# Understanding Selective Oxidations

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Abstract: Functionalizing organic molecules is an important value-creating step throughout the entire chemical value-chain. Oxyfunctionalization of *e.g.* C–H or C=C bonds is one of the most important functionalization technologies used industrially. The major challenge in this field is the prevention of side reactions and/or the consecutive over-oxidation of the desired products. Despite its importance, a fundamental understanding of the intrinsic chemistry, and the subsequent design of a tailored engineering environment, is often missing. Industrial oxidation processes are indeed to a large extent based on empirical know-how. In this mini-review, we summarize some of our previous work to help to bridge this knowledge gap and elaborate on our ongoing research.

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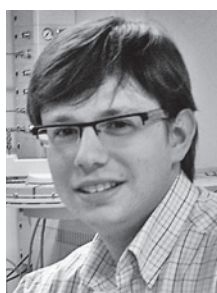
Since April 1st 2008 Ive Hermans has worked as assistant professor for heterogeneous catalysis at the Institute for Chemical and Bioengineering, ETH Zürich. He was born December 19th 1980 in Sint Truiden, Belgium. He studied chemistry at K.U.Leuven University where he graduated in 2002. He obtained his PhD in applied chemistry 2006 in the group of Prof. Pierre Jacobs and Prof. Jozef Peeters. After a post-doc at the Centre for Surface Science and Catalysis (K.U.Leuven Belgium) and in the group of Prof. Alfons Baiker at ETH Zürich, he started his own research group. In addition to his scientific education, Ive Hermans also obtained a postgraduate diploma in business administration. The research of his group mainly focuses on the chemistry and engineering of selective oxidations (aerobic autoxidations, peroxidations, epoxidations, …). For his work, Ive Hermans has received several awards such as the ExxonMobil Chemical European Science and Engineering Award 2009.

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Introduction

Managing our limited natural resources, exploring the economically viable use of renewable feedstocks, reducing or recycling waste, and keeping up with the ever-increasing demand for chemical products, are some of the huge challenges the chemical industry is facing today. Addressing these challenges will demand a reconceptualization of (chemical) production, as well as a reconsideration of the chemicals we are using. Sustainable development indeed requires an integrated vision where chemistry represents the main tool for today's development strategies.[1] Designing alternative production pathways requiring less energy input and producing a limited amount of waste (which could eventually still be used as a feedstock for other processes) has however always been the focus of process optimization for obvious economic reasons. In that sense, more sustainable processes are often also characterized by better economics, implying that economic benefits should not exclude environmentally benign processes, but could catalyze sustainable chemistry to the industrial benchmark. It is important to emphasize that often a relatively small improvement in the chemical performance of a process can trigger a non-linear effect in terms of overall improvement. For instance, a higher productivity (activity) leads to lower investment costs because smaller reactors can be used to achieve the same output, whereas a higher selectivity leads to fewer by-products, saves precious raw material, and lowers the investment and energy consumption in post-reaction separation.

Within the chemical value-chain, selective oxidations play a pivotal role, not only in the production of large quantities of bulk intermediates for the polymer industry, but also for the production of fine
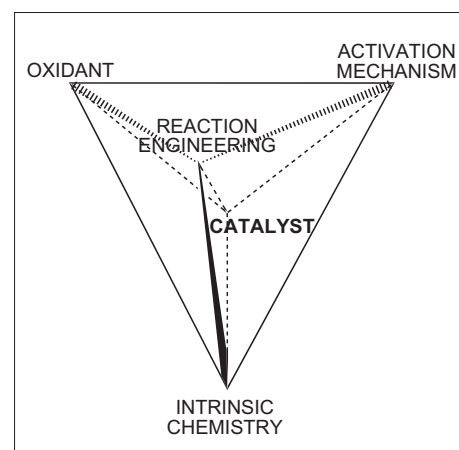

Fig. 1. Different parameters determining the performance of an oxidation process.

