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Overview of Radical Chain Oxidation Chemistry

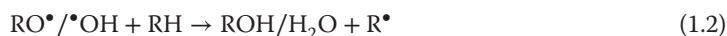
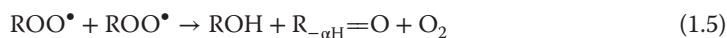
Ive Hermans

1.1

Introduction

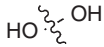
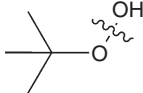
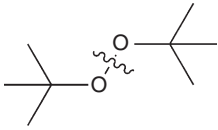
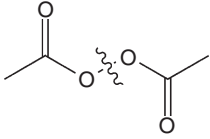
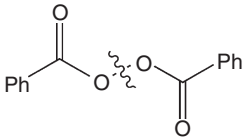
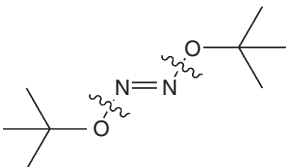
The direct reaction of triplet O_2 with hydrocarbons is usually very slow (e.g., H-abstraction), or quantum-chemically forbidden (e.g., the insertion of O_2 in a C–H bond to form a hydroperoxide). Nevertheless, those high-energy paths can be bypassed by a more efficient radical mechanism as demonstrated by the pioneering work of Bäckström [1]. Although initial studies were aimed at finding ways of preventing undesired autoxidations, it was soon recognized that the controlled oxidation of hydrocarbons can be a synthetically useful route to a wide range of oxygenated products. In subsequent chapters, some of those industrial processes are discussed in more detail. The goal of this introductory chapter is to provide a mechanistic framework for this rather complex chemistry.

In 1939, Criegee made an important contribution by showing that the primary product of cyclohexene autoxidation is the allylic hydroperoxide [2]. The classical textbook on radical pathway for the thermal autoxidation of a general hydrocarbon RH is summarized in reactions (1.1–1.5) [3–5]:

Initiation*Propagation**Termination*

In general, an initiation reaction produces radicals from closed-shell molecules. Different types of initiator molecules and their initiation barriers are summarized

Table 1.1 Common initiators for autoxidations and their initiation barriers.

	48 kcal/mol
	40 kcal/mol
	37 kcal/mol
	31 kcal/mol
	30 kcal/mol
	28 kcal/mol

in Table 1.1. Under normal autoxidation conditions, initiation takes place through O–O cleavage in hydroperoxides (viz., reaction (1.2)). This rate-controlling initiation step is rapidly followed by the fast H-abstraction from the substrate by both alkoxy and hydroxyl radicals (reaction (1.2)), producing alcohol and water, respectively.

For alkoxy radicals, a competitive side-reaction can occur in kinetic competition with H-abstraction from the substrate, namely, β C–C cleavage to produce a carbonyl compound and an alkyl radical (viz., $\text{RCH}_x\text{-CR}'\text{HO}^\bullet \rightarrow \text{RCH}_x + \text{CR}'\text{H=O}$). We discuss this reaction in Section 1.4.

When no initiators such as peroxides are initially added to a hydrocarbon mixture, an *induction* period is observed before oxygen consumption takes place. There are several hypotheses on what might happen during this induction–initiation stage: (i) the direct reaction of triplet oxygen with singlet closed-shell molecules (a thermodynamically disfavored reaction), (ii) the R–H homolysis (a reaction that is very slow due to typical C–H bond dissociation energies of 80–110 kcal/mol), and (iii) the termolecular reaction

$\text{RH} + \text{O}_2 + \text{RH} \rightarrow \text{R}^\bullet + \text{H}_2\text{O}_2 + \text{R}^\bullet$ (unlikely to be of any kinetic significance). A more reasonable explanation for the induction–initiation is the presence of (sub)parts per billion levels of compounds that are more easily cleaved. After the induction period, the rate increases very rapidly. Because of this accelerating effect, one refers to this type of reactions as being autocatalytic. However, until recently, the precise reason for this autocatalytic upswing was not very well understood and is discussed in more detail later.

The RO–OH cleavage can also be catalyzed by transition metal ions that are able to undergo one-electron redox switches such as cobalt and manganese, among others. The catalysis of autoxidations is discussed in more detail in chapters dealing with specific industrial processes.

