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BASIC PRINCIPLES OF REACTIVITY IN FREE RADICAL CHEMISTRY

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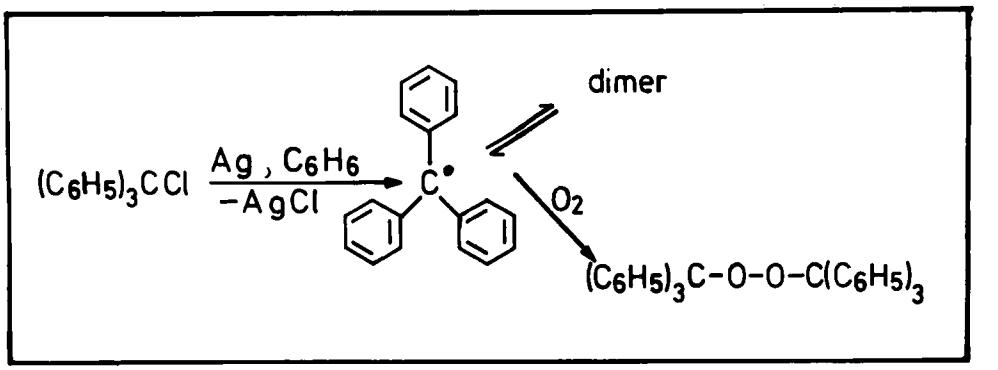
This review is concerned with an overall survey of reactivity in free radical chemistry. A concise classification is given of elementary reaction steps which can be combined in different ways to account for overall chemical transformations: radical forming reactions, radical transformations, and radical destroying reactions. From this is derived the concept of the chain reaction which leads on to an up-to-date theory for understanding reactivity in free radical processes. Finally, a few aspects of autoxidation are discussed.

KEY WORDS: Free Radicals, Review.

During the second half of the last century, in which the structural theory of organic molecules was still in its development, the isolation of molecular fragments, called radicals, was a topical goal of chemical research. Success finally turned up at the turn of the century, when M. Gomberg observed the transient appearance of a yellow colour on warming a benzene solution of triphenylmethyl chloride over silver powder. The color disappeared again on cooling or on exposure to oxygen.



The yellow colour was assigned to the highly conjugated system of the triphenylmethyl radical intermediate existing in equilibrium with its dimer, which was uncorrectly believed to be hexaphenylethane for a long time.

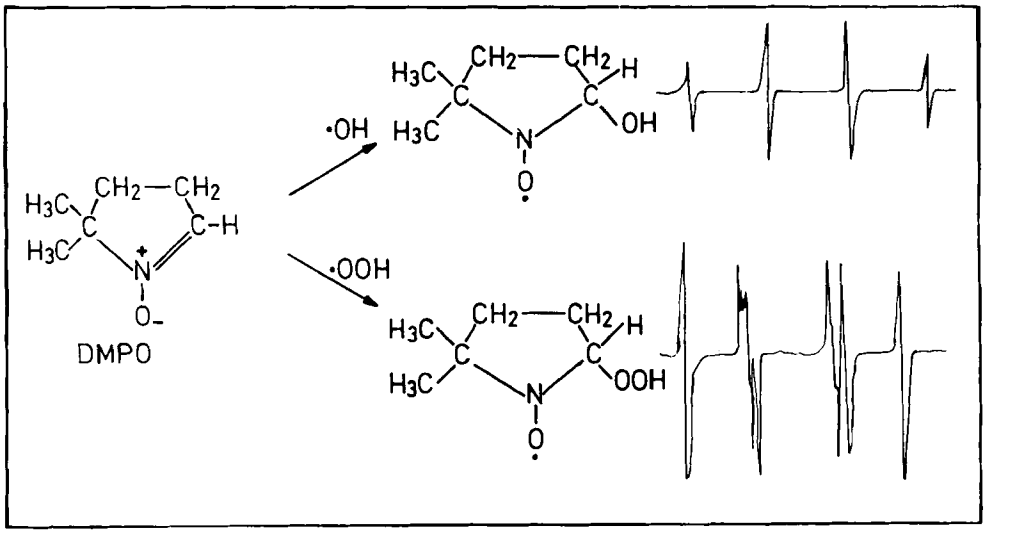
Since these observations were strong evidence for the existence of the free triphenylmethyl fragment, species of this type were subsequently called *free radicals*. After introduction of the electron pair bond, free radicals were defined as molecular or atomic entities marked by the presence of a single unpaired electron. Their fast dimerization and their capture by oxygen turned out to be typical for free radicals in

general. Molecular oxygen is itself a biradical, because two of its 12 valence electrons occupy separate orbitals with parallel spins, and, accordingly, are not paired. In singlet oxygen, in contrast, which is the excited state, all electrons are paired.

The properties of free radicals and, most of all, their reactivities are, of course, chiefly determined by the unpaired electron. There is a great driving force for reactions that bring the system back into a paired electronic state. Free radicals, accordingly, are very reactive species which undergo chemical transformations with high rates but often with low selectivity. The "stigma" of low selectivity was attributed so frequently to free radicals for such a long time that attempts to develop free radical reactions for use in synthesis (which require selectivity, of course) remained scarce, and hypotheses postulating free radical reactions in biology were considered exotic.

The use of free radical chemistry, therefore, until quite recently, remained in certain industrial processes like cracking of crude oil, chlorinations, air oxidations, and polymerizations in which selectivity was either not required or easily achieved.

A long period of about 25 years of basic research and penetration by theory were required to change this situation. With the discovery of electron spin resonance spectroscopy in 1945 the door was opened for the direct observation of the whole spectrum of persistent and transient radicals. In combination with flash methods, matrix isolation and many other advanced techniques a high level of information about conformations and delocalization of free radicals and about rates of free radical reactions became available. ESR-spectra are highly complex spectra from which, of course, very detailed information is available.



The method of *spin labelling* allows the investigation of biological structures as in membranes or of lipid protein interactions. Metalloprotein enzymes have also been investigated successfully by esr techniques. *Spin trapping* allows the capture and esr detection of transient radicals in biological systems;

The cyclic nitrone DMPO captures a hydroxy or superoxide radical, the product may be identified from the splitting pattern of the esr spectra of the nitroxide radicals so formed.

Other modern techniques, like CIDNP, polarography and further electrochemical methods, mass spectroscopy, laser flash photolysis and computational methods have

additionally contributed to obtaining a rich fund of information about structure and bonding of free radicals and about kinetic data for their reactions. I cannot discuss this in any more detail in this lecture.

Parallel with the investigation of free radicals by physical methods the mechanisms of their reactions and their reactivity were intensely investigated during the last 25 years. As a result free radical reactions are rather easy to survey today, their reactivity relationships are much better understood now, selective processes well suited for synthesis have been developed, and a rich chemistry of free radicals in biological systems has become known.