chemicals such as fragrances and pharmaceutical compounds.[2] In the last decades there has been a significant improvement in the industrial production of oxygenated molecules in terms of improved heat recovery, energy integration, abatement of tail exhaust gases, and replacement of dangerous/toxic reactants. Nevertheless, selective oxidation technology is a domain with room for improvement and this from various perspectives (Fig. 1). First of all, the fundamental knowledge of the intrinsic oxidation chemistry is lagging behind other fields such as alkylation and hydrogenation chemistry. The selection of the oxidation agent is therefore often based on trial-and-error. Energy to overcome the activation barrier can be provided *via* heat, electrical current or light. Although heat is often assumed to be an non-benign stimulus, this is not generally true. Indeed, exothermic oxidation reaction can best be performed at around 130 °C, rather than at room temperature. Working above the boiling point of water allows one to use the heat of reaction to generate steam, a pre-

cious energy carrier in an industrial plant. If an oxidation reaction is carried out at or near room temperature, the heat of reaction can only be used to slightly heat up cooling water and means actually a waste of energy. In order to avoid side-reactions and/or consecutive over-oxidation of the desired products, a catalyst is very often required to mediate the selectivity. With all these fundamental parameters fixed, one still has a degree of freedom in the engineering environment to get most out of the given system. All these different parameters should work together to optimize the performance of a selective oxidation.[3]

Understanding the Fundamentals of Oxidation Chemistry

Oxidations can be divided into homolytic and heterolytic reactions, depending on the nature of the reaction intermediates.[4] In the case of homolytic chemistry, radicals (e.g. peroxyl radicals) are formed as reactive intermediates whereas in heterolytic oxidation reactions, an active oxygen compound (e.g. a peracid or H_2O_2), or a metal ion in a high valence state (e.g. CrO_3), oxidizes the substrate in a two-electron transfer reaction, thereby preventing the formation of radicals. Normally, a stoichiometric amount of the oxidizing compound is used, in combination with a catalyst, for instance a complex of Mo(VI), V(v), or Ti(IV). The catalyst can be dissolved homogeneously in a liquid or be present in solid form.

Unless O_2 is explicitly activated on a catalyst (e.g. a silver surface as for ethylene epoxidation), aerobic oxidations often involve radical chemistry. Indeed, the direct reaction of O_2 with hydrocarbons is spin-forbidden and therefore very slow. However, if a hydrocarbon is heated in the presence of oxygen, a spontaneous oxidation will take place in which the slow direct reaction is by-passed by a much more efficient radical mechanism (reactions (1)–(6)). This type of oxidation – referred to as autoxidation – is of great industrial importance. Some large-scale examples are: the oxidation of p-xylene to terephthalic acid (44×10^6 t/y), synthesis of cyclohexanol and cyclohexanone (6×10^6 t/y), and the oxidation of cumene to cumene hydroperoxide (5×10^6 t/y). During earlier work, we discovered that the actual autoxidation mechanism is insufficiently known. It was for instance assumed that during the liquid phase autoxidation of cyclohexane, the alcohol (ROH) and ketone (Q=O) products are forming in the termination reaction of two peroxyl radicals (reaction (6)).[4] However it was known that the rate of reaction (5) is much higher than the rate of reaction (6), the ratio being referred to as the chain length ($\nu \geq 100$). This would imply that the

yield of ROH and Q=O would be much smaller than the ROOH yield, in disagreement with the experimental observations.

Using a combination of detailed experiments and theoretical calculations,[5,6] we discovered that there exists a much faster alcohol and ketone channel than known so far. This overlooked mechanism starts with the rapid abstraction of a weakly bonded αH-atom from the primary hydroperoxide product. The resulting radical ($R_{-\alpha H}$•OOH) is not stable and promptly dissociates to Q=O and •OH, immediately explaining the ketone product (reaction 7).[7]

The hydroxyl radical co-produced in reaction (7) will rapidly abstract an H-atom from the ubiquitous alkane molecules surrounding the nascent ROOH + Q=O + •OH products (reaction (8)). The resulting products can either diffuse away from each other (reaction (9)), or undergo cage-reaction (10).

