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# **Catalytic oxygen activation versus autoxidation for industrial applications: a physicochemical approach**

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## **Abstract**

The activation and use of oxygen for the oxidation and functionalization of organic substrates is among the most important reactions in a chemist's toolbox. Nevertheless, despite the vast literature on catalytic oxidation, the phenomenon of autoxidation, an ever-present background reaction that occurs in virtually every oxidation process, is often neglected. In contrast, autoxidation can affect the selectivity to a desired product, to those dictated by pure free-radical chain pathways, thus affecting the activity of any catalyst used to carry out a reaction. This critical review compares catalytic oxidation routes by transition metals versus autoxidation, particularly focusing on the industrial context, where highly selective and "green" processes are needed. Furthermore, the application of useful tests to discriminate between different oxygen activation routes, especially in the area of hydrocarbon oxidation, with the aim of an enhanced catalyst design, is described and discussed. In fact, one of the major targets of selective oxidation is the use of molecular oxygen as ultimate oxidant, combined with the development of catalysts capable to perform the catalytic cycle in a real energy and cost effective manner on a large scale. To achieve this goal, insights from metallo-proteins that could find application in some areas of industrial catalysis are presented, as well as considering the physicochemical principles that are at the fundament of oxidation and autoxidation processes.

## 1. Introduction

The impact of oxidation processes on everyday life is ubiquitous. Products like alcohols, ketones and anhydrides are obtained by partial oxidation of hydrocarbons such as butane,<sup>1</sup> propene,<sup>2</sup> o-xylene,<sup>3</sup> cyclohexane,<sup>4</sup> which in turn can be transformed into a wide range of commodities like drug precursors, plasticisers, paint additives. These oxidations are currently carried out using a range of catalysts comprising metals such as: vanadium,<sup>5</sup> molybdenum,<sup>6</sup> antimony,<sup>7</sup> silver<sup>8</sup> or copper<sup>9</sup> in the form of metal complexes, metal oxides or metal phosphates,<sup>10-12</sup> as well as metal nanoparticles, particularly for Pd, Pt and Au.<sup>13-15</sup> However, while in recent years it has often been possible to obtain catalysts with enhanced conversion, on contrary control of the selectivity, i.e. which of a set of several possible products is the major one, is still elusive and a significant amount of research is nowadays devoted to achieve this goal.<sup>16-19</sup>

The reasons for the lack of catalyst selectivity can be various and they comprise the presence of radical pathways,<sup>21-23</sup> including autoxidation processes.<sup>24-26</sup> Further factors may include the location of the active site in a region of the catalyst that does not allow shape selectivity control,<sup>27,28</sup> or lack of single site isolation.<sup>29</sup> These aspects are not trivial. Oxidation processes represent one of the key routes for functionalization of organic molecules, and a lack of selectivity means that only a fraction of the reagents introduced into the system is converted to desired products, with clear economic damage. In view of this, the development of new catalysts, especially heterogeneous, capable of promoting selective oxidation reactions is an area of strategic industrial importance. In particular, there is a strong demand for: (i) catalysts capable of energy and cost effective processes with increased selectivity, and (ii) oxidation routes using air or molecular oxygen as the ultimate oxidant.<sup>30,31</sup>

At present, a common route to drive selective oxidation by transition metals is to modify the oxidation state of the catalytically active metal centre.<sup>32-35</sup> However, the diradical nature of molecular oxygen means that it can also react with organic substrates via autoxidation pathways.<sup>36,37</sup> As these are not driven by catalysts, autoxidation reactions are difficult to study unambiguously. In addition, when metal oxides, rather than metal complexes or nanoparticles, are used to carry out selective oxidation,<sup>38,39</sup> the reaction is further complicated by the need to identify which oxygen species is responsible for the reaction. That is whether it originates from the oxidising environment or from the metal oxide, and in the latter case in which form. Several activated oxygen species can be present over metal oxides such as: O<sub>2</sub>

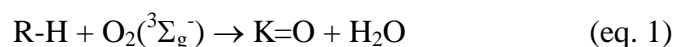
(adsorbed or peroxide group),  $O^{2-}$  (oxide anion)  $O_2^{2-}$  (peroxide anion), and  $O_2^-$  (superoxide),<sup>40-42</sup> each of them with its own reactivity, but with a final effect often remaining unclear. Moreover, if the catalysts consist of metal nanoparticles, both activity and selectivity can also be affected by factors like: particle size,<sup>43</sup> metal-support interactions,<sup>44</sup> and nanoalloy formation.<sup>45,46</sup>

However, despite the very vast literature on metals, metal oxides and metal nanoparticles,<sup>47-49</sup> collateral oxygen activation routes like autoxidation, or mechanistic tests to identify the active oxygen species during a reaction are often neglected, together with the comparison with metallo-proteins that could be relevant for oxidation reactions. This prompted us to consider a perspective focused on oxygen activation - especially in industrial context - with the aim to provide insights for: (i) source and nature of reactive oxygen species in the reaction media, (ii) effects and consequences of the presence of free-radical intermediates on the product selectivity and (iii) biologically relevant examples of oxidation as a source of inspiration in the pursuit of highly selective catalytic processes. This is done by considering the physicochemical requirements of oxygen activation and the metal centre, the dynamics of reactant diffusion - especially in liquid phase - as well as reactor design requirements.

## 2. Reactivity of oxygen

The first aspect that needs to be considered to justify the need of a catalyst, as well as the existence of autoxidation pathways, is the physicochemical nature of oxygen. Molecular oxygen in the ground state is a diradical species presenting two unpaired electrons in the same spin and therefore has a triplet spin state (spectroscopic term:  $^3\Sigma_g^-$ ).<sup>50</sup> This has implications of central importance for oxidation reactions of organic substrates, either those involving oxygen insertion into a hydrocarbon skeleton or oxidative dehydrogenation by oxygen species. In fact, organic substrates (hydrocarbons, alcohols, ketons and acids) in the ground state all have a closed shell electronic structures, and therefore are in a singlet state. However, chemical reactions involving reactants present in singlet and triplet states to yield products that are present in singlet state only, are forbidden by Wigner's spin selection rule.<sup>51,52</sup> To clarify this important aspect, that will be used also in further sections, let us

consider the generic oxidation of a hydrocarbon, for example an alkane (R-H) by means of ground state oxygen,  $O_2(^3\Sigma_g^-)$  to generate a ketone (K=O) and water (eq.1, and Table 1).



**Table 1.** Spin states for the reaction of a hydrocarbon R-H with ground state triplet oxygen  $O_2(^3\Sigma_g^-)$ , to generate a ketone (K=O) and water. For the reaction to occur, i.e. to preserve the spin, the transition state has to be a combination of the spins of the reactants and the products. That is the algebraic sum of the spins of the reactants has to have at least one term in common with the algebraic sum of the spin of the products. As in this case  $S_{\text{Reactants}} = 1$  and  $S_{\text{Products}} = 0$  the only combination is  $1 \neq 0$ , and therefore the reaction is forbidden by spin.

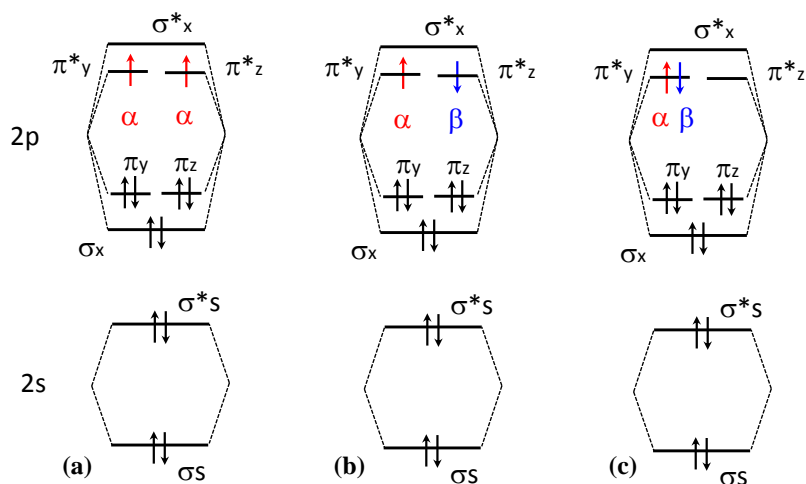
	Reactants	Transition state	Products
	$R-H + O_2(^3\Sigma_g^-)$	$R-H \cdots O_2^\ddagger$	$K=O + H_2O$
Spin	$S_{R-H} = 0 \quad S_{O_2} = 1$	Requires: $ S_{R-H} \pm S_{O_2}  =  S_{K=O} \pm S_{H_2O} $	$S_{K=O} = 0 \quad S_{H_2O} = 0$
Multiplicity of spin $2S + 1$	1      3		1      1
Spin state	Singlet    Triplet		Singlet    Singlet

Because of the spin selection rules, the transition state  $[R-H \cdots O_2]^\ddagger$  must have a total spin  $S_{R-H \cdots O_2^\ddagger}$  obtained either from an algebraic combination of  $S_{R-H}$  and  $S^3_{O_2}$  (reagents), or from  $S_{K=O}$  and  $S_{H_2O}$  (products) with at least a sum in common. Angular momenta sum vectorially, and for the reaction above the spins of the reactants are  $S_{R-H} = 1$  and  $S^3_{O_2} = 0$ , which combine to give a total spin of  $S_{\text{Reactants}} = 1$ . Whereas the two singlet products  $S_{K=O} = 0 \quad S_{H_2O} = 0$  can sum only to  $S_{\text{Products}} = 0$ . As  $S_{\text{Reactants}} \neq S_{\text{Products}}$  the reaction is forbidden by spin.