CLASSIFICATION OF ELEMENTARY STEPS IN FREE RADICAL CHEMISTRY

The mechanistic investigation of free radical chemistry has lead to the recognition of a limited set of elementary reaction steps which can be combined in many different ways to account for overall chemical transformations. In the following I will first expose you quite briefly and concisely to this classification. We will then derive from it the important concept of the chain reaction, which dominates free radical chemistry. This concept finally will lead us to an up–to–date theory for understanding

BUILDING BLOCKS OF FREE RADICAL CHEMISTRY

1. *Radical Forming Reactions* (initiation)
   thermolysis or photolysis: $A - B \xrightarrow{T/h\nu} A^{\cdot} + B^{\cdot}$
   bimolecular bond cleavage: $A - B + C = D \xrightarrow{T} A - C - D^{\cdot} + B^{\cdot}$
   electron transfer:
   $$A - B + M \nearrow A - B^{\cdot -} + M^{+} \quad \searrow A - B^{+\cdot} + M^{-}$$
2. *Radical Transformations* (chain steps)
   atom transfer: $X^{\cdot} + A - B \longrightarrow X - A + B^{\cdot}$
   addition to π-bonds: $X^{\cdot} + A = B \longrightarrow X - A - B^{\cdot}$
   β-cleavage: $X - A - B^{\cdot} \longrightarrow X^{\cdot} + A = B$
   addition to and elimination from heteroelements:
   $X^{\cdot} + PY_3 \longrightarrow XPY_3^{\cdot} \longrightarrow XPY_2 + Y^{\cdot}$
   electron transfer: $X^{\cdot} + Y^{-} \longrightarrow X^{-} + Y^{\cdot}$
3. *Radical Destroying reactions* (termination)
   dimerisation: $A^{\cdot} + B^{\cdot} \longrightarrow A - B$
   disproportionation: $A^{\cdot} + X - B - C^{\cdot} \longrightarrow A - X + B = C$
   electron transfer:
   $$A^{\cdot} + M \nearrow A^{-} + M^{+} \quad \searrow A^{+} + M^{-}$$

reactivity in free radical chemistry. Finally, I will discuss a few aspects of autoxidation.

The formation of products from starting material in Free Radical Chemistry never comes about as a simple single step transformation. It is always the result of a sequence of elementary reaction steps, which can be viewed like building blocks of a construction set. There is only a limited number of different types of building blocks available. The great range of free radical reactions, in general, is due to the variation of radicals and molecules taking part in these elementary steps on the one hand, and on the other to different ways of combining these elementary steps.

The three main classes of elementary steps can be distinguished by the function they play in the overall transformation.

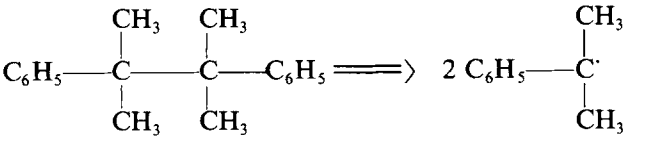
1. *Radical Forming Reactions*
   generate free radicals from closed shell molecules.
2. *Radical Transformations*
   in which one type of radical is entering a reaction step and another one is simultaneously generated as one of the products.
3. *Radical Destroying Reactions*
   in which two radicals react with one another regenerating closed shell molecules.

The possibility of radical destroying self reactions distinguishes radicals typically from carbenium ion and carbanion intermediates. The radical destroying processes are very fast reaction steps, as we will see, and, therefore, prevent in most instances the accumulation of high radical concentrations. They are the limiting factor for the lifetime and, accordingly, for the time scale of the competing radical transformations.

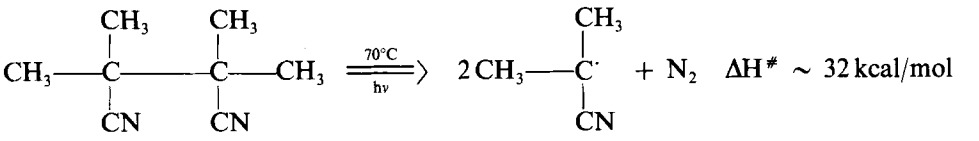
In order to come to the point, the three types of processes: radical formation, radical transformation, and radical destruction (which is also called "termination") and their combination are the basic requirement for the establishment of a chain reaction. Most free radical chemistry is, accordingly, going via chain reactions which are composed of chain initiation, chain carrying steps, and chain termination. Before we go any further with this discussion we have to consider the three types of elementary reaction steps in some more detail.

RADICAL FORMING REACTIONS

$$(CH_3)_3C{-}O{-}O{-}C(CH_3)_3 \xrightarrow[130°C]{h\nu} 2(CH_3)_3CO^{\cdot} \qquad \Delta H^{\#} \sim 36\,\text{kcal/mol}$$



$\Delta H^{\#} \sim 50\,\text{kcal/mol}$

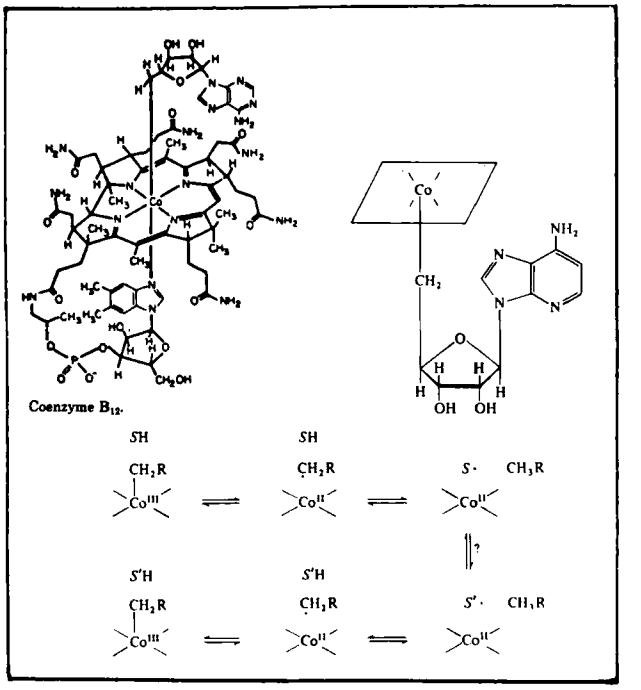


$\Delta H^{\#} \sim 32\,\text{kcal/mol}$

$$Cl{-}Cl \xrightarrow{h\nu} 2\,Cl^{\cdot}$$

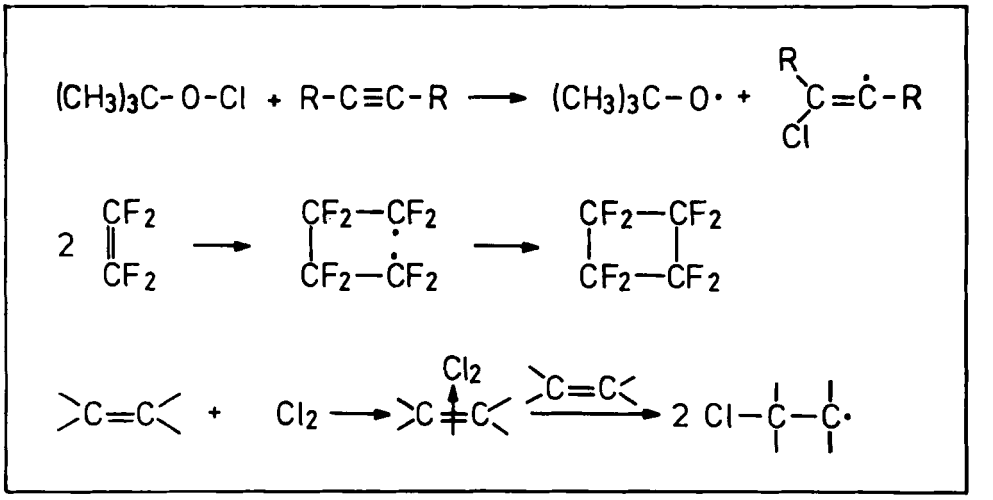
The simplest way of generating free radicals is by *thermolysis or photolysis*. The weak peroxide bond is, of course, cleaved at a lower temperature than a strong carbon-carbon bond. Substituents can enhance bond dissociations by generating repulsive steric interactions (steric acceleration of bond cleavage), which are released on dissociation. Alternatively, stabilization of the resulting radicals by conjugation with a substituent also weakens the original bond. The low thermal stability of aliphatic azo compounds like AIBN is due to the high heat of formation of the nitrogen molecules which are set free. Photoinitiators must, via a proper chromophor, be able to absorb light of sufficient energy to make bond cleavage in the excited molecule an exothermic process. High energy *radiation*, of course, can do the same. Radiation induced generation of radicals is well known in biological systems.

