Biphasic Synthesis of Hydrogen Peroxide from Carbon Monoxide, Water, and Oxygen Catalyzed by Palladium Complexes with Bidentate Nitrogen Ligands

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Hydrogen peroxide is a commercially important chemical used in large volumes for bleaching and a wide variety of chemical oxidations. In recent years H_2O_2 has become more and more popular as an environmentally friendly reagent, mainly because it produces water as its only by-product.[1] Industrially, hydrogen peroxide is produced primarily by the alternate oxidation and reduction of alkylanthraquinone derivatives.[2] Since this method is quite complex, extensive studies have been carried out in an effort to find a direct route, such as the synthesis from carbon monoxide, oxygen, and water in the presence of a palladium triphenylphosphane catalyst disclosed in 1979 by Yermakov et al. [Eq. (1)].[3]

$$O_2 + CO + H_2O \rightarrow H_2O_2 + CO_2 \qquad (1)$$

Despite the favorable thermodynamics of this reaction ($\Delta G^0 = -134\ \mathrm{kJ\,mol^{-1}}$), the catalyst was quite inefficient and a turnover number (TON, moles of hydrogen peroxide per mole of palladium) of only 5 was achieved. The rapid inactivation of the catalyst was mainly due to the oxidation of the phosphane ligand and the resulting precipitation of palladium metal. A moderate improvement of the catalyst lifetime (TON up to 87) was achieved by using the more stable triphenylarsane as the palladium ligand;[4] however, the process was still not suitable for practical applications.

In the last fifteen years, nitrogen ligands have proved to be valuable substitutes of more traditional phosphorus ligands in a number of homogeneously catalyzed reactions.[5] As part of research aimed at developing a new industrial process for the production of hydrogen peroxide, we have therefore investigated a series of palladium complexes containing bidentate nitrogen ligands **1**–**8**. Herein we describe an effective and stable catalyst for the synthesis of hydrogen peroxide from oxygen, carbon monoxide, and water, the productivity of which is quite comparable to that of commercial processes.

1,10-phenanthroline	**1**
2,2′-bipyridine	**2**
4,7-diphenyl-1,10-phenanthroline	**3**
2,9-dimethyl-1,10-phenanthroline	**4**
2,9-di-*n*-butyl-1,10-phenanthroline	**5**
2,9-diphenyl-1,10-phenanthroline	**6**
2,9-dichloro-1,10-phenanthroline	**7**
2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline	**8**

The reaction was carried out in a biphasic system in which the catalyst is soluble in the organic phase and the produced hydrogen peroxide is soluble in the aqueous phase. The biphasic system minimizes the ligand oxidation by reducing the contact with hydrogen peroxide and facilitates the separation and recycling of the catalyst by simple decantation. After screening a wide variety of organic solvents, we found that the reaction was accelerated significantly by the presence of a water-insoluble tertiary alcohol, which possibly plays an active role in the reaction mechanism by acting as ligand. Primary and secondary alcohols were also effective but, under the reaction conditions employed, they were oxidized to some extent (2% conversion was found after 10 h) to the corresponding carbonyl derivatives.[6] A mixture of 2-methyl-2-butanol, 1,2,4-tricholorobenzene (a hydrophobic solvent added in order to improve the phase separation), and water was selected as the reaction medium for the comparison of the catalysts.

Each of the catalysts were generated in situ from Pd(acetate)$_2$, four equivalents of the appropriate ligand **1**–**8**, and 40 equivalents of an acid with a weakly coordinating anion as cocatalyst. In the case of the more hydrophilic ligands such as **1**, **2**, and **4**, which afforded complexes soluble in the aqueous phase, the catalysts were transferred into the organic phase by using a highly hydrophobic acid cocatalyst (perfluorooctanoic acid), which functioned as a phase transfer anion (e.g. the partition of the complex with ligand **4** in the organic layer was <1% and >99% with trifluoroacetate and perfluorooctanoate anion, respectively).