Chain-propagation reactions neither increase nor decrease the radical population. Two elementary propagation reactions can be distinguished: H-abstractions (reactions (1.2) and (1.4)) and O_2 addition to a carbon-centered radical (reaction (1.3)). The latter reaction is normally diffusion controlled and hence rarely rate determining. As alkoxy radicals are significantly more reactive than peroxy radicals, ROO^\bullet are the predominant radical species in the reaction medium and are thus the main participants in the bimolecular propagation reactions. Although the normal rule is that the weakest C–H bond is preferably attacked, the nature of the H-abtracting species also determines the selectivity. Indeed, the more reactive the H-abtracting radical, the lower the selectivity for the weakest C–H bond, as illustrated by the rate data in Table 1.2. Table 1.2 also shows the significant reactivity differences between hydroxyl, alkoxy, and peroxy radicals, explaining why only ROO^\bullet radicals can be really termed as chain-propagating radicals.

Termination reactions such as (1.5) decrease the number of radicals and produce nonradical products such as alcohols and ketones. Mutual termination reactions of primary and secondary peroxy radicals have near-zero activation energies but unusually low Arrhenius prefactors, suggesting a strained transition state. The exothermicity of this termination is sufficient to produce electronically excited states of either the carbonyl compound or oxygen. Besides the termination reaction (1.5), peroxy radicals can also undergo a self-reaction without termination ($2\text{ROO}^\bullet \rightarrow 2\text{RO}^\bullet + \text{O}_2$) that is often ignored but is equally important as the termination channel itself [9, 10].

Tertiary alkylperoxy radicals are generally assumed to combine with tetroxides (ROOOOR) that subsequently decompose to di-*tert*-alkyl peroxides or *tert*-alkoxy radicals. The decomposition of the tertiary tetroxide has a fairly high

Table 1.2 Rate constants ($\text{M}^{-1} \text{s}^{-1}$) for hydrogen abstraction from primary, secondary, and tertiary C–H bonds by various radical species at 400 K (per H-atom) [6–8].

Attacking radical	Primary C–H	Secondary C–H	Tertiary C–H
$\bullet\text{OH}$	8.1×10^7 (1.0)	3.7×10^8 (4.6)	1.1×10^9 (13.3)
$\text{CH}_3\text{O}^\bullet$	2.1×10^4 (1.0)	2.3×10^5 (10.8)	6.0×10^5 (28.4)
$\text{CH}_3\text{OO}^\bullet$	2.6×10^{-2} (1.0)	4.8×10^{-1} (18.5)	2.7×10^1 (1053)

activation energy, making the termination of tertiary peroxy radicals slower than that of primary and secondary analogs [5].

The chain termination compensates the chain initiation and leads to a quasi-steady state in peroxy radicals. Indeed, the characteristic lifetime of ROO^\bullet radicals is given by $\tau = 1/([\text{ROO}^\bullet] \times 2k_5)$, with k_5 being the rate constant of the termination reaction (1.5). As an example, at 0.1% cyclohexane conversion, the $[\text{CyOO}^\bullet]$ concentration can be estimated at $5 \times 10^{-8} \text{ M}$ (derived from the product formation rate $= k_4 [\text{CyH}] [\text{CyOO}^\bullet]$), leading to a τ as low as $\approx 2.5 \text{ s}$, given $2k_{\text{term}} = 8.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. We emphasize that τ is much smaller than the timescale of $\approx 2000 \text{ s}$ over which the CyOO^\bullet concentration changes significantly, such that $[\text{CyOO}^\bullet]$ quasi-steady state will indeed be established and maintained throughout the oxidation process. This implies that the rate of chain initiation equals the rate of chain termination, or $k_1 [\text{CyOOH}] = k_5 [\text{CyOO}^\bullet]^2$.

The radical chain mechanism outlined here avoids the ineffective direct reaction of molecular oxygen with the substrate hydrocarbon. The fast propagation reactions produce ROOH that in turn can initiate new radical chains. As the primary product of the reaction initiates new reactions, one ends up with an autocatalytic acceleration. The propagating peroxy radicals can also mutually terminate and yield one molecule of alcohol and ketone in a one-to-one stoichiometry. The ratio between the rate of propagation and the rate of termination is referred to as the chain length and is of the order of 50–1000. As the desired chain products are more susceptible to oxidation, autooxidations are normally carried out at low conversions in order to keep the selectivity to an economically acceptable level.