One instance in which thermal bond cleavage has been evoked as a decisive step in enzymatic reactions is the cleavage of the weak carbon-cobalt bond in vitamin B_{12}.



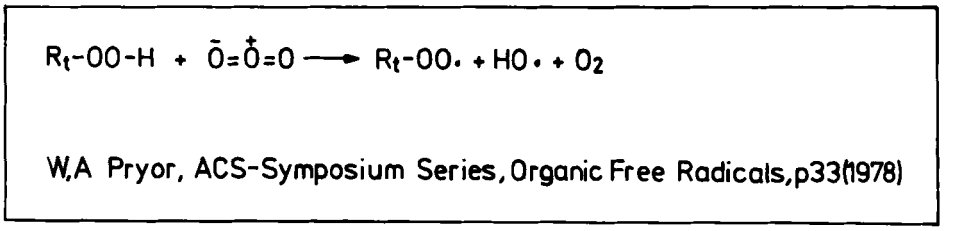
It is the initiating step for several important enzymatic isomerizations. The isomerization of the substrate radicals S· to S'· need not necessarily be a simple radical rearrangement process, however. Alkyl-cobalt bond strengths have values between 18–25 kcal/mol, according to recent work of J. Halpern. They are weaker bonds than the peroxide bond.

Radicals can also be generated in *biomolecular thermal reactions*; molecules with weak bonds are involved and a strong σ-bond is formed on collision. Typical examples are:

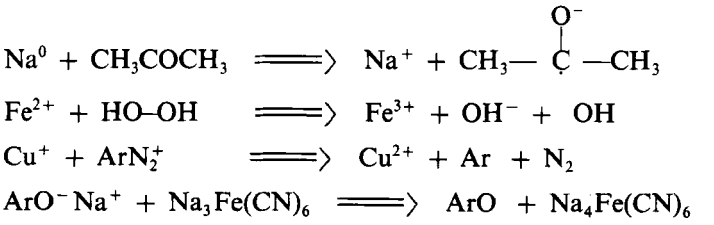


The most famous example is the spontaneous initiation of styrene polymerization.

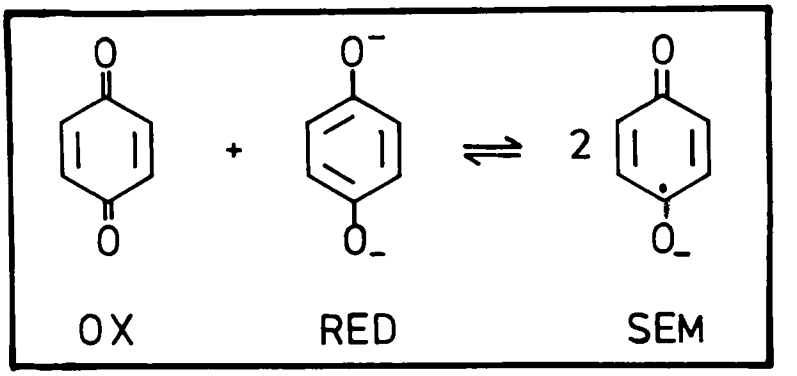
Pryor calls these reactions, quite properly, "molecule induced homolyses" and has presented evidence that the reaction of ozone with hydroperoxides, believed to be important for the autoxidation of polyunsaturated fatty acids, is of this type.



The last and possibly most important process for the generation of radicals is *Electron Transfer*. Single electron oxidizing or reducing agents, in particular transition metal ions, transfer an electron from or to an organic substrate and generate free radicals in this way.



Electron transfer between two closed shell molecules is another well known process which apears to occur, in particular, when no cleavage or formation of single bonds is required. The most prominent example, of course, is the reaction of quinone and hydroquinone type molecules to the semiquinones.

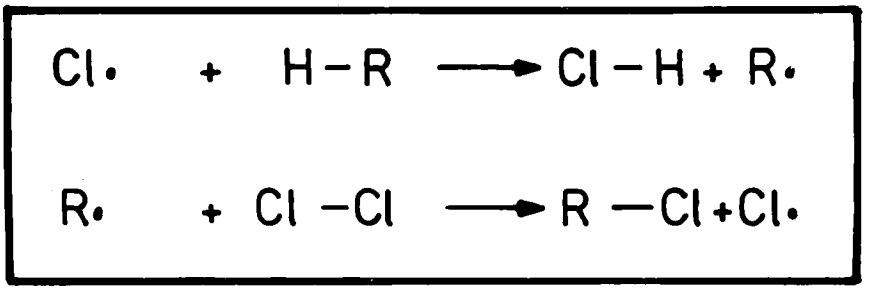


In recent years it has been recognized using special techniques that electron transfer between reducing molecules like metal organic compounds, alkoxides or metal hydrides and weakly oxidizing partners like alkyl halides or ketones can go via single electron transfer steps as an alternative to the classic scheme of nucleophile-electrophile interaction.

RADICAL TRANSFORMATIONS

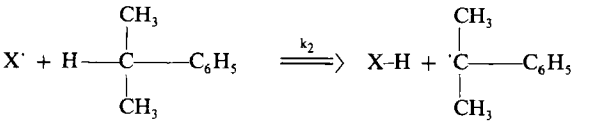
The formation of radicals is a "conditio sine qua non" for radical chemistry to occur, of course. The richness of this chemistry, however, is due to the radical transformation steps, their great variety of combination into a chain process and to the great variety of different radicals and substrates taking part in these reactions.

The first members of this class are the *atom transfer reactions* that usually result in overall substitution. Best known is the transfer of hydrogen or halogen as found in the classic chlorination chain.



Typically radical attack on hydrocarbon structures occurs with few exceptions at the periphery, at hydrogen or e.g. at halogen substituents, but almost never at carbon, where nucleophiles attack. The rates of these rection steps can be extremely fast as seen from a selection of rate constants:

Hydrogentransfer



X·	k_2(1/m·sec)	T°C
Br·	$1.2 \cdot 10^7$	40°
C_6H_5·	$\sim 10^7$	60°
t-C_4H_9-O·	$4.3 \cdot 10^4$	40°
4-Cl-C_6H_4-S·	$1.2 \cdot 10^3$	23°
Cl_3C·	$1.3 \cdot 10^2$	40°
t-C_4H_9-O-O·	$1.3 \cdot 10^{-1}$	30°
$\sim CH_2$—$\underset{\displaystyle C_6H_5}{\overset{\displaystyle |}{CH}}$·	$1.3 \cdot 10^{-3}$	60°

Halogentransfer

$CH_3^{\cdot} + X\text{-}CCl_3 \xrightarrow{k_2} CH_3\text{-}X + {}^{\cdot}CCl_3$

X	k_2[1/m·sec]	E_a
Br	$2 \cdot 10^6$	~7 kcal/mol
Cl	$\sim 10^3$	~13 kcal/mol

In cases in which the bond energy for hydrogen in the substrate and in the transfer product match closely, the transfer may become reversible:

$$C_6H_5CH_2^{\cdot} + HBr \rightleftharpoons C_6H_5CH_3 + Br^{\cdot}$$

$$D_{HBr} = 87\,\text{kcal/mol}$$

$$D_{C_6H_5CH_2\text{-}H} = 85\,\text{kcal/mol}$$

From the point of synthetic chemistry quite a variety of halogenating agents, following these principles, are known, but also oxygen functionality may be introduced into aliphatic systems in this way. The main problem is, of course, to find ways of selectively attacking a particular position in a complicated structure that offers many different carbon hydrogen bonds.