All the reactions were performed at 70 °C and at a total pressure 7100 kPa ($p_{CO} = 600$ kPa; $p_{O_2} = 6500$ kPa). An excess of oxygen was used in order to prevent the precipitation of palladium metal, which becomes predominant under reductive conditions. We observed three different reactivities, depending on the nature of the substitution at the 2,9-position of the ligand (Table 1). The unsubstituted ligands **1**, **2**, and **3**, in presence of CO, led to the formation of stable red complexes,[7] which proved ineffective for the synthesis of hydrogen peroxide.

Ligands bearing bulky substituents, such as **5** and **6**, did not form binuclear species due to the steric hindrance adjacent to the N-donor function, but instead gave unstable soluble Pd^0

Table 1. Effect of ligand on the synthesis of hydrogen peroxide by palladium catalysis.[a]

Ligand	Acid	TOF [h^{-1}][b]
1	$C_7F_{15}COOH$	0[c]
6	CF_3COOH	0[e]
2	$C_7F_{15}COOH$	0[c]
7	CF_3COOH	39
3	CF_3COOH	0[c]
8	CF_3COOH	527
4	CF_3COOH	0[d]
8	$C_7F_{15}COOH$	578
4	$C_7F_{15}COOH$	124
8	Tol-SO_3H	256
5	CF_3COOH	0[e]

[a] Ligand/acid/Pd molar ratio: 4/40/1; solvent: trichlorobenzene/2-methyl-2-butanol/water 35/25/40 (v/v/v); temperature: 70 °C; $p_{CO} = 600$ kPa; $p_{O_2} =$ 6500 kPa. [b] Turnover number frequency (calculated as moles of hydrogen peroxide per mole of palladium per hour). [c] The formation of red dimeric complexes was observed. [d] The complex was soluble in the aqueous phase. [e] The precipitation of palladium metal was observed.

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complexes that quickly dissociated, leading to the formation of palladium metal. The best results in palladium-catalyzed synthesis of hydrogen peroxide were obtained with the ligands **4** and **8**. The lower turnover frequency (TOF) obtained for catalysts with the ligand **7** indicates that such electron-withdrawing substituents have a severe negative effect on the catalytic activity. In the case of ligand **4**, the water-soluble complex was active only if it was transferred into the organic phase by using the hydrophobic perfluorooctanoate anion.

The kinetic profiles of the reaction carried out using $[Pd(\mathbf{8})X_2]$ as catalyst in a halogenated environment (X: $C_7F_{15}COO^-$; solvent: 1,2,4-trichlorobenzene/2-methyl-2-butanol/water) or in a halogen-free environment (X: toluene-4-sulfonate, solvent: toluene/2-methyl-2-butanol/water) are shown in Figure 1.

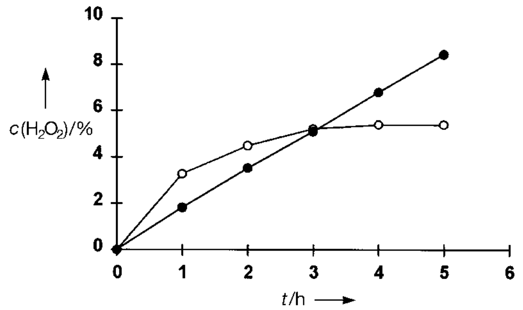

Figure 1. Effect of solvent on the synthesis of hydrogen peroxide by palladium catalysis: (○) Catalyst: $[Pd(\mathbf{8})(C_7F_{15}COO)_2]$; solvent: 1,2,4-trichlorobenzene/2-methyl-2-butanol/water; (●) catalyst: $[Pd(\mathbf{8})(TolSO_3)_2]$; solvent: toluene/2-methyl-2-butanol/water.