In the following sections, we discuss the various reaction sequences in more detail, starting with the chain initiation.

1.2

Chain Initiation

According to reaction (1.1), the ROOH molecule yields radicals upon the unimolecular scission of the 40 kcal/mol O–O bond. However, this reaction is not only slow due to the high barrier but also very inefficient to generate free radicals. Indeed, once the O–O bond has been elongated, the nascent radicals need to diffuse away from each other (i.e., out of their solvent cage in case of liquid phase reactions) before they are really free radicals. This diffusion process faces a significantly higher barrier than the in-cage radical recombination to reform the ROOH molecule. Therefore, only a small fraction of the ROOH molecules that manage to dissociate will effectively lead to free radicals. Moreover, during cyclohexane oxidation, it was observed that the addition of a small amount of cyclohexanone not only eliminates the induction period but also enhances the oxidation rate at a given conversion (i.e., at a certain O_2 consumption), as shown in Figure 1.1. This observation clearly indicates that cyclohexanone plays an important role in the chain initiation, hitherto missing in the simple unimolecular mechanisms.

Based on quantum chemical calculations, a bimolecular chain initiation mechanism was proposed between the ROOH primary product and cyclohexanone

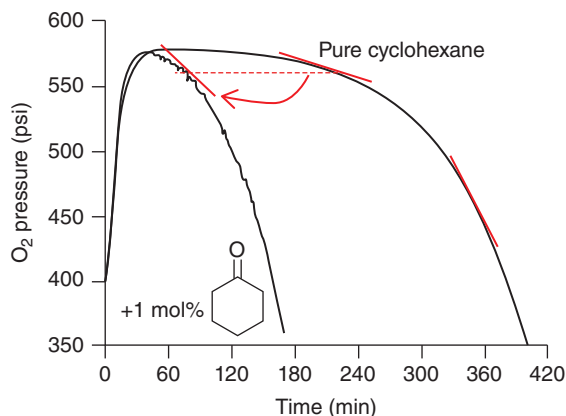


Figure 1.1 Oxygen consumption during the autoxidation of cyclohexane at 418 K with and without the addition of cyclohexanone. The red slopes signify the oxidation rate at various stages of the reaction. The initial pressure increase is due to heating, initiated at time 0.

[11–13]. In this reaction, the nascent hydroxyl radical, breaking away from the hydroperoxide molecule, abstracts the weakly bonded α H-atom from cyclohexanone, forming water and a resonance-stabilized ketonyl radical (Figure 1.2). This reaction features a significantly lower activation barrier (i.e., 28 kcal/mol) and prevents facile in-cage radical recombination. The theoretically predicted rate constant of this reaction (i.e., $0.6 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ at 418 K) quantitatively agrees with the experimentally determined rate constant ($1 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$), corroborating this thermal initiation mechanism and explaining the autocatalytic effect of cyclohexanone [11].

The hypothesis of a bimolecular initiation reaction for liquid phase autoxidations was extended beyond cyclohexanone as a reaction partner. Also other substances featuring abstractable H-atoms are able to assist in this radical formation process. The initiation barrier was found to be linearly dependent on the C–H bond strength, ranging from 30 kcal/mol for cyclohexane to 5 kcal/mol for methyl linoleate [14, 15]. Substrates that yield autoxidation products that lack weaker C–H bonds than the substrate (e.g., ethylbenzene) do not show an exponential rate increase as the chain initiation rate is not product enhanced [16].

1.3

Chain Propagation

According to traditional textbooks, the hydroperoxide is produced in the fast propagation reaction, whereas alcohol and ketone are formed in the slow termination step. As such, one would expect the hydroperoxide selectivity to be an order of magnitude higher than the alcohol and ketone selectivity. This is, however, not in agreement with the experimental observations, indicating that (an) important source(s) of alcohol and ketone is (are) missing in this model. Moreover, the