Another important group of radical transformation steps are *radical additions to π-bonds* and the reverse, *β-cleavage*. The examples on the next slide show that the activation energies for the addition of several types of radicals to carbon carbon π-bonds are rather small and the additions are therefore fast reactions. This is particularly true for electronegative radicals like bromine atoms, CF_3 and others.

$$Br^{\cdot} + CH_2{=}CH\text{-}CH_3 \rightleftharpoons Br\text{-}CH_2\text{-}\dot{C}H\text{-}CH_3$$

$$CH_3^{\cdot} + CH_2{=}CH_2 \longrightarrow CH_3\text{-}CH_2\text{-}CH_2^{\cdot} \qquad E_a = 7.9\,\text{kcal/mol}$$

$$t\text{-}C_4H_9^{\cdot} + HC{\equiv}CH \longrightarrow tC_4H_9\text{-}CH{=}\dot{C}\text{-}H \quad E_a = 5.3\,\text{kcal/mol}$$

$$CF_3^{\cdot} + C_6H_6 \longrightarrow \begin{matrix} CF_3 \\ H \end{matrix}\!>\!C\!\left(\cdot\right)\!\bigcirc \quad E_a = 4.4\,\text{kcal/mol}$$

In combination with atom transfer steps many chain reactions resulting in overall addition of small molecules to double bonds are known.

Examples for H-X Additions to Alkenes

$$\underline{\underline{X}}^{\cdot} + H_2C{=}CHR \longrightarrow X\text{-}CH_2\text{-}\dot{C}HR$$

$$X\text{-}CH_2\text{-}\dot{C}HR + Hx \longrightarrow X\text{-}CH_2\text{-}CH_2R + \underline{\underline{X}}^{\cdot}$$

For R= Alkyl HX= HBr, HSR, $HCCl_3$ etc.

For R= CN etc. HX= H–C(=O)–R, "H–R"

($RHgX + NaBH_4$)

($RBr + HSnBu_3$)

For addition steps which are close to thermoneutrality, the reverse β-cleavage sets up an equilibrium. At high temperatures the β-cleavage can become dominating, e.g. in thermal cracking of crude oil.

β-Cleavage also becomes the dominating process when carbon-oxygen double bonds are involved as these have a much stronger π-bond component than carbon-carbon double bonds. A typical example is the β-cleavage of alkoxy radicals frequently observed at slightly elevated temperatures.

$$i\text{-}C_3H_7\text{–}\underset{\displaystyle C_2H_5}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}\text{–}O^{\cdot} \rightarrow \begin{cases} i\text{-}C_3H_7\text{–}CO\text{–}CH_3 + C_2H_5^{\cdot} & 3\% \\ i\text{-}C_3H_7\text{–}CO\text{–}C_2H_5 + CH_3^{\cdot} & 0.5\% \\ CH_3\text{–}CO\text{–}C_2H_5 + i\text{-}C_3H_7^{\cdot} & >95\% \end{cases}$$

$$E_a \approx 10\text{–}15\,\text{kcal/mol}$$

A particularly fast β-cleavage reaction is the decarboxylation of acyloxy radicals. The decarbonylation of acyl radicals – a less frequent *α-cleavage* – is a much slower reaction, frequently requiring elevated temperatures.

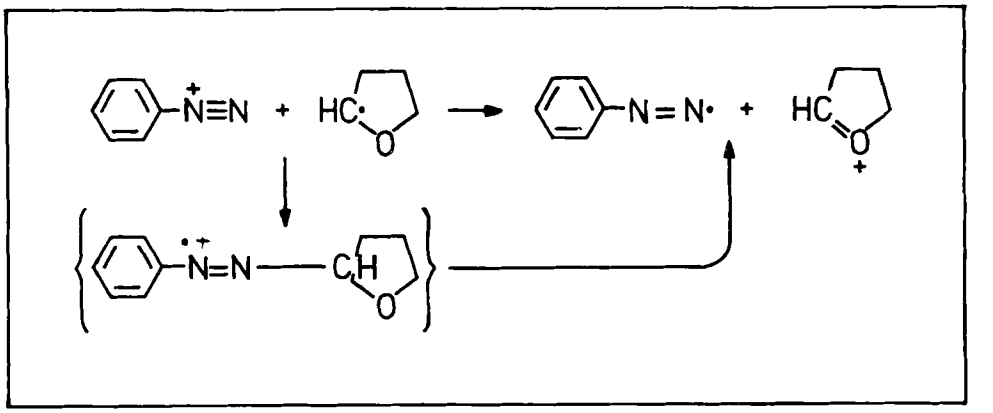
$$CH_3\text{–}COO^{\cdot} \Longrightarrow CH_3^{\cdot} + CO_2 \quad E_a \sim 1\text{–}3\,\text{kcal/mol}$$

$$CH_3\text{–}C{=}O \Longrightarrow CH_3^{\cdot} + CO \quad E_a \sim 15\,\text{kcal/mol}$$

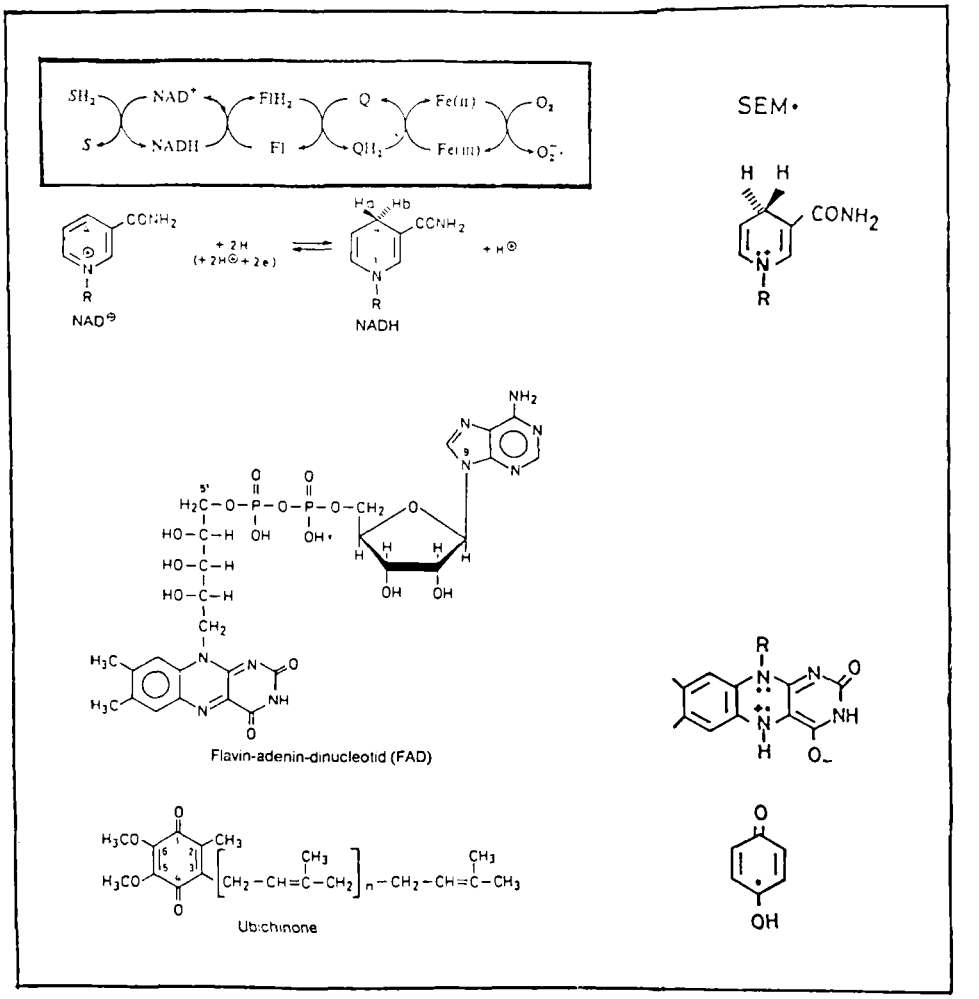
Additions, α-cleavage, or β-cleavage steps can also occur at heteroatoms, e.g. in phosphorus, silicon and boron compounds.

$$RO^{\cdot} + PR_3 \Longrightarrow \underset{\text{phosphoranyl radical}}{[R\text{–}O\text{–}\dot{P}R_3]} \begin{cases} \nearrow R^{\cdot} + OPR_3 & \beta\text{-cleavage} \\ \searrow ROPR_2 + R^{\cdot} & \alpha\text{-cleavage} \end{cases}$$

Finally, *electron transfer* can also result in radical transformation. Electron rich radicals are good donors, nitro- and diazonium groups are particularly good electron acceptors.