In spite of their strong accelerating effect on the synthesis of hydrogen peroxide, and their stabilizing effect with regard to the formation of palladium metal,[8] chlorinated solvents are not the most appropriate reaction media since they can also undergo undesired side reactions, such as the palladium-catalyzed reduction in the presence of CO and water [Eq. (2)].[9]The hydrochloric acid generated in this way, even at a low concentration (molar ratio $Cl/Pd \geq 4/1$), can act as a strongly coordinating ligand of palladium, leading to the formation of unreactive complexes and thus to inactivation of the catalyst.[10]

$$RCl + CO + H_2O \rightarrow RH + HCl + CO_2 \qquad (2)$$

Much better results in terms of catalyst stability were obtained by operating in a halogen-free solvent and by adding only sufficient hydrochloric acid (molar ratio $Cl/Pd = 1/1$) to prevent the precipitation of palladium metal. Under these conditions it was possible to achieve high TONs and produce hydrogen peroxide aqueous solutions up to 8% w/w concentration. The catalyst, which is quantitatively distributed in the organic phase, could be easily recovered and reused in several consecutive reactions, without appreciable loss of activity.

Although detailed mechanistic information is not currently available, the reaction is likely to involve the reduction of Pd^{II} species by carbon monoxide to form a Pd^0 complex via a hydride intermediate.[11] The subsequent oxidation of the Pd^0 species to afford a Pd^{II} peroxo species and eventually, under acidic conditions, hydrogen peroxide, is known.[12, 13]

In conclusion, complexation of palladium with a suitable bidentate nitrogen ligand provides an efficient catalyst for the synthesis of hydrogen peroxide from carbon monoxide, oxygen, and water. The structure of the ligand as well as the nature of the weakly coordinating anion and the solvent play a key role in determining the catalytic activity and the operational stability of the complexes; catalytic systems were developed that displayed far better catalytic activity and operational stability than in palladium-based catalytic systems described to date. The development of a continuous operation process, more suitable for an industrial application, is presently under consideration.

Experimental Section

Ligands **1**–**4** and **8** were purchased from Aldrich, and **5**–**7** were synthesized according to literature methods.[14, 15]

General procedure for the synthesis of hydrogen peroxide: $Pd(OAc)_2$ (0.07 mmol), CF_3COOH or $C_7F_{15}COOH$ (2.8 mmol), and one of the ligands **1**–**8** (0.28 mmol) were dissolved in a mixture of 1,2,4-trichlorobenzene (40 mL) and 2-methyl-2-butanol (60 mL), and stirred for 6 h at 25 °C. The resulting solution was added to water (80 mL) to form a biphasic system and poured into an autoclave containing a glass liner. The reactor was then pressured to 6500 kPa partial pressure of O_2 and 600 kPa partial pressure of CO to form a nonflammable gas mixture. The reactions were carried out for one hour at 70 °C; the mixture was stirred by a magnetically driven impeller. After the reactor was depressurized, the hydrogen peroxide concentration in the aqueous solution was measured by titration with potassium permanganate.

Kinetics measurements: $Pd(OAc)_2$ (2.5 mmol), $C_7F_{15}COOH$ (60 mmol), and **8** (20 mmol) were dissolved in a mixture of 1,2,4-trichlorobenzene (85 mL) and 2-methyl-2-butanol (15 mL), and stirred for 6 h at 25 °C. A second catalytic system was prepared in the same way by using toluene-4-sulfonic acid and toluene instead of $C_7F_{15}COOH$ and 1,2,4-trichlorobenzene, respectively. The resulting solutions were added to water (80 mL) to form a biphasic system. The comparison between the two catalysts was carried out in the same reactor as described above equipped with an automatic system to maintain both the inlet pressure and the inlet composition of the gas mixture at constant values. The reactions were carried out at 70 °C and 8100 kPa of total pressure ($p_{CO} = 600$ kPa; $p_{O_2} = 7500$ kPa). The hydrogen peroxide concentration in the aqueous phase was determined periodically during the course of each run by temporarily stopping the gas flow for one minute, which allowed the liquid phases to separate, withdrawing a measured volume of aqueous phase, and pumping an equal volume of deionized water back into the reactor.