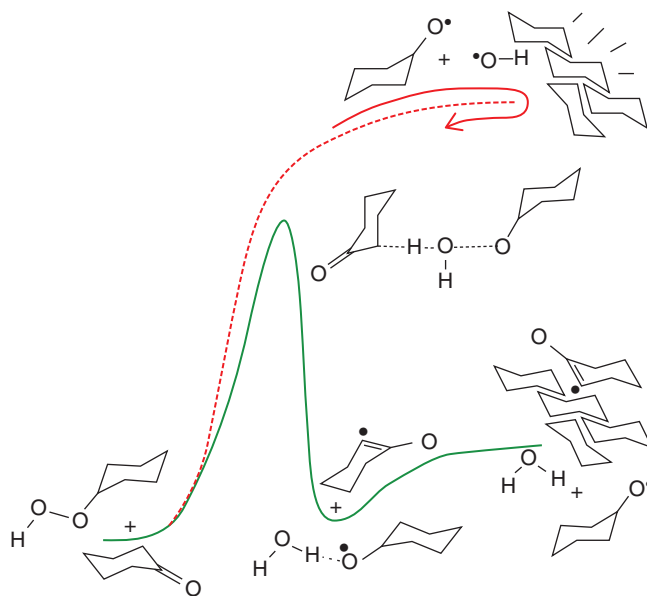


Figure 1.2 Comparison of the unimolecular RO–OH dissociation process and the bimolecular initiation between ROOH and cyclohexanone [11].

second order upswing of the alcohol and ketone as a function of the conversion indicates that these products are secondary and do not directly originate from elementary steps of the chain-carrying peroxy radicals. In addition, one observes a maximum peroxide yield as a function of the substrate conversion, indicating that there must exist a reaction that rapidly consumes the primary hydroperoxide product. Yet, such a reaction is absent from the mechanism thus far discussed.

A careful computational analysis of the reactivity of the peroxy radical with various substrates and their autoxidation products indicates that the abstraction of the α H-atom of the hydroperoxide is kinetically favored over other H-atoms. In the case of cyclohexane autoxidation, the ratio between the rate constants for H-abstraction from the cyclohexyl hydroperoxide versus cyclohexane is around ≈ 50 , indicating that sequential peroxide propagation is kinetically important, even at low conversions (i.e., high CyH/CyOOH concentration ratios) [17]. The α H-abstraction immediately yields ketone plus a hydroxyl radical as the $\text{Cy}_{-\alpha\text{H}}\bullet\text{OOH}$ species promptly dissociates without a barrier [18]. The $\bullet\text{OH}$ radical rapidly abstracts an H-atom from the ubiquitous cyclohexane substrate, rendering the overall peroxide copropagation exothermic by nearly 50 kcal/mol. As shown in Figure 1.3, the nascent products $\{\text{CyOOH} + \text{Cy}\bullet + \text{Q} = \text{O} + \text{H}_2\text{O}\}$ either can diffuse away from each other or can react together in a thermally activated solvent-cage-assisted reaction to form alcohol and alkoxy radicals. Indeed, the high exothermicity of the peroxide propagation leads to a local hotspot, facilitating the reaction between the nascent $\text{Cy}\bullet$ radical and CyOOH . As a consequence,

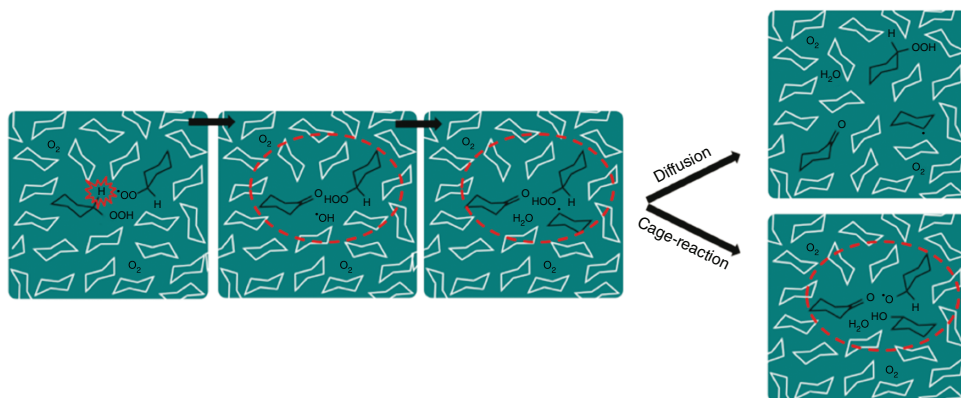


Figure 1.3 α H-abstraction from the primary cyclohexyl hydroperoxide product and subsequent chemistry.

this activated reaction can compete with the nearly temperature-independent diffusive separation, leading to a rather efficient alcohol source. As such, the consecutive cooxidation of the primary hydroperoxide product leads to the formation of ketone and alcohol in a ratio that is determined by the solvent-cage efficiency.