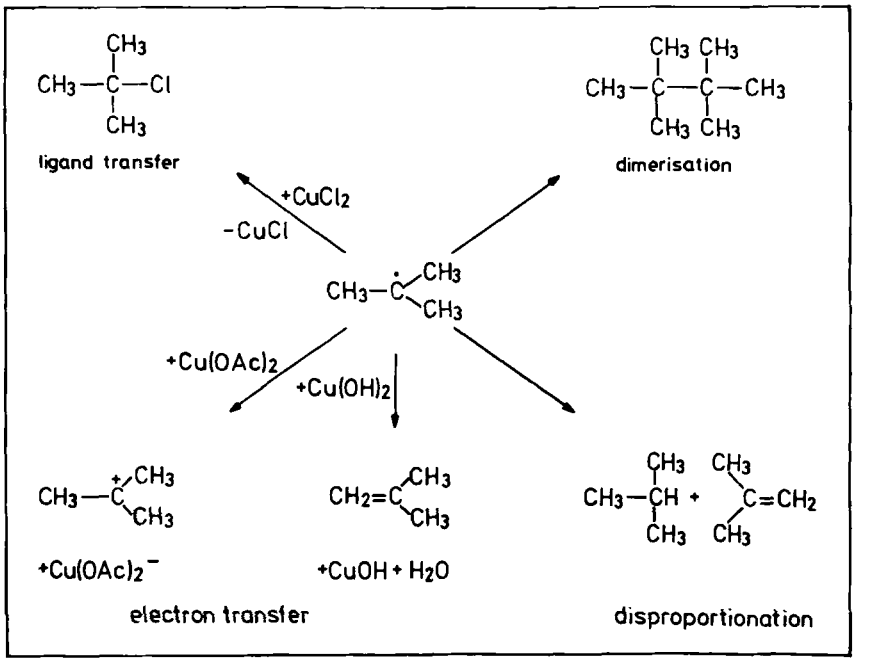
Electron transfer steps of this type are very well known, of course, in biochemistry. Biological oxidations are effected by coenzymes. Some of them function as electron carriers, others possibly as hydride carriers. A simplified sequence is outlined of the events occuring in electron transport processes involved in oxidation of a substrate by molecular oxygen.



In photosynthesis also an electron transfer chain is involved, which, however, works in the reverse direction.

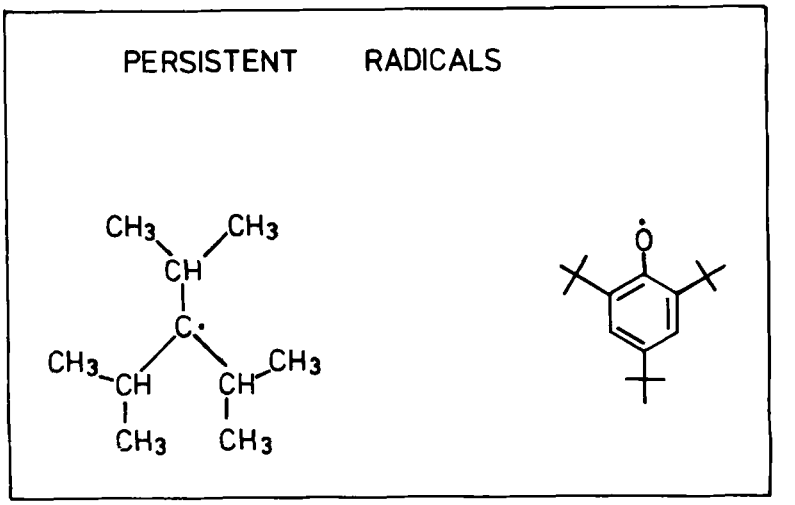
RADICAL DESTROYING PROCESSES

Three very fast reactions are responsible for the consumption of free radicals: *dimerization, disproportionation*, and *electron transfer* with or without concomitant ligand transfer.



The two self reactions, dimerization and disproportionation, are just the reverse processes of unimolecular and bimolecular formation of radicals discussed before. Because of their high exothermicity, extremely high rate constants are found for these reactions, reaching often the diffusion controlled rate limit of about 10^9 l/mol · sec. No additional activation barrier has to be passed in general for these termination reactions, irrespective of whether simple alkyl or resonance stabilized benzyl or allyl radicals are involved.

Dimerization and disproportionation become slow processes or are completely suppressed for bulky radicals, like triisopropylmethyl and others, whose approach is severely sterically hindered.



Radicals trapped in rigid matrices, like adamantane crystals, or hydrocarbons glasses at low temperature also become persistent owing to the inhibition of diffusion.

Of particularly timely interest is the question, how selectivity come about in these self reactions of radicals which need not pass an enthalpic barrier? As the competition between disproportionation and dimerization or the stereo- and regioselectivity of these termination reactions are nearly invariant to temperature changes, it has to be concluded that there exist entropy barriers responsible for the observed selectivity.

$$\lg k_{rel} = \frac{\Delta H^{\#}}{2.303\,RT} - \frac{\Delta S^{\#}}{2.303\,R}$$

This may be an important factor also for the lifetime of free radicals and for the selectivity in biological systems, e.g. the dimerization step in vitamin B_{12} chemistry. In a protein matrix, radicals probably can be locked and entropy barriers can be built up.

PRINCIPLES OF CHAIN REACTIONS

For an understanding of reactivity and selectivity in free radical chemistry a little more has to be said about the principles of chain reactions. According to the "steady state principle", radical concentrations stay rather constant at any moment of an ongoing chain. When chain initiation and termination are well defined

Initiation: $R\text{–}R \xrightarrow{k_1} 2R^{\cdot} \quad \frac{dR^{\cdot}}{dt} = 2k_1[RR]$

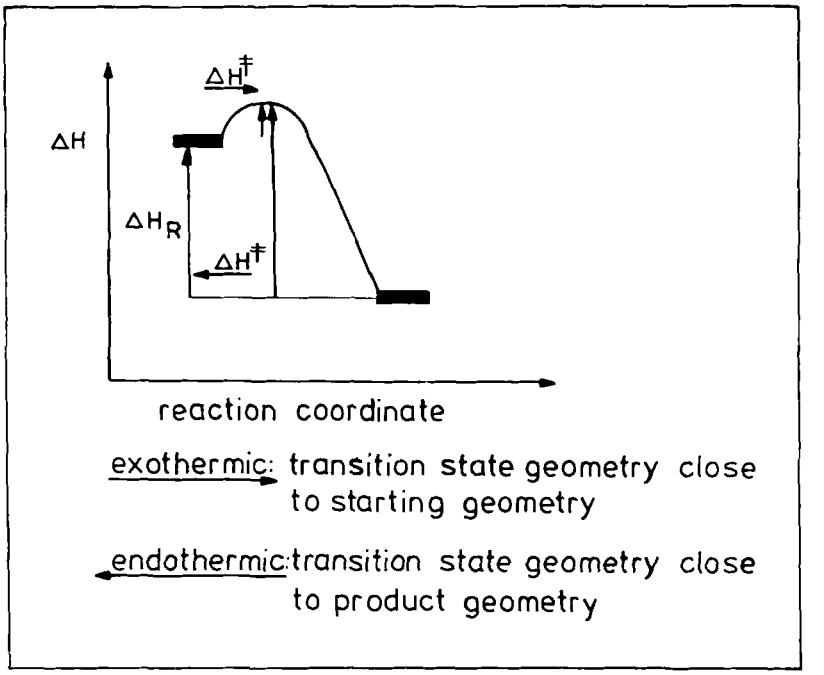
Chain: $R_1^{\cdot} + A \longrightarrow R_2^{\cdot} (+B)$