In essence, this means that a catalyst is needed to carry out oxidation reactions and oxygen activation, i.e. to change the multiplicity of spin of oxygen, and allow the reaction to occur. Though spin selection rules are rarely perceived as a potential reason for low catalyst reactivity, a metal needs to have the right spin to bind and activate oxygen. This also justifies the well-known fact that, while the oxidation of organic substrates by ground state molecular oxygen  $O_2(^3\Sigma_g^-)$  is a highly exergonic process, kinetically it is very slow in absence of catalysts.<sup>53</sup> Nevertheless, it should be stressed that triplet oxygen has a crucial role in autoxidation reactions<sup>54</sup> as well as combustion processes,<sup>55</sup> (vide infra) as this may lead to an array of products both unselective in terms of branching or oxidation states.<sup>56</sup>

On the other hand, molecular ground state oxygen has also two accessible singlet states at higher energy, (Fig. 1) for which the reaction with organic substrates in singlet state would

be, in principle, allowed by spin selection rules. In these singlet states all of the electrons are paired, but present in different  $\pi^*$  orbitals:  $\pi^* 2p_x$  and  $\pi^* 2p_y$  (state:  $^1\Sigma_g^+$ ), or in the same  $\pi^* 2p_x$  or  $\pi^* 2p_y$  orbital (state:  $^1\Delta_g$ ).  $O_2(^1\Sigma_g^+)$  and  $O_2(^1\Delta_g)$  have energies that are 156.9 kJ mol<sup>-1</sup> and 94.14 kJ mol<sup>-1</sup> above the ground state  $O_2(^3\Sigma_g^-)$  respectively.<sup>57</sup>



**Fig. 1.** Electron configuration for: (a) ground state oxygen  $O_2(^3\Sigma_g^-)$ , (b) singlet excited state with spin paired with one electron in each of the two  $\pi^*$  orbitals  $O_2(^1\Sigma_g^+)$ , and (c) singlet state oxygen with two electrons in one  $\pi^*$  orbital  $O_2(^1\Delta_g)$ . The latter is the species usually referred as ‘singlet’ oxygen.

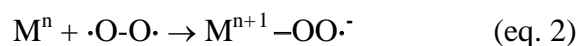
The state  $O_2(^1\Delta_g)$  is usually referred as singlet oxygen in oxidation reactions and can be obtained by electronic energy transfer from photo-excited sensitizers.<sup>58,59</sup> However, while it finds applications in some elegant organic synthesis like cycloaddition reactions of furans,<sup>60,61</sup> it is unsuitable for large scale industrial applications. This because it is extremely reactive and in turn lacks of selectivity, though the formation of  $O_2(^1\Delta_g)$  in  $TiO_2$  photocatalytic systems<sup>62</sup> could open up new applications in the area of photodegradation of organic compounds.<sup>63</sup>

### 3. Catalytic oxygen activation routes

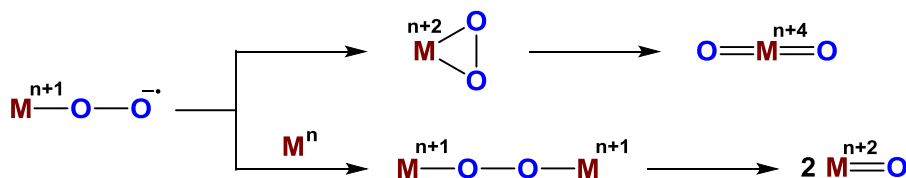
#### 3.1 Oxygen activation by a metal

In view of all these factors, alternative routes for the activation of oxygen capable of changing its spin state, as well as controlling the reactivity of the resulting activated oxygen species, are used. The most common, and exploited way to overcome spin selection rules, is

the activation of paramagnetic ground state oxygen by means of another paramagnetic centre. In most cases this is a transition metal M at an appropriate oxidation state  $n$ .<sup>64,65</sup> The  $M^n$  centre donates one electron to a triplet state oxygen to generate oxygen superoxide  $O_2^{\bullet-}$  (or  $O_2^-$ ) with the formation of a neutral superoxo metal complex, (eq. 2).<sup>66</sup>



Because of the spin selection rules, appropriate oxidation states for the metal are those in which the starting metal centre  $M^n$  is paramagnetic, i.e. contains unpaired electrons, allowing reactions with  $O_2(^3\Sigma_g^-)$ . For transition metals, among the most common elements used in catalysis are:  $Fe^{2+,3+}$ ,  $Cu^{2+}$ ,  $Mo^{3+,5+}$ ,  $Co^{2+,3+}$ ,  $Ni^{1+,2+,3+}$  and  $Mn^{2+,3+,4+}$ .<sup>67</sup> Once the superoxide radical ( $M^{n+1}-O_2^{\bullet-}$ ) is formed, an array of metal-oxygen species can be obtained,<sup>68</sup> including: metal peroxo monomer ( $M^{n+2}-O_2^{2-}$ ), and metal peroxide dimer species ( $M^{n+1}-O_2^{2-}-M^{n+1}$ ), also known as  $\eta$ -peroxo and  $\mu$ -peroxo complexes respectively (Scheme 1). These cases are frequent when metals like Mo or V are used for the catalysed oxidation of alkanes in presence of oxygen donors,<sup>69,70</sup> as well as the epoxidation of alkenes by Cr, Mo and W.<sup>71</sup> The peroxo species can further evolve to a single dioxo-metal ( $M^{n+4}=O_2$ ) centre or two oxo-metal ( $M^{n+2}=O$ ) centres (Scheme 1).<sup>72</sup>

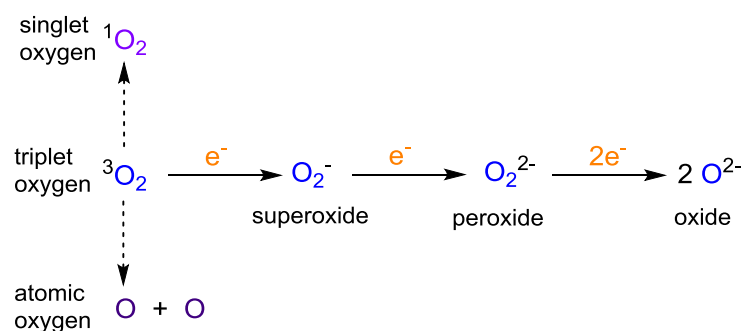


**Scheme 1.** After the initial formation of a metal superoxo species ( $M^{n+1}-O_2^{\bullet-}$ ), this can evolve to a single metal dioxo species ( $M^{n+4}=O_2$ ) or to two metal oxo species ( $M^{n+2}=O$ ) via  $\eta$ -superoxo and  $\mu$ -peroxo complexes respectively. Each intermediate however, can be an active complex for an oxidation reaction, without necessarily undergoing the last step.

Whether the oxygen addition to the metal evolves to a single dioxo species or to two oxo units, the final point of each route (Scheme 1) is the donation of four electrons to molecular oxygen, in a process known as metal centred oxygen transfer reaction.<sup>73</sup> A route that can take place for metals like: Ti, V, Cr, Mn, Ir, Nb, Ta, Mo, W, Ru and Os.<sup>74,75</sup> In view of this,

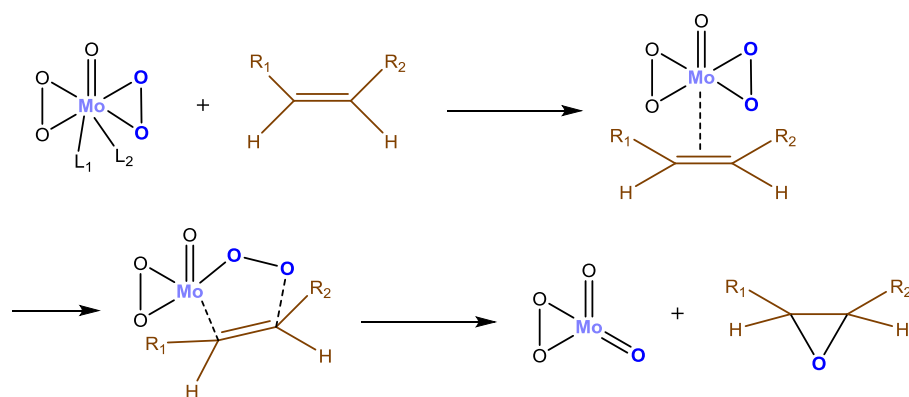


ground state oxygen activation routes could be summarised in terms of electron count (Scheme 2).



**Scheme 2.** Molecular oxygen activation routes in terms of electron count. Ground state triplet oxygen can be activated by a sequential electron transfer in a sequence that evolves as: triplet oxygen, superoxide, peroxide and oxide species. Activation can also occur without electron transfer by means of singlet oxygen formation by irradiation and inter system crossing, or dissociation of molecular oxygen to atomic oxygen.

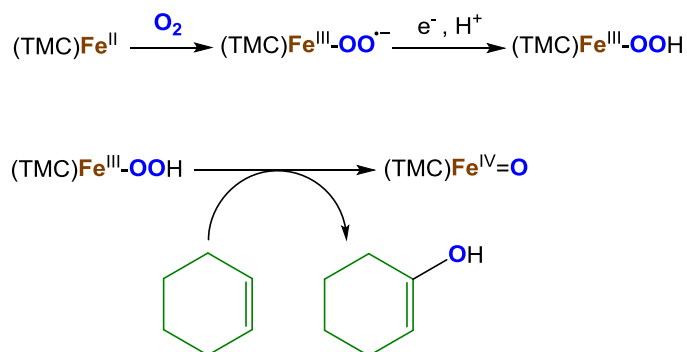
However,  $\eta$ -peroxo species can also be reactive species themselves, without the need to evolve to oxo-metal species. For example in the Sharpless mechanism for the epoxidation of alkenes,<sup>76</sup> one of the oxygen atoms of the original molecular oxygen ends up in the oxidation product, whereas the other oxygen atom forms a single oxo-metal species (Fig. 2).<sup>77</sup>



**Fig. 2.** Epoxidation reaction of alkenes via Sharpless mechanism. A molybdenum peroxo complex like  $\text{MoO}(\text{O}_2)\text{L}_1\text{L}_2$ , where  $\text{L}_1$  is hexamethylphosphoramide (HMPA) and  $\text{L}_2$  is  $\text{H}_2\text{O}$  is used. A  $\eta$ -peroxo reagent is responsible for the epoxidation reaction of the alkene by transferring one oxygen atom to the substrate and simultaneous formation of a oxo-metal species (figure adapted from Ref. 76).

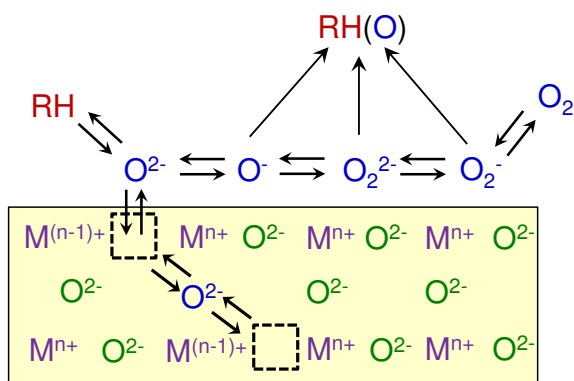
Among these metal-oxygen species, metal superoxo complexes ( $\text{M}^{\text{n}+1}-\text{O}_2^{\bullet-}$ ) and metal oxo species ( $\text{M}^{\text{n}+2}=\text{O}$ ) are possibly those for which most of the research interest and studies are focussed. For instance, metal-superoxo species have attracted much attention recently for fine chemical applications, especially because of the existence of  $\text{Fe}^{\text{III}}$ -superoxo or  $\text{Cu}^{\text{II}}$ -superoxo intermediates that are believed to play key roles in oxygenation reactions by non-heme iron

enzymes.<sup>78</sup> Remarkably these superoxo complexes are able to carry out oxidation of industrially relevant substrates like cyclohexene and cyclooctene under mild conditions to give allylic oxidation products (Fig. 3).