Although the diffusive separation (reaction (9)) faces a lower barrier than cage-reaction (10), the latter channel can compete, due to the formation of a local hot-spot. This nano-sized hot-spot is generated by the high exothermicity of the previous reaction steps (7) and (8), generating together approx. 50 kcal mol^{-1}.[6] Kinetic modeling experiments show that in case of cyclohexane, reaction (10) accounts for 70% of the reaction flux, in close agreement with the theoretical predictions.[6] More reactive substrates such as toluene and ethylbenzene feature cage-efficiencies of only 56 and 22%, respectively.[8,9] For those substrates, the alkyl radicals are more stabilized, leading to a higher barrier for reaction (10). In the case of cyclohexane oxidation, the alkoxy radicals co-produced in cage-reaction (10) were found to be responsible for the majority of ring-opened by-products, rather than the over-oxidation of cyclohexanone as assumed so far.[10] This hitherto unknown s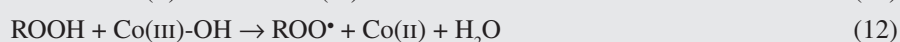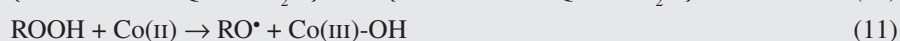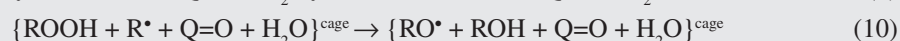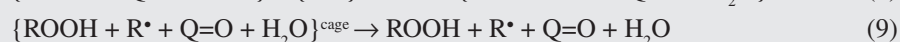olvent-cage effect in radical autoxidations readily explains quantitatively the observed product distributions for a wide range of substrates.

The role of reaction (1) as the dominant initiation mechanism was also questioned. Indeed, this reaction is not only very slow due to its 40 kcal mol^{-1} activation barrier (despite the fact that the reaction is unimolecular), it is also very inefficient in the liquid phase as the nascent radicals will preferably recombine within their solvent cage, rather than to diffuse away from eac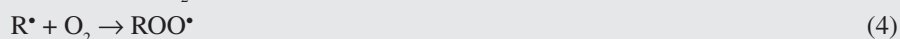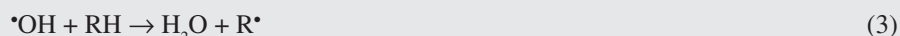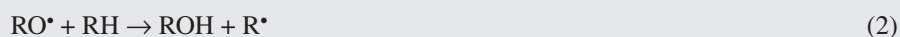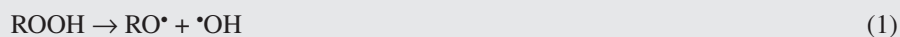h other and initiate a radical chain.[11] It was shown that the actual initiation mechanism is a bimolecular reaction of the primary hydroperoxide product with either the substrate (e.g. in the case of ethylbenzene), or with one of the reaction products (e.g. cyclohexanone in the case of cyclohexane oxidation).[11] The latter reaction also explains the autocatalytic nature of cyclohexane autoxidation: during the reaction, cyclohexanone is produced which accelerates the initiation mechanism.

The knowledge generated in our elaborating alkane oxidation studies is now being extended in the direction of olefins. More precisely, we are studying the oxidation of renewable terpenes (e.g. α-pinene (Fig. 2), limonene, …). Such compounds are used in fragrance and flavor industry. In the case of alkenes, the peroxyl radical can not only abstract weakly bonded allylic H-atoms, but also add to the C=C double bond (Scheme 1). The adduct is able to rearrange to the corresponding epoxide, thereby releasing alkoxy radicals (RO•).[12]

Catalyzing Autoxidations

There are two different ways in which autoxidations can be catalyzed: i) either by accelerating the rate-determining initiation reaction, or ii) via the introduction of species which are more efficient chain-carriers than peroxyl radicals (catalyzing the propagation).

$$ROOH \rightarrow RO^\bullet + {}^\bullet OH \tag{1}$$

$$RO^\bullet + RH \rightarrow ROH + R^\bullet \tag{2}$$

$${}^\bullet OH + RH \rightarrow H_2O + R^\bullet \tag{3}$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \tag{4}$$

$$ROO^\bullet + RH \rightarrow ROOH + R^\bullet \tag{5}$$

$$ROO^\bullet + ROO^\bullet \rightarrow ROH + Q{=}O + O_2 \tag{6}$$

$$ROO^\bullet + ROOH \rightarrow ROOH + Q{=}O + {}^\bullet OH \tag{7}$$

$$\{ROOH + Q{=}O + {}^\bullet OH\} + \{RH\}^{cage\text{-}wall} \rightarrow \{ROOH + R^\bullet + Q{=}O + H_2O\}^{cage} \tag{8}$$

