a phenoxyl radical coordinated to copper. This appears to have been replicated in the model system shown (Scheme 1) [17].

However, there are various other systems, notably some hydrocarbon oxidases based on iron, which appear at first sight to involve radicals, but which in some subtle, incompletely understood way do not.

One fascinating aspect of these systems has been the superficially successful endeavour to mimic their action in the laboratory using small-molecule systems. A pertinent example is methane monooxygenase, which will oxidise aliphatic hydrocarbons to alcohols. When the enzyme is used to catalyze the oxidation of the cyclopropane derivative shown in Scheme 2, the cyclopropylcarbinol is a significant product, yet the hypothetical cyclopropylcarbinyl radical intermediate is known to rearrange so fast that it does so only marginally less rapidly than the time of a molecular vibration. When the same compound is oxidized using the model iron complexes designed to mimic the prosthetic group of the enzyme, exclusively rearranged compounds are formed [18]. So the challenge is not only greater understanding of those systems in which radical processes have been clearly established, for example by unambiguous spectroscopic means, but also to understand those in which it appears that radicals are involved, but for which it is becoming clear that they are are never "free".

Biosynthetic pathways in the plant kingdom have been studied for many years. Possibly the very low efficiency of phenol oxidative coupling in early studies on alkaloid biosynthesis may even have contributed to the poor image of radical chemistry in the 1950s and 60s. More recently, interest in aspects of secondary metabolism in plants seems to have declined, perhaps because of lack of funding, although occasional reports of novel radical-based pathways continue to appear. One particularly important development has been made recently, pertinent to one of the major constituents of biomass [19]. This is the discovery that oxidation of monolignols, e.g. coniferyl alcohol, to lignans and lignins is under strict biochemical control, just as is, for example, prostaglandin synthesis. This is in marked contrast to the random free-radical process which had hitherto been widely accepted. This control depends on the presence of members of a new class of "dirigent" (i.e. pathway directing) proteins. These direct the dimerization, but are *not* responsible for the phenol oxidation. The original result, with a protein from *Forsythia suspensa*, is shown below.



Finally, I should mention the smallest, least reactive, but arguably one of the most important of them all, nitric oxide. NO was designated "molecule of the year" by the editors of *Science* magazine in 1992. Now this key biochemical messenger has yielded Nobel Prizes and an explosion of new data [20].

I have, of course, been very selective. Inevitably, there are whole areas of radical chemistry which I have not touched upon. What about gas-phase reactions, including ozone depletion in the upper atmosphere? What about redox properties, and radical ion chemistry? What about biradicals (in particular the fascinating story of the enediyne antibiotics)? When *is* a radical "free," and what are "caged" radicals?

But I hope that I have informed you that there is a world of radical chemistry out there that gets scant mention in most basic texts, much of which is conceptually not difficult, and which is largely solvent independent, since electrically neutral species are commonly involved – although it *is* usually necessary to keep the oxygen out!

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