**Fig. 3.** Oxygen activation by (TMC)-Fe<sup>II</sup> complex and superoxide (TMC)-Fe<sup>II</sup>(O<sub>2</sub><sup>-</sup>) formation. The resulting metal hydroperoxide species, (TMC)-Fe<sup>III</sup>-OOH, is active in the hydroxylation reaction of cyclohexene to cyclohexenol. TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (figure adapted from Ref. 78).

Oxo-metal species (M=O) instead, should be considered as a special case, and particularly for gas phase reactions involving catalysts based on metal oxides that present high oxygen lattice mobility. In fact, in this case the oxo-metal species is not the final stage of a catalytic process, (like in Fig. 2 or Fig. 3) but it can rather be the catalytically active species, in a scheme known as Mars and van Krevelen mechanism.<sup>79</sup> Focusing on the oxidation of a hydrocarbon, the Mars and van Krevelen mechanism consists of two stages. The first step involves the C-H bond activation of the hydrocarbon by electron and proton transfer from the hydrocarbon to the metal oxide. The metal is part of a surface metal oxide layer, initially at oxidation state M<sup>n+</sup>(O<sup>2-</sup>). Lattice oxygen transfer takes place and as O<sup>2-</sup> reacts with the hydrocarbon, in a set of equilibria also involving O<sup>-</sup> and O<sub>2</sub><sup>2-</sup>, this leaves an oxygen vacancy and a reduced metal in oxidation state M<sup>(n-1)+</sup> (Fig. 4) The second step is the re-oxidation of the catalyst by molecular oxygen present in the reaction atmosphere. This re-inserts O<sup>2-</sup> to the metal oxide lattice, and is often coupled with formation of water.<sup>80</sup>



**Fig. 4.** Mars and van Krevelen mechanism. Lattice oxygen  $O^{2-}$  from a metal oxide is the active species in the oxidation of a hydrocarbon  $RH$  to a generic oxidation product  $RH(O)$ . During the process the lattice metal centre is reduced from  $M^{n+}$  to  $M^{(n-1)+}$ . The metal is re-oxidised at the end of the cycle by  $O_2$  present in the reaction atmosphere.  $O_2$  from gas phase is re-inserted into the lattice by means of equilibria involving  $O_2^{2-}$  and  $O^-$ .

This reaction scheme occurs in many catalysed oxidations of hydrocarbons by metal oxides, such as: (i) propene oxidation to acrolein by molybdenum and bismuth oxides<sup>81</sup> (ii) total oxidation of volatile organic compounds like benzene and hexane by cerium oxides,<sup>82</sup> and (iii) oxidative dehydrogenation by vanadium oxides.<sup>83</sup> This mechanism is quite important both in industrial applications and for fundamental studies. In fact, due to the transfer of lattice components from the metal oxide to the products, this also leads to correlations between the catalytic activity and thermodynamic parameters characterizing the lattice, like the metal-oxygen bond strength.<sup>84</sup> Interestingly, despite the fact that this mechanism is exclusively regarded to take place for gas/solid reactions, convincing evidence that it can also operate for liquid/solid reactions has been found when phosphovanadomolybdates ( $H_5PV_2Mo_{10}O_{40}$ ) are used for C-H activation of anthracene and xanthene in the liquid phase.<sup>85</sup>

From the mechanistic and classification point of view, oxygen activation routes that lead to the formation of metal oxo and dioxo species (Scheme 1) are usually classed as heterolytic oxygen activation.<sup>86,87</sup> That is a two electron process in a reaction pathway where ionic species may be present, but not free-radical species. Conversely, homolytic oxygen activation routes, mediated by transition metal ions are also possible, and in this case they are one electron processes. This difference is crucial because in this case free-radicals that can initiate uncontrollable, i.e. unselective chain reactions, are created. This is a frequent case in the decomposition of peroxide species<sup>88</sup> and autoxidation processes.<sup>89</sup> Strictly speaking an

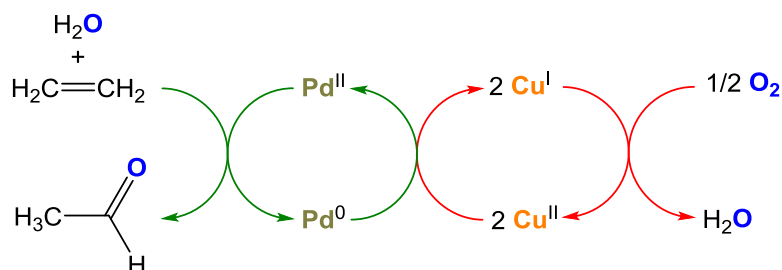
iron(III)-superoxide like the one reported in Fig. 3 is also capable of initiating free-radical chain reactions. This route is favoured because the active species, metal superoxide ( $M^{n+1}-O_2^{\bullet}$ ) is a radical itself and can be reactive without evolution to oxo-metal species. This is important, because free-radical autoxidation is a largely indiscriminate process that can give high selectivities only with molecules containing one reactive position and that give a stable product, e.g. the oxidation of toluene to benzoic acid.<sup>90</sup> Since the prevalence of one mechanism (heterolytic or homolytic) over the other has consequences for the selectivity of an oxidation process, and hence its industrial applicability, these two different activation routes will be described in detail (sections 3.2 to 4.3).

For completeness it should be said that transition metals can also activate oxygen by means of a quantum mechanical mechanism known as spin-orbit coupling (SOC).<sup>91</sup> This generates an effect known as spin-inversion, (i.e. a flip in the spin state of an electron from up to down or vice versa), especially when the metal is heavy and possesses a set of excited states with unpaired electrons close in energy to the ground state.<sup>92</sup> The combination of these factors, may allow ‘spin forbidden reactions’<sup>93</sup> where the reactants and the products of a given transition state have different spin-states and therefore would formally be forbidden. The reaction can take place by the ‘hopping’ of the transition state between energy surfaces at different multiplicity by virtue of the spin inversion. One of the most notable examples of these exceptions to the spin selection rules is the oxidation of methane to methanol by  $FeO^+$  centres.<sup>94</sup> This unconventional oxygen activation mechanism will not be at the centre of this review, though it is important to mention it, to highlight the richness of activation oxygen routes that transition metals can achieve.

### 3.2 Heterolytic oxygen activation mechanisms

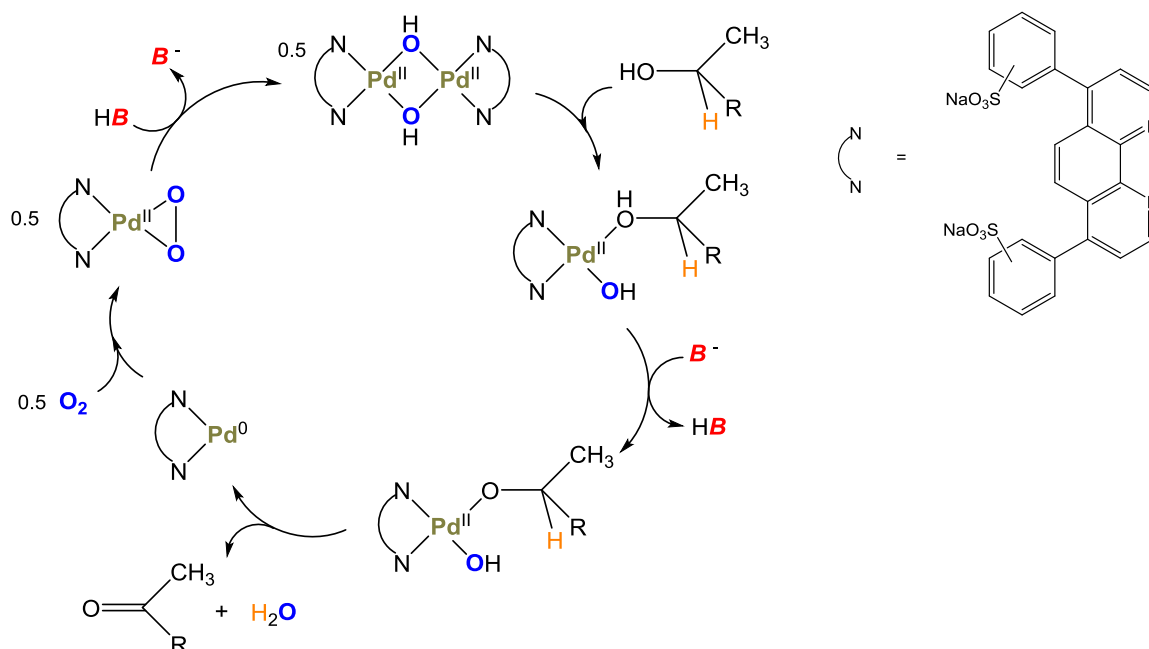
The distinct feature of heterolytic oxygen activation is to be a process that proceeds without free-radicals as intermediates. In this mechanism the organic substrate is oxidised in a two electron process by a metal centre in high oxidation state, e.g.  $M^{n+2}$  to lead to an oxidised substrate and a reduced metal centre in oxidation state  $M^n$ . This reduced form of the metal is then re-oxidised to  $M^{n+2}$  by means of an electron transfer mediator,<sup>95</sup> that can be another metal, or ideally oxygen (like in the Mars and van Krevelen mechanism). One of the most notable examples of this route, that highlights the oxidation/reduction cycle of the metal, as

well as the role of the electron transfer mediator, is the Wacker process for the oxidation of alkenes to aldehydes.<sup>96</sup> The system uses PdCl<sub>2</sub> as the active catalyst. Pd<sup>II</sup> oxidises an alkene to an aldehyde and it is reduced to Pd<sup>0</sup>. However, as Pd<sup>0</sup> is notoriously difficult to be re-oxidised by molecular oxygen to Pd<sup>II</sup>, the re-oxidation is achieved by means of a Cu<sup>II</sup>/Cu<sup>I</sup> couple (Scheme 3).