$$\{ROOH + R^\bullet + Q{=}O + H_2O\}^{cage} \rightarrow ROOH + R^\bullet + Q{=}O + H_2O \tag{9}$$

$$\{ROOH + R^\bullet + Q{=}O + H_2O\}^{cage} \rightarrow \{RO^\bullet + ROH + Q{=}O + H_2O\}^{cage} \tag{10}$$

$$ROOH + Co(II) \rightarrow RO^\bullet + Co(III)\text{-}OH \tag{11}$$

$$ROOH + Co(III)\text{-}OH \rightarrow ROO^\bullet + Co(II) + H_2O \tag{12}$$
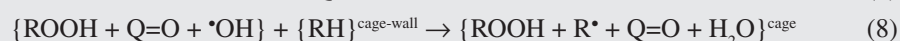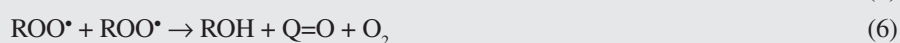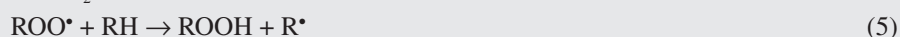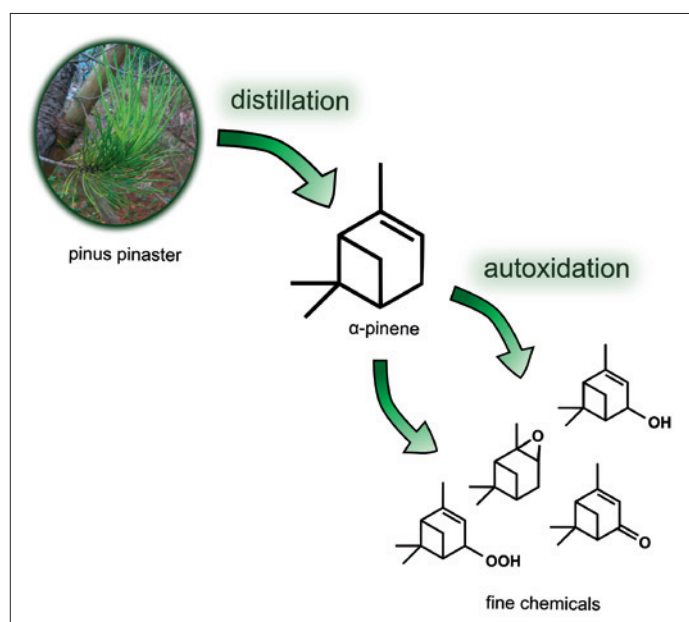
Fig. 2. Value chain of α-pinene, extracted from *pinus pinaster*.

Fig. 3. Scanning electron microscopy picture of supported Cr_2O_3 particles. The insert shows the Electron Diffraction Pattern of the particles obtained in a Transmission Electron Microscopy study, demonstrating the crystalline nature of the particles, composed of smaller building blocks.[16]
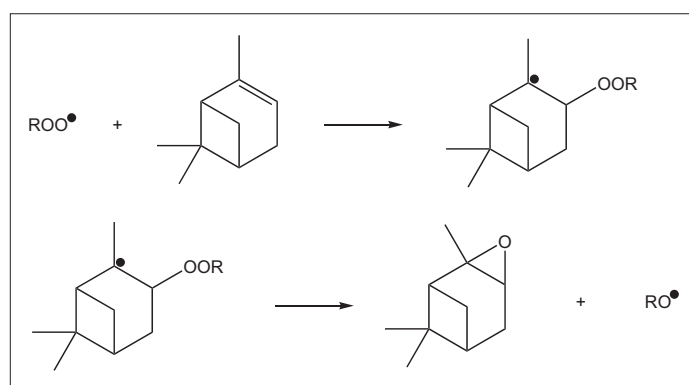
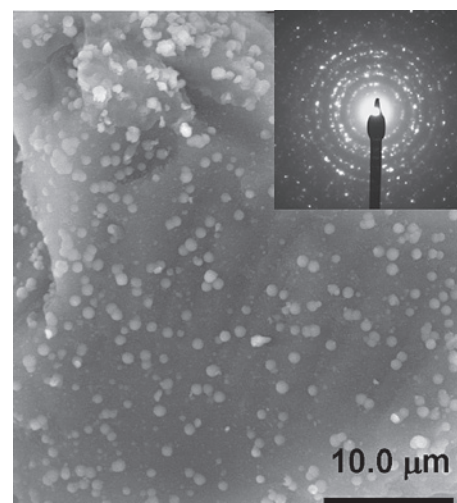Scheme 1. Addition of ROO• radicals to the C=C bond of α-pinene and the subsequent formation of pinene oxide.