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"Base Flipping": Photodamaged DNA – RNA Duplexes Are Poor Substrates for Photoreactivating DNA-Repair Enzymes**

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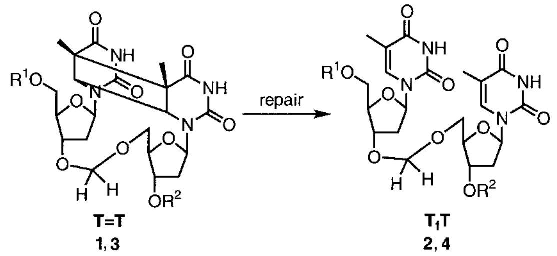
cis-syn Cyclobutane pyrimidine dimers (photodimers) are the main DNA lesions formed on irradiation of cells with UV light.[1] They are responsible for cell death, the development of various skin cancers, and therefore represent a severe threat to all organisms that are exposed to sunlight.[2] All organisms have developed DNA repair processes,[1–3] in order to remove UV-induced lesions from the genome and to overcome DNA damage. The observation that certain genome sites are repaired with greatly reduced efficiency, giving rise to mutation hot spots,[3a, 4] has shifted the investigation of the factors that determine the effectiveness of lesion recognition into the center of DNA repair research. It is currently believed that lesion-specific repair enzymes recognize structural alterations of the normal DNA duplex which are maybe caused by weakened hydrogen bonds and π-stacking interactions around a DNA lesion. Crystallographic data show that many repair enzymes subsequently "flip" the damaged base out of the DNA duplex for repair.[5] This process could be influenced by the DNA packing, which may shield DNA lesions,[6] and by the local DNA sequence and conformation.[7] A first indication that DNA repair might be influenced by the duplex conformation, stems from the discovery that dsDNA-specific repair enzymes remove lesions from DNA – RNA hybrids,[8] which are in an atypical A-like conformation, with reduced efficiency.[9]

In order to learn if and to what extent the duplex conformation is able to influence the DNA-photolyase repair process, depicted schematically in Scheme 1, we investigated the extent to which A- and B-type double strands are destabilized by a photolesion, which has been incorporated site-specifically into the DNA strand. The repair was probed with a DNA-photolyase, which is believed to recognize the *cis-syn* photolesions in an extrahelical, "flipped-out" conformation.[5d] The presented thermodynamic data reveal that photodimers significantly destabilize a B-duplex but decrease the stability of an A-like duplex only to a small extent. The low destabilization was found to correlate with less efficient repair, which indicates that the local DNA conformation might modulate the DNA lesion "flipping" process.



T=T
1, 3

T$_f$T
2, 4

1, 2: $R^1 = R^2 = H$
3, 4: R^1 = DMTr, R^2 = $P(N\mathit{i}Pr_2)OCH_2CH_2CN$

Scheme 1. The starting material **1** and **2** of the phosphoamidite building blocks **3** and **4**, which were used for the synthesis of lesion-containing DNA single and DNA – DNA and DNA – RNA double strands. The repair occurs under cleavage of the cyclobutane ring catalyzed by photolyase DNA-repair enzymes.

In order to allow the preparation of oligonucleotides with a site-specific *cis-syn* photolesion in sufficient amounts for this investigation, all studies were performed with the recently introduced formacetal-linked[10] *cis-syn* photodimer analogue **1** (Scheme 1), which is readily available in gram quantities.[11] This compound was shown to be a good photolyase substrate since DNA photolyases ignore the central intradimer phosphodiester moiety during the repair process.[12] Compound **1** and the reference compound **2** were converted into the phosphoamidites **3** and **4**, respectively, and incorporated into the GC-rich 12mer and the AT-rich 14mer oligonucleotides **5** – **8** (Table 1) using previously published procedures.[11] The oligonucleotides were annealed with 1.0 equivalent (1.3 equivalents for the enzymatic studies) of the complementary DNA or RNA strand to give the DNA – DNA duplexes **9** – **12** (B-conformation) and the DNA – RNA duplexes **13** – **16** (A-like conformation).[8] The reference duplexes **9**, **11**, **13**, and **15** were prepared for comparison.

Circular dichroism (CD) studies with all duplexes were performed to investigate their conformations in solution.[13] The CD spectra were recorded at 25 °C ($c_{\text{oligo}} = 5\ \mu\text{M}$) and represent an average of two independent measurements (Figure 1). The CD spectrum of the reference DNA – DNA duplex **9** and of the photodimer-containing DNA – DNA duplex **10** are very similar and feature all the characteristics of

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