**Scheme 3.** Wacker process for the oxidation of ethylene to acetaldehyde. Two couples of metals are used: Pd<sup>0</sup>/Pd<sup>II</sup>, which is the real substrate oxidation metal, and Cu<sup>I</sup>/Cu<sup>II</sup> as electron transfer mediator. The latter is needed to re-oxidise Pd<sup>0</sup> to Pd<sup>II</sup> (scheme adapted from Ref. 96).

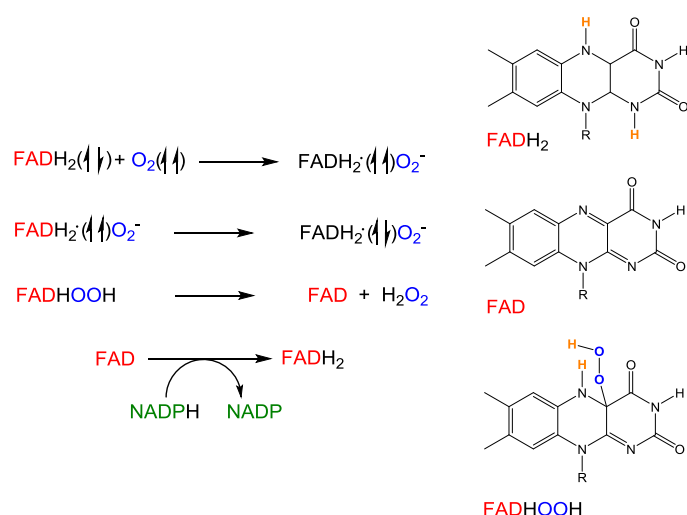
In this scheme PdCl<sub>2</sub> is the substrate selective redox catalyst, while CuCl<sub>2</sub> is the electron transfer mediator. A remarkable exception to a scheme like this was identified for a water-soluble palladium(II)-bathophenanthroline complex, for the oxidation of alcohols, which could be easily re-oxidised by molecular oxygen.<sup>97</sup> Consequently, this reaction does not make use of an additional metal to restore the active palladium species (Scheme 4).



**Scheme 4.** Selective alcohol oxidation by means of palladium(II)-bathophenanthroline complex in water. Unlike the Wacker process no additional metal as electron transfer mediator is needed. However, the catalyst needs to be assisted by a base (B) in order to carry out proton transfer and complete the catalytic cycle (scheme adapted from Ref. 97).

The use of water as a solvent and air as the oxidant makes this reaction interesting from both economic and environmental points of view. However, it should be stressed that such a scheme requires the use of a base to promote proton transfer and therefore complete the catalytic cycle. These examples highlight the challenges, yet to be resolved, to identify a catalyst comprising a single metal (or a combination of metal-oxygen species) that is capable to complete the catalytic oxidation cycle in all its entirety without the need of a second metal, a base, or a reducing agent (*vide infra*).

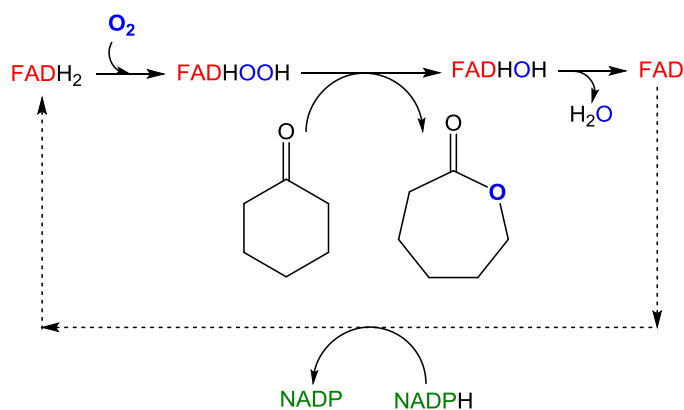
The latter is important, as the heterolytic mechanism is also believed to occur in a vast class of enzymes, namely monooxygenases.<sup>98,99</sup> In monooxygenases an oxygen transfer from a metal centre, in high oxidation state, to the substrate occurs. The metal centre is often Fe or Cu<sup>100</sup> and the electron transfer can be achieved by means of a co-factor like flavin (Scheme 5).<sup>101</sup>



**Scheme 5.** Activation of oxygen by reduced flavin (FADH<sub>2</sub>). After binding with oxygen spin inversion occurs, this initially forms a superoxide species and then an unstable hydroperoxide intermediate (FADHOOH). FADHOOH is responsible for the oxygen transfer to an organic substrate and formation of flavin in oxidized form (FAD). Flavin regeneration takes place by means of NADPH as reductant, and it is stoichiometrically used in the catalytic cycle.

In this reaction scheme, an electron is transferred from a reduced flavin molecule to ground state triplet oxygen to yield a caged radical pair, which after spin inversion leads to flavin hydroperoxide (Scheme 5). The last intermediate is unstable in aqueous solution and heterolytically dissociates to H<sub>2</sub>O<sub>2</sub> and flavin in oxidised form. As a consequence a reducing agent - for flavin based enzymes often NADPH (nicotinamide adenine dinucleotide

phosphate), - is needed to restore the cofactor to its original reduced form. It can then re-bind oxygen and repeat the catalytic cycle.<sup>102</sup> A nice example of this mechanism for an industrially relevant reaction is the Baeyer-Villinger oxidation of cyclohexanone to  $\epsilon$ -caprolactone using acinetobacter containing flavin (Fig. 5).<sup>103</sup>

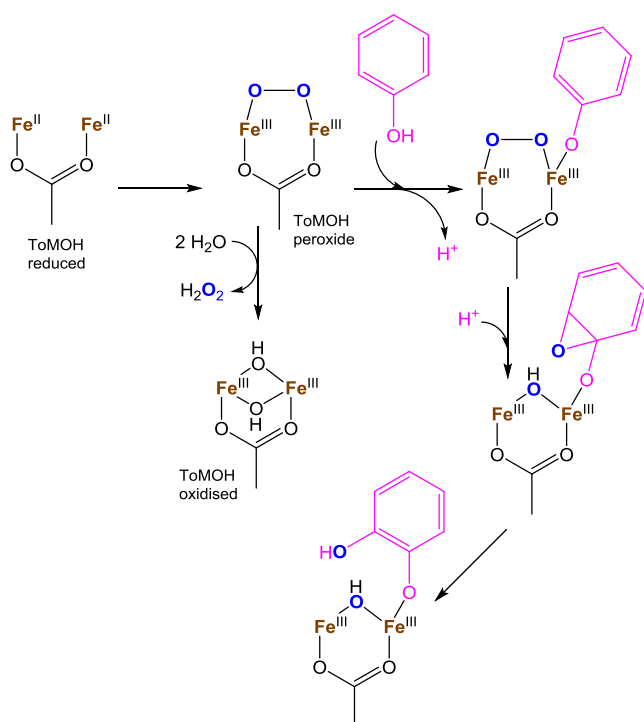


**Fig. 5.** Baeyer-Villinger oxidation of cyclohexanone to  $\epsilon$ -caprolactone using acinetobacter containing flavin. After oxygen activation by means of flavin (FADH<sub>2</sub>), the intermediate FADHOOH inserts an oxygen atom into cyclohexanone. The oxydised flavin (FAD), is then reduced by NADP used in stoichiometric amount.

The need of a reducing agent to carry out an oxidation reaction may appear counterintuitive, but this is required if the active metal centre is in reduced state at the beginning of the cycle, rather than in oxidized state (like in the Mars and van Krevelen mechanism or the Wacker process). Transition metals combined with flavin also promote very elegant and highly selective oxidation processes in Nature, but as the reducing agent NADPH is consumed stoichiometrically, it has not yet been possible to replicate these systems on a large scale. A similar argument is used for pure heme metallo-porphyrines where the reducing agent is NADH (nicotinamide adenine dinucleotide) or ascorbic acid.<sup>104,105</sup> There has been extensive interest in the porphyrin based catalysts for oxidation reactions, in a laboratory context, using NaBH<sub>4</sub> or H<sub>2</sub> as reducing agents.<sup>106</sup> These include: Mn-porphyrins for the oxidation of alkenes,<sup>107</sup> Fe- and Zn-porphyrins immobilized in nanotubes for cyclohexane and n-heptane oxidation,<sup>108</sup> and grafting of Ru-porphyrin over MCM-48 for the epoxidation of styrene.<sup>109</sup> However, because of the need of a reducing agent (NADH, NADPH, NaBH<sub>4</sub> or H<sub>2</sub>) to carry out an oxidation reaction, as well as the general low operational stability displayed by heme based metal catalysts,<sup>110</sup> this route has not found full industrial application. At present notable exceptions are found only for very high priced fine chemicals such as drug metabolites in the

hydroxylation of testosterone, diclofenac and phenacetin,<sup>111</sup> thus suggesting that more work in this area is needed.

In fact, a real goal in catalyst design for oxidation of organic substrates (and especially for the selective oxidation of alkanes), would be to obtain a catalyst that can mimic biological systems but without the need of a sacrificial reductant. A promising example in this direction was shown for a di-iron(III) centre isolated from *Pseudomonas* sp. OX1.<sup>112</sup> This is capable of carrying out hydroxylation of aryl compounds with high activity as well as suggesting that dioxygen activation may be reversible (Fig. 6). That is the oxidised hydroxylase also decomposes hydrogen peroxide to liberate dioxygen in the absence of reducing equivalents.



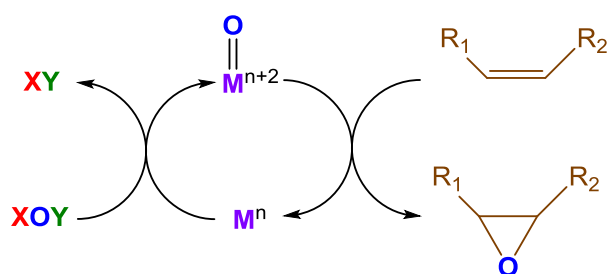
**Fig. 6.** Reaction mechanism for the phenol hydroxylation reaction by Fe-Fe centre, isolated from *Pseudomonas* sp. OX1. ToMOH = toluene monooxygenase. Molecular oxygen activation occurs by means of both Fe centres of the active site, to form a Fe<sup>III</sup>-OO-Fe<sup>III</sup> peroxide. This, by oxygen transfer, generates the final hydroxylated product via an epoxide intermediate (figure adapted from Ref. 112).

Nevertheless, more research would be needed in this area, not only to improve the stability of these materials, but also to ensure that peroxides, which can be formed during the oxidation process undergo a heterolytic cleavage like in biological systems.<sup>113</sup> This is needed to avoid homolytic cleavage, which has a negative effect on product selectivity by generating free-radical pathways.