Transition metal ions which are able to undergo one-electron redox reactions (*e.g.* $Co^{2+/3+}$, $Mn^{2+/3+}$, $Fe^{2+/3+}$, …) are known to accelerate the initiation rate *via* the so-called Haber-Weiss mechanism (Fenton chemistry, reactions (11), (12)).[5]

In the presence of such catalytic ions, reactions (11) and (12) take over the role of ROO• in the destruction of ROOH. However, several other reactions must take place in addition to reactions (11) and (12) in order to explain the observed inhibition at higher catalyst concentrations. Indeed, although the deperoxidation reaction seems to be first order in Co(II) up to ≈100 μM, above a certain critical catalyst concentration the reaction rate actually decreases.[13] At the moment this effect is under investigation in our group.

So far only homogeneous catalysts have been successfully used for autoxidations. However, from a technical point of view heterogeneous catalysts could offer certain advantages such as ease of recyclability.

An important problem arising during the application of heterogeneous catalysts for liquid phase reactions is leaching. Leaching of the active elements not only reduces the lifetime of the catalyst, it also causes contamination of the product stream. One transition metal ion which is particularly active in autoxidations is chromium: it not only catalyzes the chain initiation, but also the dehydration of the hydroperoxide to the ketone, the most desired reaction product. Obviously, chromium is too noxious to be used as a homogeneous catalyst and its appropriate immobilization is an important prerequisite for up-scaling. Unlike other transition metal ions, such as cobalt and manganese, chromium is difficult to immobilize.[14] However, inspired by the low solubility of Cr_2O_3 we decided to explore the performance of nano-sized Cr_2O_3 particles.[15,16] In order to avoid a decreasing activity, due to agglomeration (particle growth) under reaction conditions, the Cr_2O_3 particles were immediately immo-

bilized on an inert silica support during their synthesis. In our approach, Cr(VI) was slowly added to a buffered aqueous solution, containing hydrazine. This causes an immediate reduction of Cr(VI) to Cr(III) and triggers its hydrolysis. The formation of nano-sized colloids was monitored with dynamic light scattering (DLS). This aqueous solution was continuously pumped over a chromatographic column containing silica powder. Using a process called colloid precipitation, the amorphous hydroxyoxide colloids are trapped on the support (Fig. 3).[16] Upon vacuum drying of the solid, a silica-supported chromium catalyst is obtained. Electron diffraction and transmission electron microscopy demonstrated that the initially amorphous particles are transformed (upon the loss of water) into crystalline Cr_2O_3 agglomerates, composed of small nano-sized building blocks. These materials turned out to be active and stable catalysts for the autoxidation of cyclohexane.

During our research we discovered that not only transition metal ions but also hydrogen bond acceptors (Lewis bases) are active as autoxidation catalysts as they can stabilize the •OH radical, breaking away from RO-OH.[17] The most remarkable discovery was that even Teflon, a material deemed completely inert, can accelerate deperoxidation.

N-hydroxyphthalimide (NHPI) is an example of the second type of autoxidation catalysts.[18] The >NO–H bond strength is similar to the ROO–H bond strength, explaining why the corresponding phthalimide-*N*-oxyl radical (PINO•) is also able to abstract H-atoms from alkanes (reaction (13)). However, PINO• radicals

also react with ROO–H in an equilibrated reaction (reaction (14), Scheme 2). The catalytic enhancement (C.E., *i.e.* the ratio of the RH oxidation rate in the presence of NHPI over the rate in absence of NHPI) was found to be proportional to the rate of reaction (13) and the equilibrium constant of reaction (14).[19]