$R_2^{\cdot} + C \longrightarrow R_1^{\cdot} + \text{product}$

Termination: $2R'^{\cdot} \xrightarrow{k_2} R'\text{–}R' \quad \frac{-dR^{\cdot}}{dt} = 2k_2[R'^{\cdot}]^2$

the steady state radical concentration and, accordingly, the life time of a radical center between its birth and its termination can be calculated. It is of the order of 1 sec. If the chain length, i.e. the number of chain cycles during the life time is 100.000 or more, then one has to conclude that only very fast elementary steps, i.e. generally only exothermic steps, can enter into a radical chain. According to the Hammond principle, exothermic reaction steps have early transition states which resemble in energy as well as in geometry more the starting state than the products. Again the question has to be discussed how to achieve selectivity in reactions like these which are product determining in chain reactions.

Structure reactivity relationships have been discussed, even for chain reactions, for a long time on the basis of the presumed influence of a substituent or of a structure variation in general on the "stability" of the radical species taking part in a reaction or in a reaction series, quite in contrast to the expectation from the Hammond principle. The distinction between kinetic and thermodynamic stability was often ignored, and a separation of steric and electronic effects was seldom achieved. It is not unexpected, therefore, that conclusions frequently were drawn by circular argument. A typical example is the question of autoxidation:



Circular — Argumentation

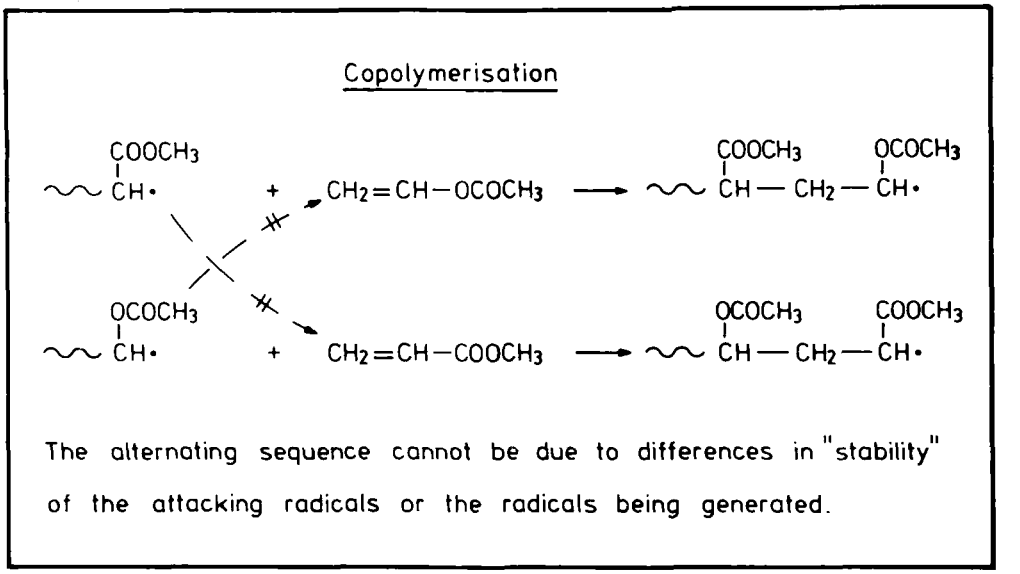
1. $CH_3CH_2-OC_2H_5 + CH_3\underset{\underset{OO\cdot}{|}}{CH}-OC_2H_5 \longrightarrow CH_3\overset{\cdot}{C}H-OC_2H_5 + CH_3\underset{\underset{OOH}{|}}{CH}-OC_2H_5$

2. $CH_3\overset{\cdot}{C}H-OC_2H_5 + O_2 \longrightarrow CH_3\underset{\underset{OO\cdot}{|}}{CH}-OC_2H_5$

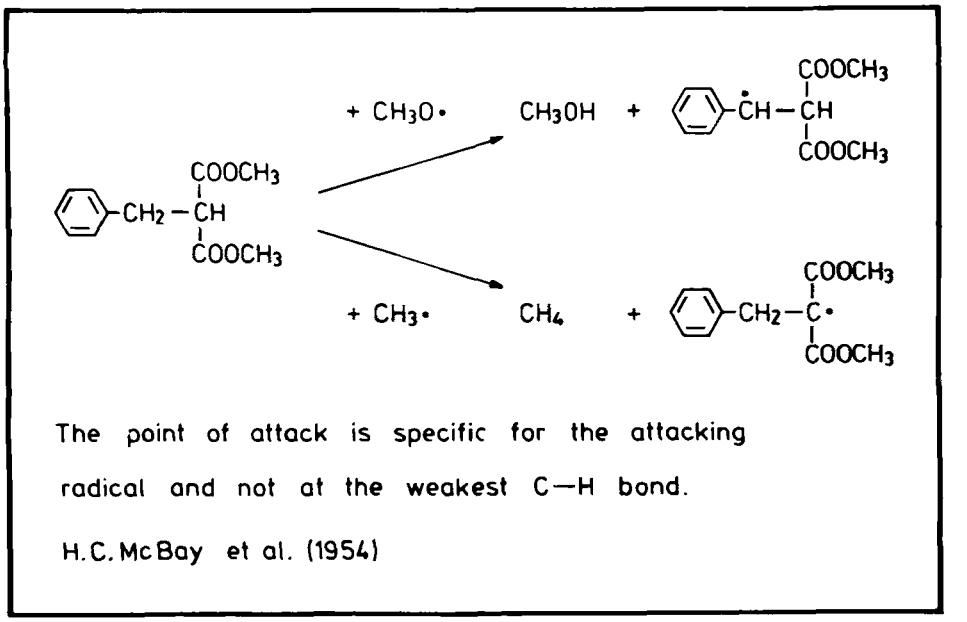
A says: "Autoxidation of ethers in the α-position is a fast and efficient process because α-ethoxyethyl radicals are stabilized by resonance".

B says: "α-Ethoxyethyl radicals are stabilized by resonance. This is obvious from their efficient and preferential formation in the autoxidation chain".

Clearly, no interpretation of reactivity data is achieved in this way. Strangely, this type of reasoning persists in many textbooks and, occasionally, even in the most recent literature despite the fact that convincing experimental results and arguments disproving the relationships between reactivity and radical stability can be found in the older literature:.

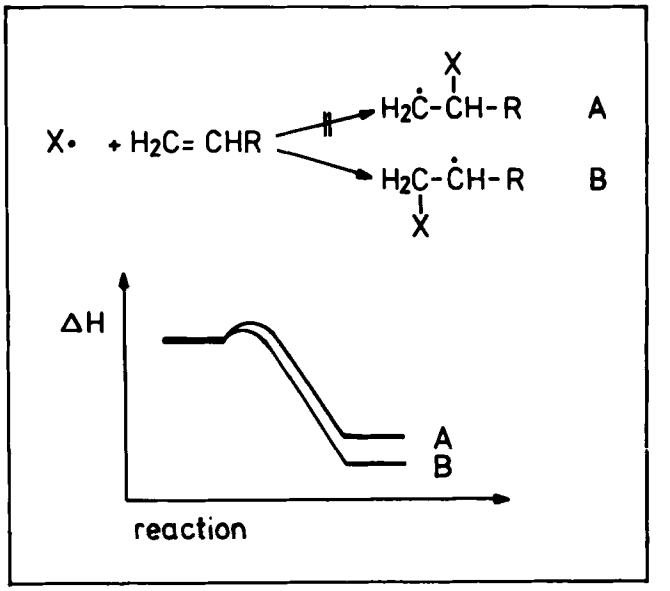


The alternating sequence in certain copolymers, which is due to differences in selectivity of the two types of radical end groups, cannot be explained on the basis of the different "radical stabilities" of these two types of radicals.