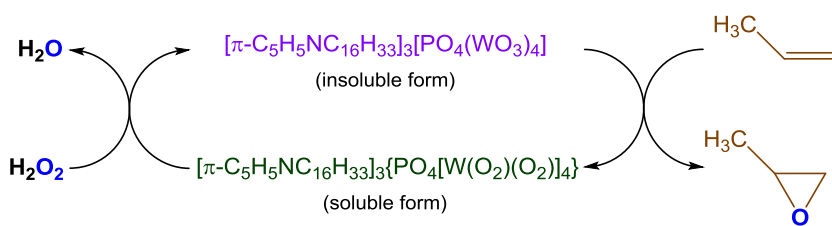
### 3.2.1 Oxygen donors for catalytic oxygen transfer

An alternative heterolytic oxygen activation route, currently used in several industrial applications, is catalytic oxygen transfer.<sup>114,115</sup> This process makes use of a single oxygen donor, which consists of peroxides like hydrogen peroxide or alkyl hydroperoxides ( $\text{H}_2\text{O}_2$ ,  $\text{RO}_2\text{H}$ ). In this process, the peroxide species transfers a single oxygen atom to an organic substrate, leading to an oxidised substrate and a co-product (Scheme 6).



**Scheme 6.** General catalytic oxygen transfer mechanism by a metal centre and an oxygen transfer donor. In this scheme  $\text{XOY}$  is a general oxygen donor, which after oxygen transfer to the metal centre leads to the by-product  $\text{XY}$ . In the process the metal acts like an oxygen carrier that transfers one oxygen atom from a donor to the organic substrate. In this general example an epoxidation reaction is illustrated.

This is carried out by means of a catalytic reaction mediated by a transition metal,<sup>116</sup> and can be applied to the difficult activation and functionalization of C-H bonds in hydrocarbons like alkanes.<sup>117</sup> The oxygen donor can be either organic or inorganic. The most common organic donors are:  $\text{H}_2\text{O}_2$ , TBPH,  $\text{O}_3$ ,  $\text{N}_2\text{O}$  and peracids ( $\text{RCO}_3\text{H}$ ); whereas inorganic donors include:  $\text{HNO}_3$ ,  $\text{NaClO}$ ,  $\text{NaClO}_2$  and  $\text{KHSO}_5$ .<sup>118</sup> These can be used for reactions ranging from hydroxylation, allylic oxidation, epoxidation, to oxidative cleavage. This route is quite important in an industrial context, and the choice of the oxygen donor is driven by the nature of the co-product and the weight percentage of the oxygen in the donor species.<sup>119</sup> In fact, due to the increased demand of green chemical processes, currently preferred donors are  $\text{H}_2\text{O}_2$  and  $\text{NaClO}_2$  as they lead to  $\text{H}_2\text{O}$  and  $\text{NaCl}$  as co-products respectively.<sup>120</sup> By using this route metal centres comprising Cu and Ni anchored to polymers can efficiently catalyse the conversion of styrene into styrene oxide with high selectivity.<sup>121</sup> Further examples include the epoxidation of propene to propene oxide using tungstate phosphate based catalysts like:  $[\pi\text{-C}_5\text{H}_5\text{NC}_{16}\text{H}_{33}]_3\text{-}[\text{PO}_4(\text{WO}_3)]_4$ ,<sup>122</sup> (Fig. 7) or biomimetic asymmetric dihydroxylation of alkenes using catalytic amounts of  $\text{OsO}_4$ , and  $\text{H}_2\text{O}_2$  as the terminal oxidant.<sup>123</sup>



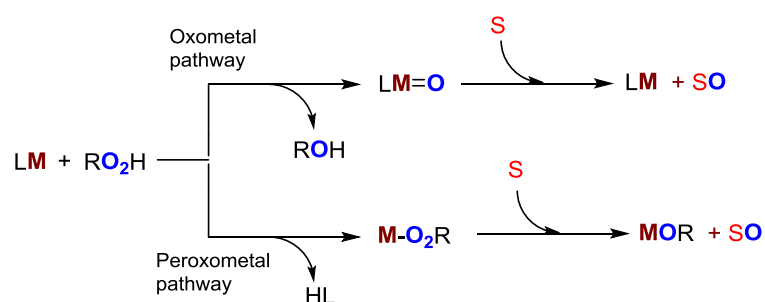
**Fig. 7.** Catalytic oxygen transfer by means of  $\text{H}_2\text{O}_2$  as oxygen donor and a tungstate phosphate based catalyst for the epoxidation reaction of propene. In this particular case the oxidized (purple) and reduced (green) form of the catalyst have different solubility in the reaction media (organic solvent), thus making this also a phase transfer reaction (figure adapted from Ref. 122).

An additional feature in the use of  $\text{H}_2\text{O}_2$  compared to  $\text{O}_2$  that is appreciated in industrial context, is that  $\text{H}_2\text{O}_2$  is miscible with water and relatively easy to handle. However, as substantial negative aspect,  $\text{H}_2\text{O}_2$  can undergo radical-induced decomposition to  $\text{H}_2\text{O}$  and  $\text{O}_2$  by impurities and traces of metals (see section 4.2).<sup>124</sup>

In this context, tert-butyl hydroperoxide (TBPH) is probably the second most common oxygen donor in transition metal catalysed oxidations employing catalytic oxygen transfer. It finds applications for the oxidation of  $\alpha$ -pinene by means of metals salts of Cu, Co, Mn and Pd<sup>125</sup> and for the manufacture of oxygenated terpenes.<sup>126</sup> Further examples include: cyclohexene oxidation to cyclohexane epoxide by Ru clusters,<sup>127</sup> epoxidation of styrene and styrene from Mn supported on MCM-41,<sup>128</sup> asymmetric epoxidation of allylic alcohols by V centres.<sup>129</sup> When TBPH is used, the by-product of the reaction is tert-butyl alcohol (TB-OH), which can be recycled by subsequent reaction with  $\text{H}_2\text{O}_2$  in acid media.<sup>130</sup> It is this recyclability aspect that further drives the choice of oxygen donors for transition metals catalysed oxidations to inorganic oxidants. For example, species like NaBrO, NaBrO<sub>2</sub>, NaClO and NaClO<sub>2</sub> are all active towards alcohol oxidation of alcohols, alkenes and phenols to aldehydes or ketones.<sup>131,132</sup>

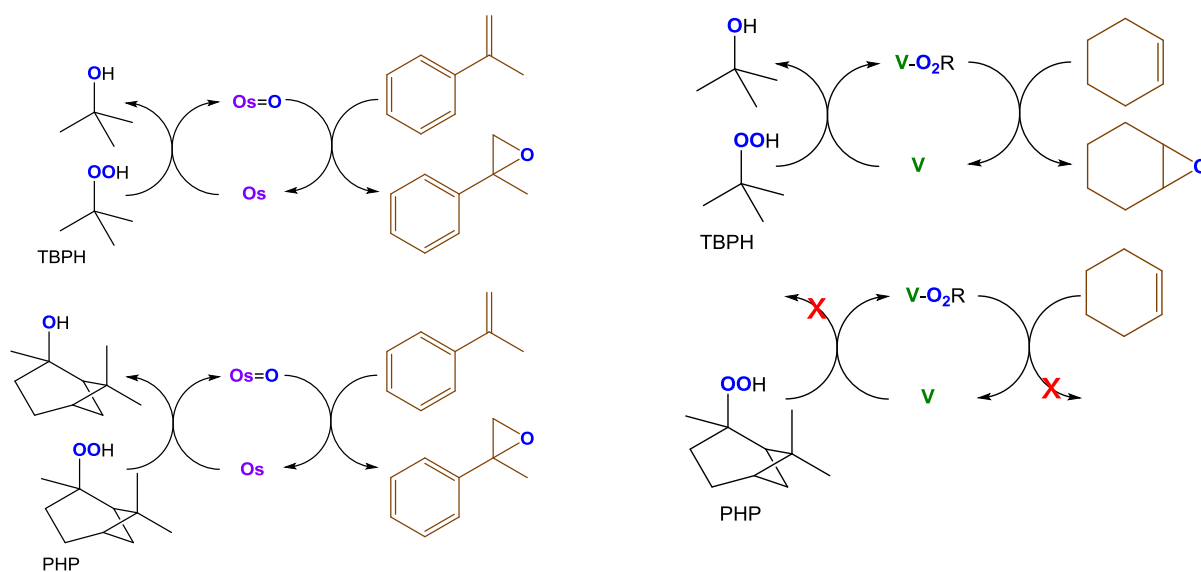
However, despite the large availability of metal species that can catalyse oxidation reactions, there is a major drawback in the use of oxygen donors like  $\text{H}_2\text{O}_2$ , TBPH (or peroxy species in general). This is the competition of homolytic peroxide decomposition routes, which lead to free-radical oxidation pathways that may severely affect the selectivity to a desired product.<sup>133</sup> As a consequence, it would be useful to have a tool to discriminate between: (i) oxo-metal pathway that will involve the formation of metal oxo ( $\text{M}=\text{O}$ ) species in a

heterolytic oxygen activation route, or (ii) a peroxometal pathway that involves the formation of M-OOR species and in turn a homolytic oxygen activation route (scheme 8).<sup>134</sup>



**Scheme 8.** The reaction of an organic peroxide as oxygen transfer agent to a metal centre can in principle take place either via the formation of an oxo-metal species (oxometal pathway), or the formation of a metal alkyl peroxide intermediate (peroxometal pathway), (scheme adapted from Ref. 135).

An elegant method to tackle this important mechanistic aspect was developed by Sheldon and co-workers by means of bulky hydroperoxides in the study of an array of epoxidation reactions.<sup>135</sup> The principle of this method is to analyse the relative reactivities of tert-butyl hydroperoxide (TBHP) versus pinane-hydroperoxide (PHP) in the role of oxygen donors towards different organic substrates and metals. PHP is a very bulky hydroperoxide that does not easily adsorb to a metal centre.<sup>136</sup> Therefore, if the rate-limiting step of the oxidation reaction is the intermolecular oxygen transfer from a peroxometal species (M-OOR) to the substrate, the bulky PHP will be substantially unreactive. In contrast, if the process involves the reaction of an oxo-metal (M=O) species with the substrate as the rate-limiting step, no substantial difference in activity and selectivity should be observed using either TBHP or PHP. Exploring an array of catalysts comprising metals like: Cr, Mo, Ru, Se, V, and Zr for the epoxidation and allylic oxidation of alkenes, it was possible to conclude that Mo and V were operating via a peroxo metal route, while all the other metals were operating via an oxo-metal pathway (Fig. 8).