$$PINO^\bullet + RH \rightarrow NHPI + R^\bullet \qquad (13)$$

$$NHPI + ROO^\bullet \leftrightharpoons PINO^\bullet + ROOH \quad (14)$$

From this mechanism it can be concluded that also other >NO–H components can act as an autoxidation catalyst, and that their activity highly depends on the >NO–H bond strength, as verified by numerous experiments. If the >NO–H bond is too weak, the barrier of reaction (13) will be too high and the catalyst will actually work as an inhibitor as the long-living *N*-oxyl radicals terminate with other radicals. If the >NO–H bond is however too strong, reaction (13) will be very fast but equilibrium (14) is completely shifted towards the reactants. The fundamental question in this chemistry can be formulated as: does one need more reactive radicals, or just more radicals?[20] The actual success of NHPI is explained by the fact that the >NO–H bond strength is slightly weaker than the ROO–H strength (leading to a favorable shift of equilibrium (14) towards the PINO$^\bullet$ radicals), whereas the PINO$^\bullet$ radicals are more reactive towards the substrate than ROO$^\bullet$ radicals (*viz.* deviation from Evans-Polanyi correlation between activation barrier and reaction enthalpy). This, in combination with the fact that PINO$^\bullet$ radicals cannot terminate as efficiently as peroxyl radicals, explains the remarkable rate enhancement.[21] It is also interesting to emphasize a synergetic effect between NHPI-type compounds and transition metal ions such as cobalt. This effect can be ascribed to an induced shift of equilibrium (14) towards the more efficient chain carrier PINO$^\bullet$ as the cobalt ions destroy ROOH (*vide supra*).

A severe disadvantage of NHPI is however its price and the fact that one should use a solvent to dissolve the catalyst. Immobilization of NHPI on silica and silica-alumina was studied.[22] The activity of the systems strongly depends on the surface density of silanol groups (Si–OH) as identified by solid-state NMR. If the support is too polar it causes rapid catalyst deactivation. After one catalytic run, all sorts of by-products (*e.g.* adipic acid in case of cyclohexane oxidation) stick to the surface, as demonstrated by infrared spectroscopy, causing the observed deactivation.
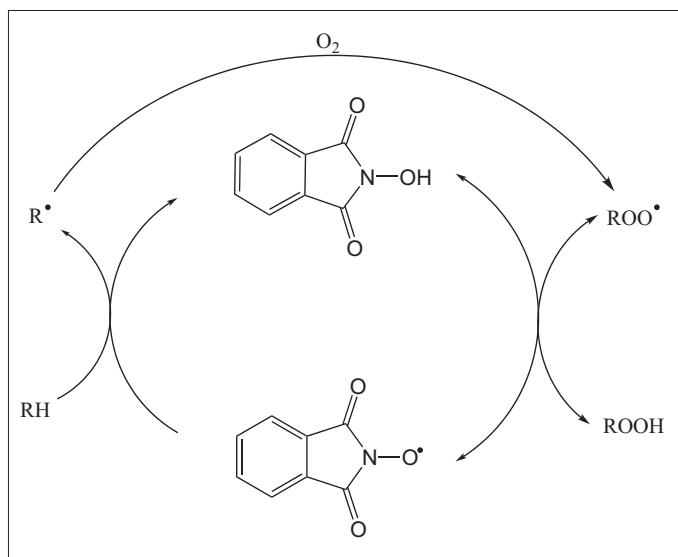
Scheme 2. Cycling of NHPI and PINO$^\bullet$ in the aerobic oxidation of hydrocarbons.[19]
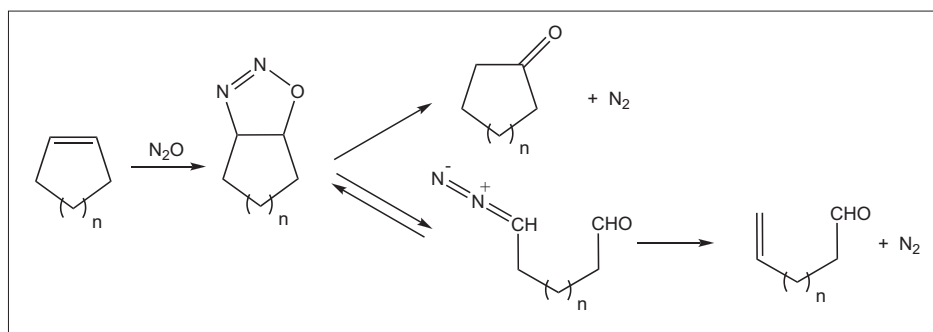
Scheme 3. Formation and decomposition of the oxadiazole intermediate in the N$_2$O ketonization of olefins.