The cage efficiency predominantly depends on the stability of the R^\bullet radical that determines the barrier of the cage reaction. Comparing the cage efficiency observed for various substrates such as cyclohexane [17], toluene [19], and ethylbenzene [16] confirms a systematic trend and readily explains the difference in alcohol-to-ketone ratio for those substrates (see Figure 1.4).

The high reactivity of the primary hydroperoxide product toward chain-carrying peroxy radicals readily explains the relatively high yields of alcohol

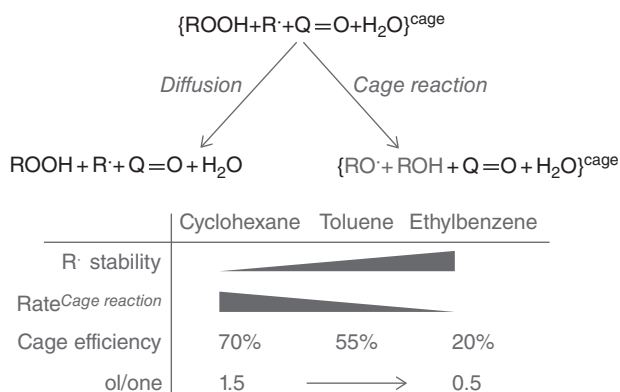
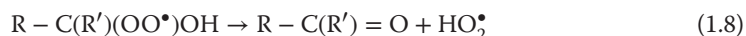
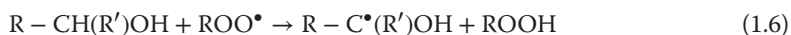


Figure 1.4 Effect of the substrate on the solvent-cage efficiency and alcohol-to-ketone ratio.

and ketone, the ratio of which is determined by the efficiency of a selectivity-controlling solvent-cage reaction. There is hence no need to ascribe the formation of alcohol and ketone to slow peroxy radical cross-reactions.

Analogous to the hydroperoxide copropagation, one has to consider the α H-abstraction from the alcohol product (reaction (1.6)). Although slower than for the hydroperoxide, this tertiary cooxidation reaction is important as the α -hydroxylperoxyl radical, formed after O_2 addition (reaction (1.7)), readily eliminates HO_2^\bullet (reaction (1.8)) [20], a known chain-terminating radical. Indeed, HO_2^\bullet reacts in a head-to-tail manner with the chain-carrying peroxy radicals to form hydroperoxide plus oxygen [21]. This termination reaction is about 500 times faster than the mutual termination reaction between secondary peroxy radicals. As a consequence, the cooxidation of alcohol slows down the overall autoxidation reaction and explains in a very elegant manner the inhibiting effect of alcohols on the autoxidation of various substrates.



Cooxidation of the ketone product via abstraction of a weakly bound α H-atom was, in the case of cyclohexane oxidation, assumed to be the predominant source of ring-opened by-products such as adipic acid, glutaric acid, and 6-hydroxy caproic acid [4, 5]. This hypothesis was based on two wrong assumptions. (i) It was assumed, based on Evans–Polanyi correlations between activation energy and reaction enthalpy, that the α H-abstraction from cyclohexanone would be fast due to the weak α C–H bond strength. However, the resonance stabilization, the main reason for this low bond strength, is not yet operative in the α H-abstraction transition state and hence does not contribute to a significantly lower reaction barrier compared with the parent substrate. (ii) Experiments where ^{13}C -labeled cyclohexanone was initially added to the cyclohexane substrate suggested the cyclohexanone cooxidation to be the most important source of by-products. However, in those early experiments, substantial amounts of ketone were added, that is, even more than what is formed during a normal autoxidation experiment, perturbing the kinetic network and leading to the wrong conclusion that this would be the most important source of by-products. This was later confirmed by the observation that although more by-products are formed upon initial addition of cyclohexanone, the relative increase in waste diminishes as a function of the conversion. This clearly illustrates that there is a significantly more important source of by-products than cyclohexanone [17].