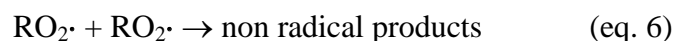
**Fig. 8.** Catalytic oxygen transfer for the oxidation of  $\alpha$ -methyl styrene to 2-phenylpropylene oxide by  $\text{OsO}_4^-$  salts (left). As the reaction takes place by means of a metal oxo species, this is not affected by the use of TBPH as oxygen donor or the bulky PHP. Catalytic oxygen transfer for the oxidation of cyclohexane to cyclohexene oxide by means of  $\text{V}(\text{acac})_2$  complexes (right). As in this case the reaction occurs via metal-alkyl peroxide formation, this step is inhibited in presence of bulky PHP. The use of TBPH versus PHP can therefore provide a tool to discriminate between oxo and peroxy oxygen transfer activation routes.

#### 4. Homolytic oxygen activation mechanism and autoxidation

As mentioned in the previous section, the key point of homolytic oxygen activation is the presence and active role of free-radicals as reactive intermediates.<sup>137</sup> This can start in two ways: (i) by thermal homolytic cleavage of an initiator (often an alkyl hydroperoxide), or (ii) by reaction of trace amounts of hydroperoxides with a transition metal. Thermal peroxide decomposition should always be considered as a possible pathway for reaction temperatures in the range of 130-150 °C and above.<sup>138</sup> Instead, transition metal induced peroxide cleavage usually involves metals presenting a variable oxidation state, the most common being Mn, Fe, Co, Ni and Cu.<sup>139-141</sup> If alkyl hydroperoxide ( $\text{ROOH}$ ) species are present in the reaction mixture, these metals promote the formation of alkoxy ( $\text{RO}\cdot$ ) and alkylperoxy ( $\text{ROO}\cdot$ ) radicals, which can further react with the organic substrate in a free-radical chain process in a process known as autoxidation. Autoxidation, which is still an oxygen activation, is central because if this takes place no selectivity control is possible by the metal centre, and the resultant selectivity will be driven by the free-radical chain process only.<sup>142</sup>

## 4.1 Reactivity of oxygen in autoxidation processes

A simplified scheme - yet useful to develop our reasoning - of homolytic oxygen activation for the autoxidation of hydrocarbons is given in eq. 3-6.<sup>143</sup>



This is classically subdivided as initiation (eq. 3), propagation (eq. 4 and eq. 5) and termination (eq. 6). The initiator species, In, of eq. 3, can either be a thermally decomposed peroxide, or the resultant from the reaction of traces amounts of hydroperoxides in solution with a transition metal (either in traces or not). It is then in the propagation step (eq. 4) that ground state oxygen  $\text{O}_2(^3\Sigma_g^-)$ , usually unreactive toward oxidations, enters the mechanism. In fact, we can re-write eq.4 by considering the formation of intermediate transition state  $[\text{R}\cdots\text{O}_2]^\ddagger$  and the spin  $S$  of reactants and products, (and their multiplicity), by applying the same reasoning carried out in section 1, (Table 2).

**Table 2.** Spin states for the reaction of an alkyl radical  $\text{R}\cdot$  with ground state triplet oxygen  $\text{O}_2(^3\Sigma_g^-)$ , to generate an alkyl peroxide species  $\text{ROO}\cdot$ . By applying the same rules described in section 2, in this case the reactants give the series  $S = 3/2$  and  $1/2$ , whereas the product has the only term  $S = 1/2$ . As the two series have a term in common,  $1/2$  the reaction takes place, in this case on a doublet potential energy surface.

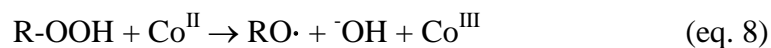
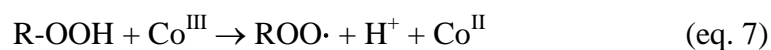
	Reactants	Transition state	Products
	$\text{R}\cdot + \text{O}_2(^3\Sigma_g^-) \rightarrow$	$\text{R}\cdots\text{O}_2^\ddagger \rightarrow$	$\text{R}-\text{O}_2\cdot$
Spin	$S_{\text{R}\cdot} = 1/2 \quad S_{\text{O}_2} = 1$	Requires: $ S_{\text{R}\cdot} \pm S_{\text{O}_2}  =  S_{\text{RO}_2\cdot} $	$S_{\text{RO}_2\cdot} = 1/2$
Multiplicity of spin $2S + 1$	2      3		2
Spin state	Doublet    Triplet		Doublet

In this case the two reagent molecules have spins  $S = 1/2$  and  $S = 1$  for  $\text{R}\cdot$  and  $\text{O}_2(^3\Sigma_g^-)$  respectively. These can combine to give total spins  $S_{\text{Reactants}}$  of  $3/2$  and  $1/2$  whereas the only product - alkyl peroxide - gives a total spin  $S_{\text{Product}}$  of  $S = 1/2$  (doublet). It should be noted that in this case the two series of reagents and product have a term in common,  $1/2$ , therefore the reaction may now proceed on a doublet potential energy surface,<sup>144</sup> and it does. In fact, the reaction of molecular ground state oxygen with a carbon centred radical, is so fast that for

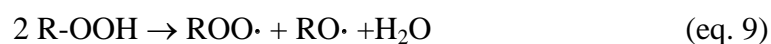
every practical purpose it can be considered energetically barrier-less, and limited by diffusion of O<sub>2</sub> in the reaction media only.<sup>145</sup> Finally, by using the same argument on the multiplicity of spin for eq.5, which is a hydrogen abstraction reaction, this may also proceed via a doublet potential energy surface, although with an activation energy in the range of 60 kJ mol<sup>-1</sup>.<sup>146</sup>

## 4.2 Autoxidation promoted by metals

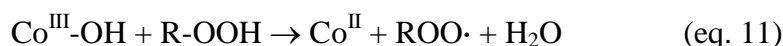
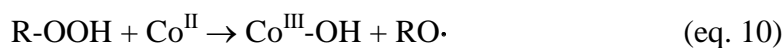
The central aspect of the autoxidation is to have a metal ion that, in combination with a peroxide species like the same ROOH, acts as an initiator (eq. 3). The reaction is autocatalytic, in the sense that the alkyl hydroperoxide species ROOH accelerates the reaction by undergoing homolysis induced by the metal to a chain initiating radical. It is this process that is referred to as autoxidation. The best example of this, is possibly the Haber-Weiss cycle<sup>147</sup> for the decomposition of alkyl peroxides, and considered to be an essential part of the Co-promoted oxidation of cyclohexane by Co(acac)<sub>2</sub> or Co-naphthenate complexes (eq. 7-9).<sup>148</sup>



Net equation:



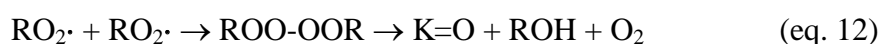
Both the alkyl peroxide (ROO·) and the alkoxy (RO·) radicals can take part in the hydrogen abstraction reaction and therefore propagate the reaction. The alkoxy radical is more reactive with an activation energy in the range of 20 kJ mol<sup>-1</sup>.<sup>149</sup> A variation to this scheme, with respect to eq. 7 and eq. 8 has also been reported:<sup>150</sup>



Which leads to the same net eq. 9. It is still disputed which steps, between eq. 7 and eq. 8 or between eq. 10 and eq. 11, are rate determining,<sup>151,152</sup> as well as which of the various cobalt

species, is the most dominant in solution. A recent study by Hermans and co-workers comprising both computational and kinetic studies of the autoxidation of cyclohexane by means of UV-Vis spectroscopy suggested that the dominant species is  $\text{Co}^{\text{II}}$ .<sup>153</sup>

Additionally, considering a more detailed view of eq.6 in the case of alkanes (either linear, branched or cyclic) this step can lead to the expected partial oxidation products alcohol and ketone at once:



where  $\text{K=O}$  and  $\text{ROH}$  denotes a ketone and an alcohol respectively. Beside the product formation, this step is important because for every two oxygen molecules consumed in the propagation step (eq. 4 and eq. 5 combined), one oxygen molecule is regenerated in the termination step (eq. 6 or eq. 12) thus further contributing to the propagation of the reaction (eq. 4). In view of this, the metal is capable of accelerating the reaction, and so it is by definition a catalyst for the hydrocarbon oxidation. However, this acceleration occurs by increasing the concentration of species (through  $\text{R-OOH}$  or  $\text{R-OO}\cdot$ ) which are chain carriers in the radical pathway of the reaction and therefore promotes catalytic autoxidation processes via a free-radical chain mechanism. As a consequence the metal acts more like an initiator, and should be better defined like a promoter of autoxidation pathways.<sup>154</sup> This is a central aspect that has implications on both catalyst design and assessment whether an oxidation process involving metals is truly catalytic or not. In fact, if the metal acts just like an initiator, no actual selectivity control is possible, as this is under the control of the chain carriers  $\text{RO}\cdot$  and  $\text{ROO}\cdot$ . Moreover, as the termination/condensation step of a free-radical chain process always produces oxygen this can further sustain competing autoxidation during the catalytic process.

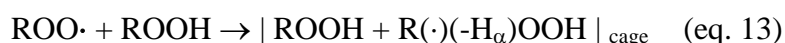
As a consequence, autoxidation can easily cause data misinterpretation with ‘catalytic’ materials that are actually promoters rather than real catalysts, and where selectivity control is impossible.<sup>90,96,134,155</sup> Therefore, it is essential to carry out accurate control tests for every oxidation reaction, especially on hydrocarbons as substrates, in order to discriminate between a real catalytic, i.e. heterolytic process, versus a ubiquitous but often parasitic, homolytic process.

### 4.3 Autoxidation: a closer look

Autoxidation reactions, however, consist of a substantial number of steps in addition to those reported in the simplified scheme of eq. 3-6 and eq. 12. In fact, there are at least three further aspects that play a crucial role in autoxidation processes, but that are often neglected both in literature and laboratory practice. These are: (i) abstraction of a hydrogen in  $\alpha$ -position to functional group,<sup>156</sup> (ii) presence of solvent cages<sup>157</sup> and (iii) characterization of the reaction products.<sup>158</sup> In view of their importance these aspects are now treated singularly and in detail.