Exploring Different Oxidation Agents

The oxidant is a crucial design parameter for selective oxidations (Fig. 1). Besides oxygen, many other oxidation agents can be used (*e.g.* HNO$_3$, H$_2$O$_2$, *t*-butyl hydroperoxide, …). HNO$_3$ is used both on a bulk scale (*e.g.* the oxidation of cyclohexanol/cyclohexanone to adipic acid) and on a smaller scale (*e.g.* the oxidation of 5-ethyl-2-methylpyridine to nicotinic acid or vitamin B3). During this reaction, HNO$_3$ is stoichiometrically reduced to NO$_x$ (responsible for acid rain) and N$_2$O (a severe greenhouse gas). Although this is generally considered to be an environmental issue, the NO$_x$ is in reality recycled in an associated HNO$_3$ plant. The remaining tail gas, containing N$_2$O (nitrous oxide or laughing gas), is catalytically treated before being released into the air. If the amount of N$_2$O can be minimized, HNO$_3$ acts as an oxygen shuttle. At the moment, our group works on a strategy to achieve the required NO$_x$ re-oxidation *in situ* such that only catalytic amounts of HNO$_3$ would be required. However, also N$_2$O can be used as a valuable oxidant. Indeed, inspired by old work by ICI,[23] Panov *et al.* reported the mild oxi-

dation of olefins with N$_2$O to ketones.[24] A detailed mechanistic study demonstrated that the oxadiazole intermediate, formed in a rate-determining cycloaddition of N$_2$O to the C=C bond, can either eliminate N$_2$ and yield the corresponding carbonyl compound, or decompose to a diazo compound which can, depending on the substrate, give rise to by-products (Scheme 3).[25]

Many substrates can be oxidized in high yield, including bi-unsaturated compounds.[26] Conversion of such dienes to diketones with traditional organic chemistry (*e.g.* Wacker oxidation or epoxidation, followed by isomerization) is very difficult. Using N$_2$O, renewable fatty methyl esters such as methyl oleate and methyl linoleate, or even mixtures of both ('biodiesel'), can be selectively oxidized under relative mild conditions (220–240 °C and 20–40 bar STP N$_2$O). Using this technology, the melting-point of a bio-diesel mixture can be increased from below 0 °C to ±30 °C,[26] opening the possibility to use such compounds as low-temperature lubricants, rather than to burn them in a combustion engine. An industrial valorization of this new N$_2$O chemistry is found in two new BASF processes,[27] making

cyclopentanone from cyclopentene and cyclododecanone from cyclododecatriene, both commodity chemicals.

An oxidant of increasing interest is H_2O_2, producing only H_2O as a harmless waste product. It is however important that the generated value-increase justifies the use of such an expensive oxidant as H_2O_2. Indeed, H_2O_2 has to be produced in a two-step oxidation–hydrogenation process. Despite the significant price reduction during the last couple of years, due to economy of scale production advantages, H_2O_2 is still too expensive for the production of bulk intermediates such as adipic acid. Roughly speaking there are two interesting reaction types where the use of H_2O_2 is justified. The first one is the formation of singlet oxygen ($^1O_2$),[28] a more reactive, electronically excited form of oxygen. Certain metal ions such as Mo(VI) and W(VI) but also La(III) are able to catalyze the decomposition of H_2O_2 to singlet O_2 ($^1\Delta_g$).[29] This reaction is proposed to proceed *via* the formation of η^2-peroxo species and shows a maximum activity under basic conditions, although the molecular mechanism is not fully understood. Singlet oxygen can react in a number of ways as shown in Scheme 4. The first reaction is the [$2\pi+2\pi$] cyclo-addition to alkenes without abstractable hydrogen atoms in allylic position. This reaction results in the formation of a dioxetane. The second possible reaction is the [$4\pi+2\pi$] cyclo-addition for dienes and even aromatic systems, yielding endoperoxides. The third reaction mode is the so-called 'ene' or 'Schenk' reaction for alkenes with abstractable hydrogen atoms in allylic position which produces allylic hydroperoxides. This singlet oxygen chemistry has already found application in the synthesis of fine chemicals. For the production of bulk or commodity chemicals, the H_2O_2 efficiency is still too low, compared to the value-increase. The low product yield is mainly caused by collisional quenching of the electronically excited $^1O_2$ with either the solvent, or in the case with immobilized systems, also the catalyst.[30] At the moment we are investigating whether these issues could be minimized by a tailored reaction environment.