1.4

Formation of Ring-Opened By-Products in the Case of Cyclohexane Oxidation

Having ruled out the overoxidation of cyclohexanone as a major source of ring-opened by-products, we turned our attention to the cyclohexoxyl radicals, coproduced in the activated cage reaction following the peroxide cooxidation (see Figures 1.3 and 1.4). As mentioned in the introduction, alkoxy radicals not only can abstract H-atoms but also can undergo C–C bond scission [5]. In the case of cyclohexoxyl radicals, this competing unimolecular reaction leads to the formation of ω -formyl radicals that can lead either to decarbonylation under oxygen starvation conditions or to a primary peroxy radical that can form 6-hydroperoxy- and 6-hydroxycaproic acids, that is, the primary ring-opened by-products (see Figure 1.5) [22]. No reaction mechanism can be found to explain the formation of these primary by-products from cyclohexanone. Consecutive cooxidation of these primary by-products leads to the experimentally observed secondary by-products such as adipic and glutaric acids, among several others [22]. This straightforward mechanism to explain the formation of a complex mixture of various by-products based on the copropagation of the primary hydroperoxide product corroborates the importance of that step.

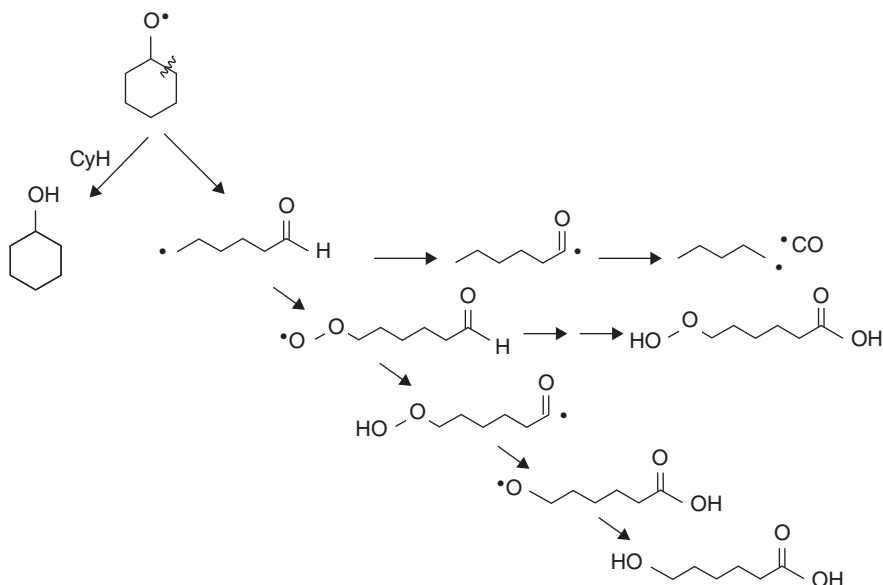


Figure 1.5 Competing reactions for the cyclohexoxyl radical: formation of the primary ring-opened by-products [22].

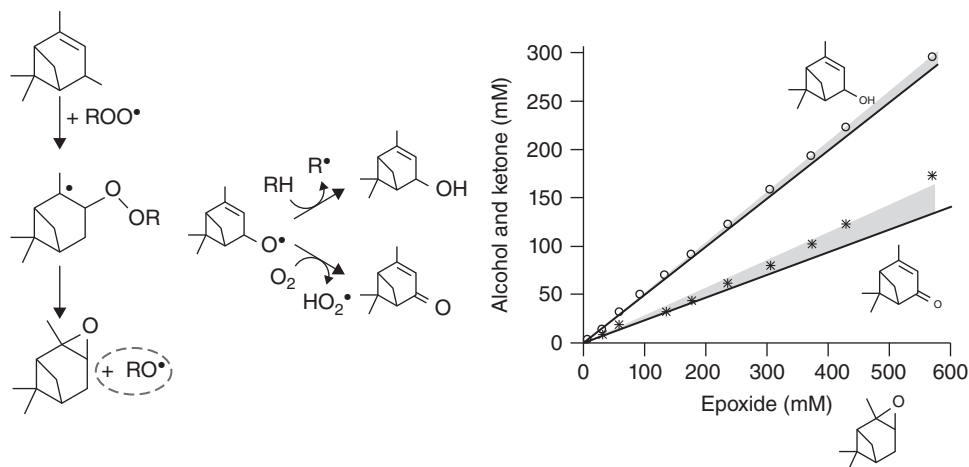


Figure 1.6 Addition of peroxy radical to C=C bond of α -pinene and consecutive alkoxyl radical chemistry [23].