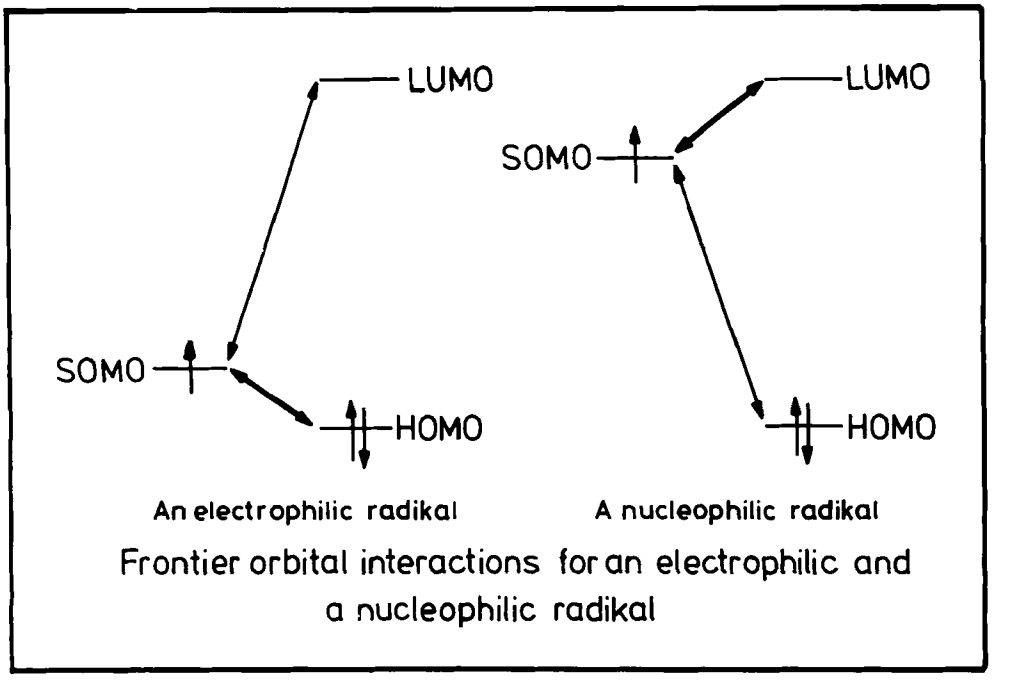


Benzylmalonic ester is attacked at different sites by different radicals. "Nucleophilic" methyl radicals attack at the point of lowest electron density. Electrophilic methoxy radicals, in contrast, prefer the point of higher electron density in the benzylic position. The rule that the most stable radical is generated with preference is definitely not in accord with these results.

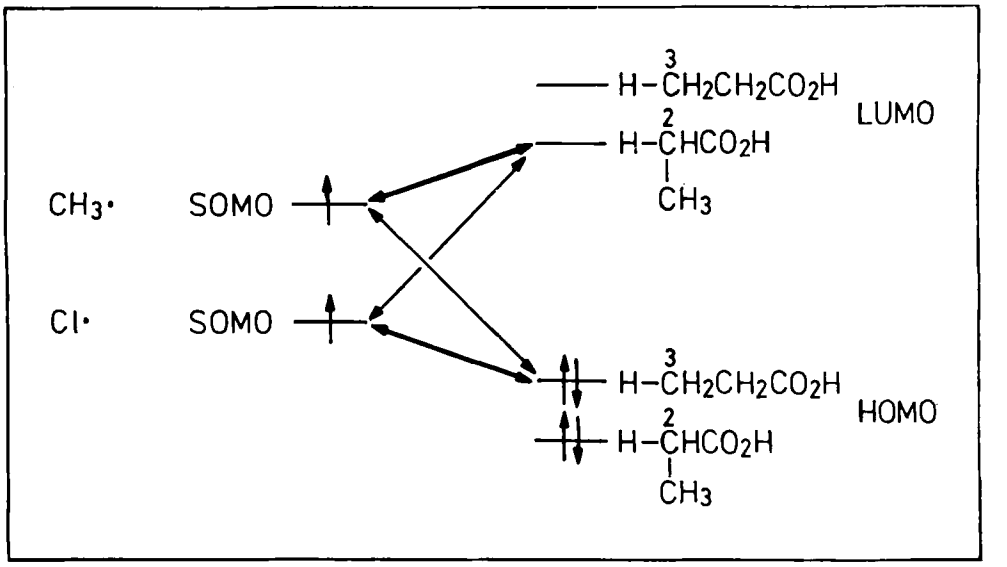
Another question is the prefered terminal attack at alkenes by all types of radicals.



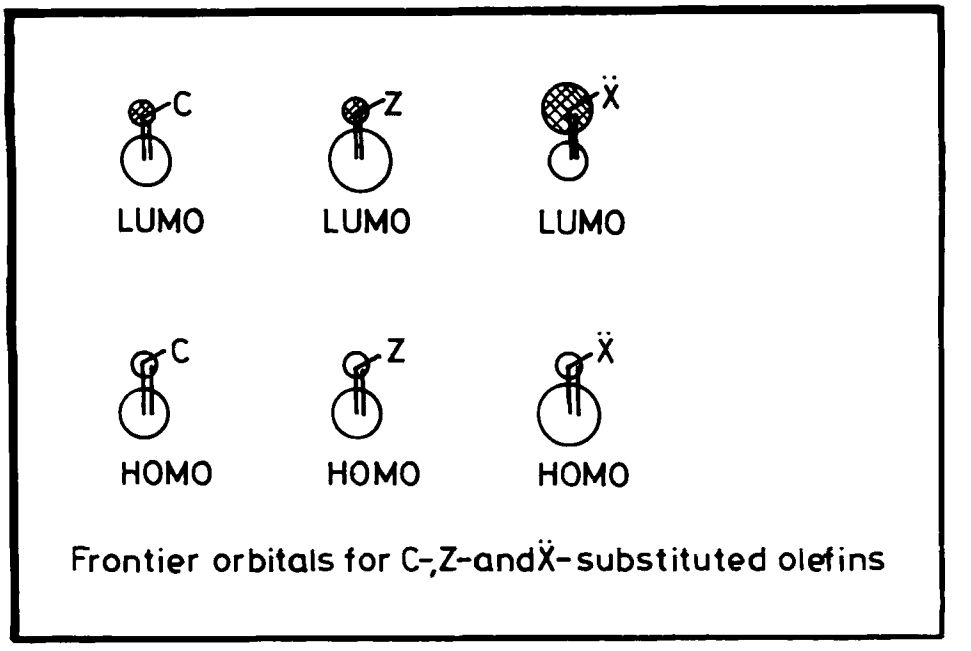
An interpretation based on the different stability of the two different radical products is certainly not appropriate for an exothermic reaction like this one.



An answer to these open questions and an interpretation of reactivity and selectivity in many free radical reactions comes from *Frontier Orbital Theory*, which is particularly suited for early transition state reactions. The quality of the interaction of the single occupied orbital of the radical (SOMO) with one of the frontier orbitals of the substrate (HOMO or LUMO) determines the rate and accordingly the selectivity of the reaction.



Low lying SOMO'S of electronegative radicals interact preferentially with the HOMO of the substrate, which is usually on a similar energy level. Electron rich nucleophilic radicals, e.g. alkylradicals have high lying SOMO'S, and therefore, interact preferentially with the LUMO of the substrate. In this way polar effects like those discussed for copolymerization or different selectivities of different radicals can be explained easily.