#### 4.3.1 Hydrogen abstraction of H in $\alpha$ to a functional group

Recent kinetics and computational studies by Hermans and co-workers of the liquid phase autoxidation of hydrocarbons<sup>159-161</sup> highlighted that chain carriers like ROO· (or RO·) not only abstract H atom(s) from the reactant (eq. 5), but they can also abstract  $H_\alpha$  atom(s) from ketones and alcohols, as well as alkyl hydro-peroxide intermediates. In general,  $H_\alpha$  abstraction from partial oxidation products like alcohols and ketones should not be surprising in view of higher acidity of these  $H_\alpha$  atoms compared to the initial alkane substrate. Yet this process is important because it is responsible for the formation of secondary products and hence lower selectivity. In contrast, the  $H_\alpha$  abstraction from an alkyl hydro-peroxide intermediate is an interesting case and for different reasons. Firstly, it highlights the importance of solvent cage effects. And secondly, it shows that the product ketone can be obtained at a much earlier stage than the termination step (eq. 12) during the autoxidation process. In fact, considering the reactivity of the ROO· radical towards the alkyl-hydroperoxide, ROOH this leads to eq. 13.



Where the notation  $\text{R}(\cdot)(-\text{H}_\alpha)$  stands for a substrate that is now a radical species without a  $H_\alpha$ , and the two bars | | specify species that are now in a solvent cage. The latter is also an important aspect, because the two products ROOH and  $\text{R}(\cdot)(-\text{H}_\alpha)\text{OOH}$  can further react inside the solvent cage to give the ketone (eq. 14)

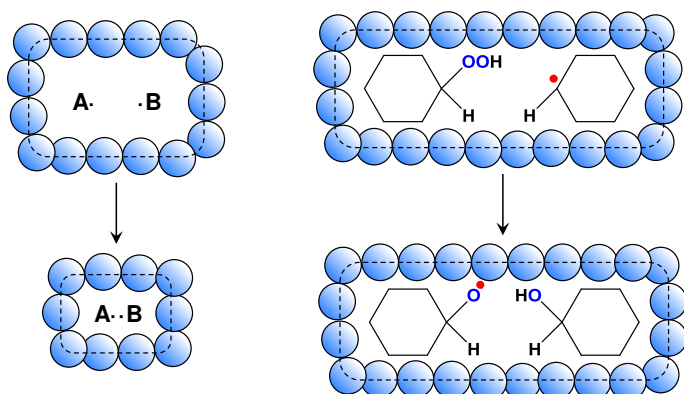




This sequence of reactions shows that the evolution of the classical autoxidation scheme up to termination is not necessary to obtain the product ketone (K=O). The formation of this product can take place much earlier in a free-radical chain process, and be triggered by the same chain carrier ROO·.

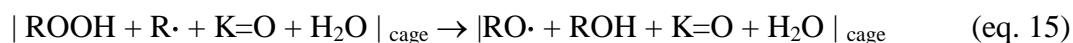
### 4.3.2 Solvent cages

A further important phenomenon in autoxidation reactions that is very often neglected in the literature is that several free-radical reactions do not take place via radical intermediates as species that are free in solution. These radical intermediates are rather constrained in a solvent cage.<sup>162,163</sup> The term “cage effect” is defined as a phenomenon in which the probability of recombination of a thermally (or photochemically) generated radical pair is significantly higher in solution than in the gas phase.<sup>164</sup> This also applies to pairs where only one partner is a radical as in eq. 13 and eq. 14 (Fig. 9).



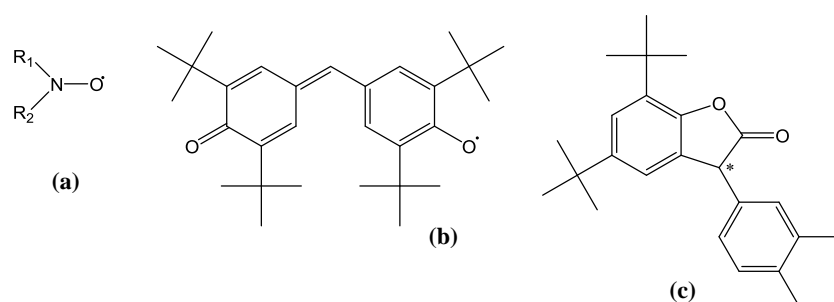
**Fig. 9.** Radical recombination in solvent cage (left) and radical recombination reaction between alkyl peroxy radical and alkyl radical (right) to alkoxy radical and alcohol formation.

This is significant because a vast class of oxidation reactions (regardless the nature of the substrate, hydrocarbon, alcohol, aldehyde, ketone, etc...) take place in solution, and the cage effect may have a large impact on the reactivity of the intermediates. Taking into account this effect, it was possible to postulate that in the case of hydrocarbon autoxidation, not only the ketone can be obtained before the termination step, but also the alcohol.<sup>165</sup>



It is also worth noting that, if eq. 15 is operating, the alkyl peroxide ROOH is not a chain carrier but is stoichiometrically consumed for each new molecule of ketone and alcohol formed. In view of this, if this route takes place, the concentration of ROOH should exhibit a maximum as a function of time,<sup>166</sup> (as a consequence of the ROOH generation in eq. 5 and eq. 13, and the competitive ROOH consumption in eq. 15). This has been experimentally observed in the autoxidation of cyclohexane carried out in pure cyclohexane (i.e. solvent free) or in pure acetonitrile as solvent, (though when acetonitrile was used a smoother maximum was observed).<sup>166</sup> In contrast, in the case of cyclohexane oxidation by means of MnAPO-5 catalysts a continuous increase of ROOH concentration with time is observed.<sup>167</sup> This suggests that solvent cage effect is not operating in the latter case, and that autoxidation may be inhibited.

However, as these tests and characterizations can be difficult to perform, further ‘rules’ can be used to assess if solvent cages are operating or not. Firstly, solvent cages do not occur in the gas phase; secondly, the amount of product formed in the cage is independent from the concentration of the initial peroxide; and finally, the cage products are not retarded or eliminated by radical scavengers.<sup>168</sup> The use of scavengers, in particular, is possibly the most popular method to assess the presence of cages, and more generally the possible presence of radical pathways. For instance, to assess whether a reaction is radical in nature, scavengers like dialkyl nitroxides<sup>169</sup> galvinoxyl radical<sup>170</sup> or benzofuranones<sup>171</sup> can be used, targeted respectively to carbon centred radicals, oxygen centred radicals, or both simultaneously (Fig. 10).



**Fig. 10.** Radical scavengers for the identification of radical intermediates or solvent cages. (a) alkyl nitroxide for the trapping of C-centred radicals, (b) galvinoxyl radical for the trapping of O-centred radicals, and (c) benzofuranone for the trapping of C- or O-centred radicals. In cases (a) and (b) the scavenging reaction occurs by direct combination of the radical to the scavenger. In case (c) the scavenging takes place by a set of sequential reactions instead. The carbon or oxygen centred radicals R $\cdot$ , ROO $\cdot$ , RO $\cdot$  firstly abstract the H\* in the benzofuranone, with consequent R-H, R-OOH, R-OH and benzofuranone radical formation. The resulting benzofuranone radical scavenges the R $\cdot$ , ROO $\cdot$ , and RO $\cdot$  species in solution.

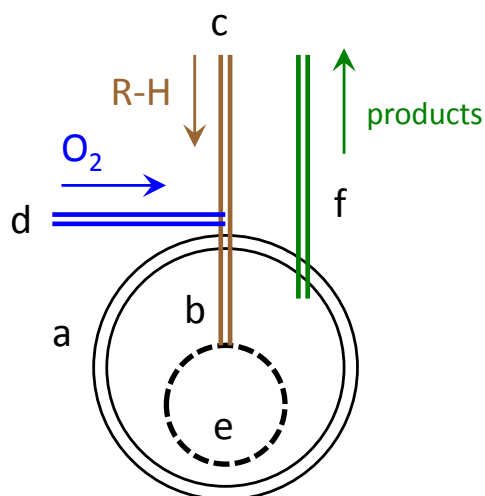
The use of radical scavengers to investigate solvent cage effects has been successfully employed in the study of the thermal decomposition of di-tert-butylperoxy oxalate to di-tert-butyl peroxide as a reaction necessarily generating radicals. This was carried out by using 2,6-di-tert-butyl-4-methylphenol (BMP) as an oxygen centred radical scavenger. Excess of BMP did not suppress the product formation, which occurs via alkoxy radicals, thus showing the reaction takes place via a solvent cage route.<sup>172</sup>

### 4.3.3 Characterization of the reaction products in autoxidation processes

One more major difficulty that needed to be considered in the study of ubiquitous autoxidation processes is the analysis of the reaction mixture. In fact, as the temperature of a hydrocarbon substrate is increased above ca. 100 °C the yields of hydro-peroxides decrease, as a consequence of thermal decomposition and very complex mixtures containing ketones, alcohols, acids, and esters are obtained.<sup>173</sup> Medium chain hydrocarbons can easily lead to mixtures containing more than thirty different products.<sup>174</sup> Moreover, as the autoxidation process is triggered by traces of metals reacting with peroxides, the material that constitutes the reactor walls can also play a role. Studies on the autoxidation of aldehydes<sup>175</sup> showed that if the reaction was carried out in polyethylene (and therefore metal free) flasks rather than glass (which also contains metals) the autoxidation pathway was severely suppressed. This also shows the challenges to transfer results from experiments carried out in a laboratory set-up to an industrial set-up where reactors walls made of metal only, are mostly used.

Oxygen diffusion is also an important aspect to determine the final composition of a reaction mixture, especially in the case of liquid phase oxidations. Studies carried out by Jensen and co-workers showed that the occurrence of branching reactions by autoxidation at low conversions, may increase the oxidation rate, i.e. oxygen consumption, to a point where it is difficult to maintain molecular oxygen saturation in the liquid.<sup>176</sup> If this occurs, the reaction rate becomes controlled by the rate of oxygen mass transfer rather than the catalytic oxidation process itself. If a metal is also present, this may render kinetic interpretations of the results of such experiments meaningless.<sup>96,177</sup> Therefore, it is essential that during these tests oxygen saturation is preserved either by its constant supply under pressure, or accurate

mixing of the reaction mixture by an appropriate reactor design, or both. A schematic of the experimental set-up used by Jensen to minimize these issues is reported in figure 11.