1.5

Complications in the Case of Olefin Autoxidation

The reactions discussed so far form a consistent and generic mechanism for the thermal autoxidation of saturated hydrocarbons. In the case of unsaturated compounds, an additional channel opens for the peroxy radicals, namely, the addition to the C=C bond, followed by the formation of an epoxide upon elimination of an alkoxyl radical (see Figure 1.6). These unsaturated alkoxyl radicals are, however, special in the sense that they not only can abstract H-atoms from the substrate (forming alcohol) but also can react with O_2 to form the corresponding ketone. Experimental evidence for this is found in the nearly linear correlation between the alcohol and ketone increase as a function of the epoxide yield (see Figure 1.6) [23]. Yet, at increasing conversion, additional alcohol and ketone is formed as indicated by the green areas in Figure 1.6. This additional alcohol and ketone stems from the consecutive cooxidation of the hydroperoxide product analogs as shown in Figure 1.3 for unsaturated substrates. The 10% efficiency of the activated solvent-cage reaction matches very well with the values in Figure 1.4.

At increasing O_2 pressure, one observes a decrease in epoxide selectivity and a steady increase in reaction rate [24]. Both effects are coupled and related to the competitive O_2 addition to the ROO^\bullet -to-C=C adduct, as shown in Figure 1.7. Indeed, this leads to the formation of a new type of peroxy radical that will ultimately yield a dialkyl peroxide that promptly dissociates to new radicals due to the very weak O–O bond (see Table 1.1).

We emphasize that the efficiency of this radical epoxidation mechanism depends on the substrate (i.e., the ease at which the chain-carrying peroxy radicals abstract αH -atoms or add to the C=C bond) [25], and sometimes even on the precise geometric conformer [26, 27]. However, the maximum theoretical

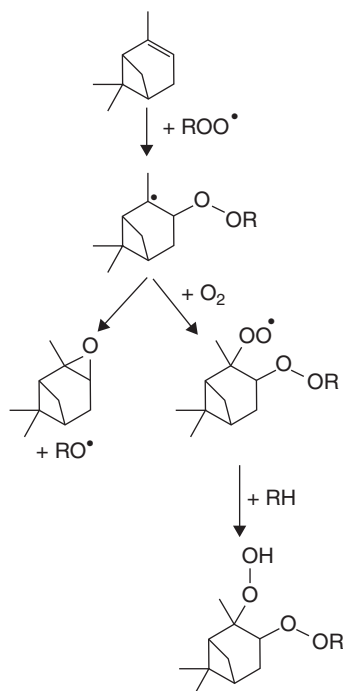


Figure 1.7 Competing O_2 addition at higher oxygen partial pressures, leading to a drop in epoxide selectivity and an increase in initiation rate via the formation of labile dialkyl peroxide.

epoxide yield in this mechanism is restricted to 50%. Yet, in a recent case study on the autoxidation of β -caryophyllene, epoxide selectivities as high as 70% were observed [28]. A detailed study revealed that the spontaneous epoxidation of β -caryophyllene constitutes a rare case of unsensitized electron transfer from an olefin to triplet oxygen under mild conditions. The formation of a caryophyllene-derived radical cation via electron transfer is proposed as the initiation mechanism. Subsequent reaction of the radical cation with O_2 yields a dioxetane via a chain mechanism with typical chain lengths that can exceed 100. The dioxetane acts as an excellent *in situ* epoxidation agent under the reaction conditions.

1.6

Summary and Conclusions

Hydrocarbon autoxidation takes place via a complex set of radical reactions, some of which were only recently identified. One of the mechanistic difficulties is that the reactions can only be indirectly investigated by monitoring the evolution of stable products. The input of quantum-chemical calculations, in combination with theoretical kinetics, turned out to be a crucial tool to construct a generic mechanism. One of the new insights is the importance of the copropagation of the primary hydroperoxide product. A solvent-cage reaction, activated by the exothermicity of this secondary step, leads to the formation of the desired alcohol and

ketone products, as well as undesired ring-opened byproducts in the case of cyclohexane oxidation. In the case of unsaturated hydrocarbons, a peroxy addition mechanism to the unsaturated bond leads to the formation of epoxides in addition to allylic products.

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