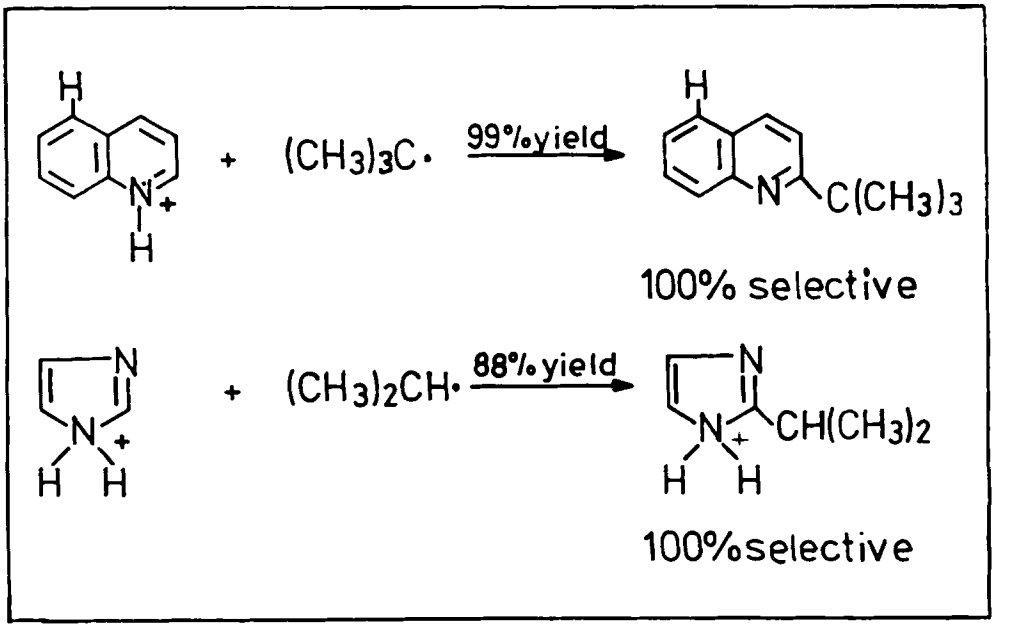
Frontier orbitals for C-,Z-andẌ-substituted olefins

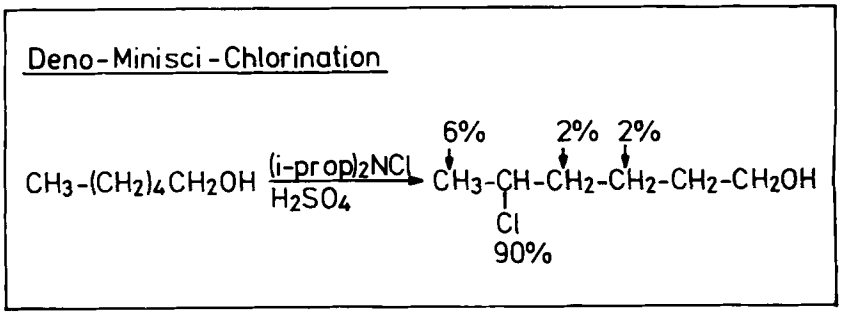
The preference for anti Markovnikoff radical attack at terminal alkenes is, accordingly, the result of preferred attack of the site which has the highest coefficient in the frontier orbital. LUMO and HOMO generally have the highest coefficient at the terminal carbons. The exceptional x-substituted alkenes react, because of their high lying frontier orbitals, usually by HOMO-SOMO interaction.

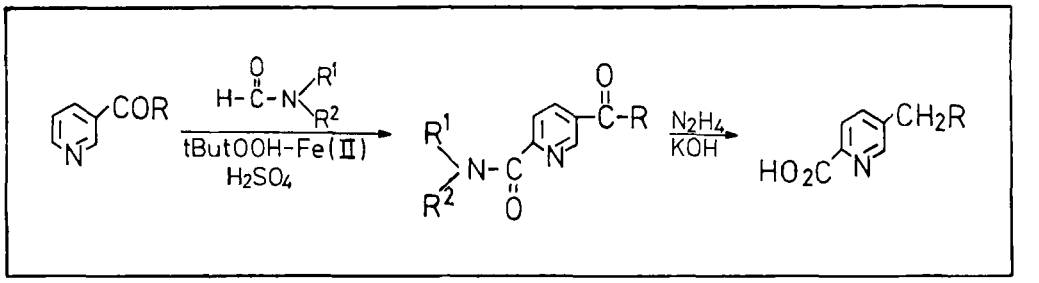
In addition, of course, steric effects may become important and have to be taken into account in each case.

In contrast to earlier beliefs, differences in exothermicity of a reaction or in the stabilities of the radicals generated in a chain step usually have only little effect on rates and selectivities.

Highly selective free radical reactions became possible when these ideas were taken into account, as shown for a few examples from the recent literature.







Let me at the end of my lecture discuss briefly one of the most important radical chain reactions, autoxidation, which also has, great significance in biological systems, e.g. for PUFA oxidation in membranes. A simple view of the unbranched autoxidation chain is shown:

Autoxidation Chain and Termination

Chain

1. R—H + •OOR ⟶ R• + HOOR

2. R• + O_2 ⟶ ROO•

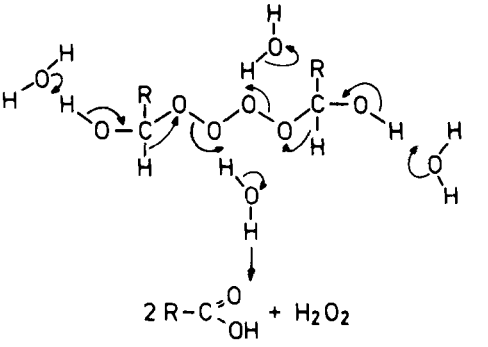
Termination:

2. ROO• ⟶ R-O-O-O-O-R

ROOOOR ⟶ 2 RO• + O_2

⟶ ROOR + O_2 (Cage)

Possible ionic decay of α-Hydroxy tetroxides:



The selectivity of oxygen attack is determined in the hydrogen abstraction step, 1, which is also the slower step under usual conditions and, therefore, also partly responsible for the overall rate. As the O–H bond in hydroperoxides is a weak bond of $\sim D = 90$ kcal/mol, only few hydrogen transfer steps are exothermic. The weakest bonds, i.e. tertiary and benzylic C–H bonds, are oxidized preferentially, indicating partial reactivity control by the stability of the radical products. This need not be necessarily the main factor, however, because C–H bonds in the α-position of ethers, which are not particularly weak bonds, are also oxidized with high rates. Favored SOMO–HOMO interactions offer an alternative explanation of great predictive power also in this example.

The high overall rate of autoxidation of ethers, which is frequently quoted as additional evidence for the stability of α-alkoxyalkyl radicals, is in fact due to the lack of an efficient chain termination step. The fastest dimerization process in this system leads to tetroxides, which mostly decompose again into radicals. α-C–H bonds of alcohols, which probably have quite similar bond strengths, are much more resistant to autoxidation. Alcoholic beverages, starch and cellulose, keep well, at least in principle, even if exposed to air. It has been shown that in aqueous solution an efficient chain termination is available in this system. The termination mechanism may be a fast, ionic decomposition of the tetroxide favored by hydrogen bonding and by the possibility of fast proton transfer to and from the α-hydroxy groups. A possible reaction path is proposed above.

Overall rate data and selectivity data of chain reactions are not generally suited for obtaining information about thermodynamic radical stabilities and, as a rule, they do not often depend on them. In the case of autoxidation the rate is even strongly influenced by the termination process as we have seen.

Accepted by Prof. H. Sies