**Fig. 11.** Stirred flow microreactor for the assessment of the oxygen diffusion in the oxidation of hydrocarbon, by Jensen and co-workers. The microreactor consists of two Pyrex glass spheres: a larger outside sphere (a) and a smaller, eccentrically located, and perforated inside sphere (b). A liquid hydrocarbon is delivered to a T joint (c) immediately above the reactor and mixed with a stream of oxygen introduced at the second arm (d). The oxygen/hydrocarbon mixture is injected into sphere A from sphere B through the perforations (e) located symmetrically in the base of the inside sphere ensure very efficient "ideal mixing" of the oxygen, hydrocarbon, and reaction products in the reactor. The outlet from the reactor (f) is located at the top of the outside sphere (figure adapted from Ref. 177).

The cumulative effect of all these aspects shows the complexity of autoxidation reactions, along with any oxidation reaction that produces alkyl peroxides or alkyl hydroperoxide species during the process, as this will result in a parallel autoxidation pathway that can mask the actual catalytic efficiency of a system.<sup>148,154,155</sup>

#### 4.4 Methane and hydrocarbons partial oxidation

The selective oxidation of C-H bond is possibly one of the long-standing challenges in chemistry and catalysis because of its relevance both in industry and academia.<sup>178</sup> This because of the need to valorise natural gas and new fossil fuel resources, and especially alkanes.<sup>179</sup> In this context, the mild oxidation of methane to useful products like methanol or formaldehyde, rather than full combustion to CO<sub>2</sub>, has a very important role. In fact, methane is the principal constituent of natural gas, and according to the International Energy Agency

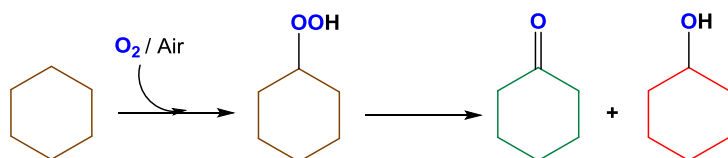
the world's energy demand from natural gas is expected to increase by 30–40% in a 25 years perspective.<sup>180</sup> On the other hand, the partial oxidation of methane into value-added products is among the most challenging to carry out, and the main reason for this is the high CH<sub>3</sub>–H bond dissociation energy (ca. 439 kJ mol<sup>-1</sup>).<sup>181</sup> A very large number of studies has been dedicated to this subject.<sup>182-184</sup> In this review, and with a focus to physicochemical aspects, among the most notable advances in this area there are yttrium stabilised zirconia catalysts<sup>185</sup> and N-bridged high-valent diiron-oxo species.<sup>186</sup>

In particular, yttrium stabilized zirconia catalysts (YSZ) appear to be promising materials for the oxidation of methane into methanol,<sup>187,188</sup> possibly operating via Mars and van Krevelen mechanism. Remarkably, if a dual catalyst bed is used, comprising a phase of LaMoO<sub>3</sub> and a phase of YSZ, the activation of ground state oxygen O<sub>2</sub>(<sup>3</sup>Σ<sub>g</sub><sup>-</sup>), to form singlet oxygen O<sub>2</sub>(<sup>1</sup>Δ<sub>g</sub>), was observed at the gas/solid interface of LaMnO<sub>3</sub>. This allows to use oxygen in singlet state in a controlled manner. Conversely the use of N-bridged porphyrin platforms<sup>186</sup> to carry out the methane oxidation under mild conditions was inspired by methane monooxygenase enzymes.<sup>189</sup> In this case the key feature for molecular oxygen activation is the formation of a Fe(IV)NFe(III)OO(R) complex, capable to provide heterolytic cleavage of the O–O bond,<sup>186</sup> which is an essential step to avoid runaway autoxidation products.

#### 4.4.1 Cyclohexane oxidation: an exploited case of autoxidation

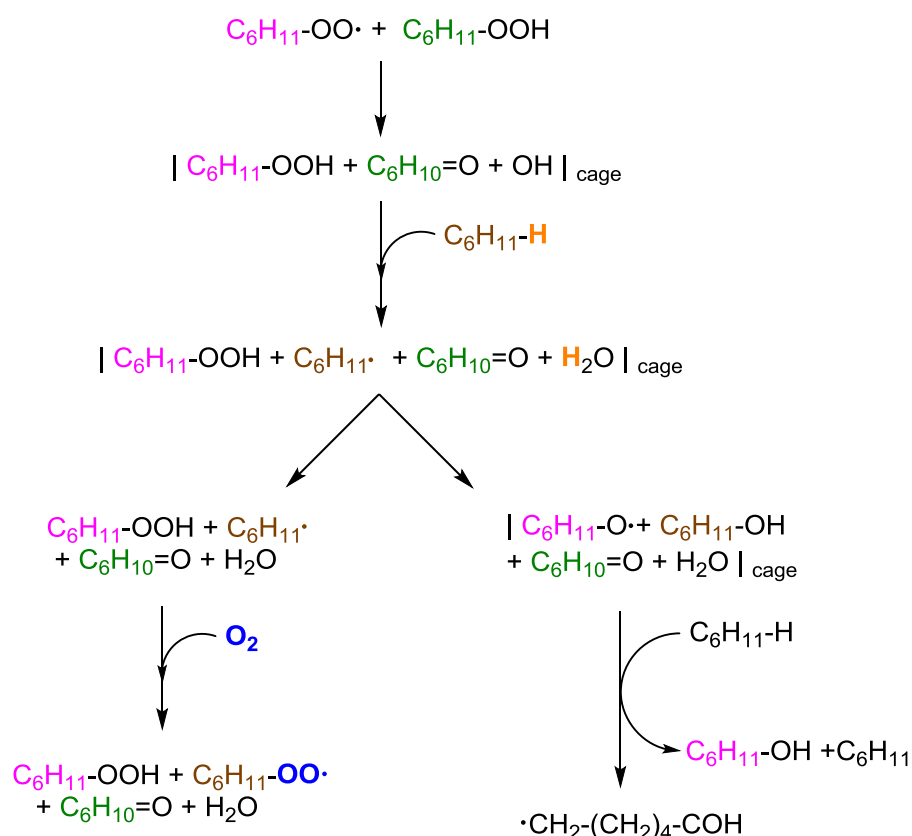
There are, however, processes where autoxidation is used deliberately. Possibly the most remarkable example is the oxidation of cyclohexane to cyclohexanol and cyclohexanone as precursors of nylon-6,6 and nylon-6 respectively.<sup>190,191</sup> This reaction is carried out industrially by means of Co(II)-naphthenate, Co(II)-(acac)<sub>2</sub> or Fe(III)-(acac)<sub>3</sub>,<sup>192,193</sup> which promote a Haber-Weiss cycle, and in turn autoxidation pathways like those described in section 4.2. Applied to cyclohexane these lead to a reaction mixture known as “K/A oil” (where K is the ketone – cyclohexanone - and A the alcohol - cyclohexanol). If nylon-6 is desired, the K/A oil is treated afterwards with HNO<sub>3</sub> to convert cyclohexanol to cyclohexanone and from this adipic acid is obtained. Since in this reaction the ‘catalyst’ Co(II)-naphthenate, is actually a promoter of a free-radical autoxidation pathway, no selectivity control is possible but that dictated by the radical chain process itself. Moreover,

because of the relatively high temperature required for the reaction, (ca. 140 °C) several reaction products can be obtained, (besides cyclohexane and cyclohexane also and adipic acid, and derivatives from ring opening and reactions of  $\omega$ -formyl radicals). In view of this, the conversion of this reaction is deliberately limited at around 4-5% in industrial processes,<sup>194,195</sup> with the aim to preserve selectivity to alcohol and ketone above 85%, and minimize by-product formation (Fig. 12).



**Fig. 12.** General scheme for cyclohexane autoxidation by means of air and metal salts. An alkyl hydroperoxide is formed and this leads to cyclohexanol and cyclohexanone as major products.

The oxidation of cyclohexane has been the subject of several studies, both in industry and academia, due to the peculiarity of its autoxidation mechanism and its industrial relevance. This includes the use of metal complexes,<sup>196</sup> metal oxides<sup>197,198</sup> metal nanoparticles,<sup>199,200</sup> and investigation of both liquid and gas phase systems.<sup>201</sup> For example, the oxidation of cyclohexane over MoO<sub>3</sub> in gas phase, investigated by means of EPR spin trapping in aerobic and anaerobic conditions, showed evidence of a Mars and Van Krevelen mechanism.<sup>202</sup> In contrast the use of metal nanoparticle based systems like Au/MgO or Au/ZSM-5 in liquid phase, showed an enhancement of the autoxidation pathway only, thus suggesting that the metal in this case is actually a promoter.<sup>148,154</sup> To date one of the most complete schemes in the propagation reaction of the alkyl peroxide radical is the one obtained by Jacobs and co-workers (Scheme 9) It also considers the formation of ring opening products like formyl species<sup>165</sup> thus showing the variety of combinations that reactions just involving ground state triplet oxygen can achieve when compared to pure catalytic processes involving heterolytic oxygen activation.



**Scheme 9.** Reaction scheme for the autoxidation of cyclohexanone to cyclohexanone and cyclohexanol that considers ring opening products (like formyl radical) and solvent cages effect. An array of products is obtained. Note that the product ketone K=O will always be in excess to the alcohol if autoxidation is operating.

The important aspect is that if autoxidation is operating, and if in presence of water, the amount of ketone will be in excess to the amount of alcohol.<sup>203</sup> Therefore any metal species that could be capable to invert this trend, i.e. yields more alcohol and less ketone, would be diagnostic of a real catalytic process taking place, possibly at the catalyst surface if a heterogeneous system is used.

## 5. Concluding remarks

Molecular oxygen is possibly one of the most extraordinary molecules one can think of, despite its apparent simplicity. This immediately leads to a complex treatment in order to explain both its peculiar reactivity and activation, as well as lack of reactivity under ordinary conditions. Transition metals are possibly the best option to activate oxygen in a controlled manner and chemists have used them since the very beginning of the systematic study of

oxidation reactions. Nevertheless, virtually any oxidation reaction can produce trace amounts of peroxides, and the combined effect of a metal or temperature can trigger autoxidation pathways that are difficult to control and can hamper the selectivity control of virtually any catalyst present in the reaction mixture. In view of this, we believe that autoxidation pathways should never be neglected in oxidation studies in order to ascertain the real nature of the catalytic process, as well as to provide insights in how to improve catalytic systems. Biological systems like metallo-proteins are proven to be capable to control these reactions under mild conditions, though via pathways that are still not fully understood. However, their full application in an industrial context is still precluded by their limited operational resistance. Nevertheless, a real advance in the design of more selective catalytic oxidation systems will come from catalysts that mimic biological systems but without the need of a sacrificial reductant, base or additional metal as an electron transfer reagent. This will facilitate true heterolytic and selective oxygen activation pathways versus homolytic and unselective activation routes.

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