Another potential use for H_2O_2 as an oxidant is epoxidation of olefins. Within the domain of heterolytic oxidation chemistry, one of the most remarkable breakthroughs of the last decades is the discovery of the versatile oxidation system, based on the combination of the heterogeneous catalyst TS-1 and H_2O_2.[2] TS-1 is a crystalline, microporous silicalite material (MFI structure, 5.5 Å channels) in which Ti is substituted for some of the Si atoms. The epoxidation of propylene, the hydroxylation of phenol, the ammoximation of cyclohexanone to cyclohexanone oxime and of cyclododecanone to cyclododecanone oxime are four processes which have already been commercialized. Nevertheless, despite the industrial success, many aspects of the TS-1/H_2O_2 system are still unrevealed. For instance, what does the active site look like? Is it a single Ti-site as widely assumed, or could it be a dimer site as suggested by recent observations? This question is actually very important for the development of epoxidation catalysts which can be used for large substrates. Another crucial point is the here undesired decomposition of H_2O_2 to O_2. This side-reaction not only reduces the overall efficiency in H_2O_2, it also creates a safety issue as explosive gas mixtures could build-up in the reactor. For this reason, alkyl hydroperoxides (ROOH) are also often used as epoxidation agents.

In our laboratory, we aim at a better understanding of the activation of hydro and alkyl peroxides. To this end, we perform kinetic experiments on well-designed model catalysts, obtained by *e.g.* grafting of molecular complexes, as well as industrial catalysts to come to a structure activity relationship. These kinetic studies are complemented by Raman spectroscopy studies in micro-reactors to monitor the time evolution of the peroxide intermediates.
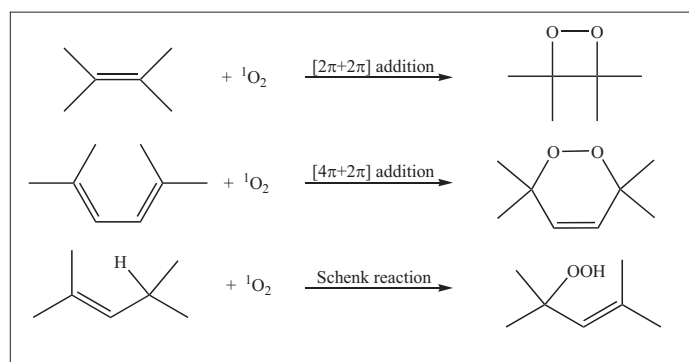
Scaling-up Promising Results

Scaling-up laboratory results to pilot plant scale, or industrial production, remains a difficult challenge for selective oxidations. Some of the reasons are: strong influence of the reactor surface to volume ratio on the chemistry (*e.g.* quenching of intermediates), heat exchange problems, and complex hydrodynamic behavior of gas-liquid-solid reactions. Studying reactions under conditions which can be easily scaled-up can reduce this lead time. New emerging engineering technologies such as micro-structured reactors,[31] are moving from an academic exercise to the industrial practice,[32] not only for pharmaceutical compounds, but even for commodity chemicals. Our laboratory follows those new technological developments and collaborate with reactor designers to achieve an optimal reaction environment.

Conclusions

Selective oxidation is a fascinating discipline where industrial and intellectual challenges meet. Despite the technical improvements made in the past decade, the chemistry of most of the existing processes is only superficially understood. Given the industrial impact of oxidations, a rational optimization or (re)design of oxidation processes can have a significant impact on the sustainability of the chemical industry. Preventing the formation of waste, using less (expensive) oxidants, and improving the heat integration are just a few of the challenges in this field where chemistry and chemical engineering should work closely together to make a leap forward.

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