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Catalytic Oxidation of 2-Aminophenol to Questiomycin A by Dioxygen in the Presence of Cobaloxime Derivatives. Free Radical Intermediates

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Abstract: The multistep oxidative dehydrogenation of 2-aminophenol to Questiomycin A, catalyzed by cobaloxime(II) derivatives, involves ESR-detectable 2-aminophenoxyl type free radical intermediates.

We have previously reported that 2-aminophenol (AP) can be catalytically oxidized by O_2 to 2-amino-3*H*-phenoxazin-3-one (APX) in the presence of cobalt(II) salts[1] or a novel cobalt(II) phthalocyanine derivative[2]. The reaction takes place under ambient conditions. Kinetic studies gave information on the rate-determining step, which is also the first stage of this multistep redox reaction. Indirect evidence indicated that it probably began with the formation of a free radical from AP coordinated to the cobalt atom. It was not, however, possible to obtain insight into the series of steps necessary for the overall transformation to occur.

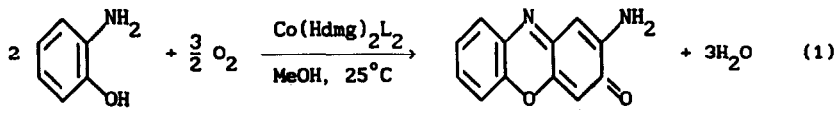
2-Amino-3*H*-phenoxazin-3-one, also known as questiomycin A, is related to the naturally occurring antibiotic actinomycin D, which acts by inhibiting DNA-directed RNA synthesis[3,4]. APX has been used as a model for the behavior of actinomycin D, with special reference to its reduction to an N-10 centered radical anion[4,5].

The metabolism of AP in human erythrocytes has been shown to produce APX via intervention of human oxyhemoglobin[6], a natural oxygen carrier. It is of interest to see if this catalytic process also involves free radical intermediates, which could be dangerous if formed in the biosynthesis of actinomycin D.

We now report a new catalyst system for the oxidative conversion of AP to APX, which (i) provides a selective route to APX, and (ii) permits the ESR detection of free radical intermediates *en route* to APX. The latter sheds light on the nature of the biologically important series of reactions leading to APX.

We have found that the oxidation of AP to APX by O_2 is catalyzed by the cobaloxime(II) derivatives $Co(Hdmg)_2L_2$, where $Hdmg^-$ is the monoanion dimethylglyoxime, and L = Ph_3P, Ph_3As, and Ph_3Sb (eq. 1). The reaction takes place at room temperature and 1 bar O_2 pressure in MeOH or acetone as solvents, eq. (1). (Uncatalyzed AP oxidation is at least a 100 times slower than the catalytic reaction.) Cobaloxime(II) species are known to form superoxo and μ-peroxo complexes which are active intermediates in catalytic oxidations[7,8].

We followed reaction (1) in MeOH by measuring the volume of dioxygen absorbed by the solution and simultaneously monitored the amount of AP, APX and any other component by HPLC. At intervals, the ESR spectra of the reacting mixtures were also recorded.



(AP) (APX)

The results show that if L = Ph_3As, or Ph_3Sb, the overall stoichiometry of eq. 1 is strictly valid: the molar amount of O_2 consumed for 1 mol APX formed is 1.50 ± 0.02 mol/mol. At 2.5 mmol/L catalyst and 25 mmol/L AP concentration in MeOH, typical selectivities of 90 % or better were observed. However, in acetone the selectivity dropped to ca. 40 %. When L = Ph_3P, ca. 70 % of the phosphine was also oxidized to Ph_3PO during the first 20 % of AP conversion.

Dioxygen is reduced to H_2O rather than H_2O_2, which is demonstrated by the lack of formation of Ph_3AsO. The latter is rapidly formed when H_2O_2 is added to a solution containing Ph_3As.

If the reaction is followed by ESR spectroscopy at room temperature, two different free radicals, I and III, can be detected one after the other, at the initial and final stages of the reaction, respectively. The identity of these radicals has been confirmed by simulation of the ESR spectra recorded in MeOH and MeOD. The best coupling constants are listed in TABLE 1. The data for radical I are in good agreement with reported values[9-11]. Radical III has not been described previously; its spectra are shown in Fig. 1. In CH_3OD each quintet of both of the main doublets collapses to a triplet of 1:1:1 intensity ratio, which proves that coupling with the 2-NH_2 group is the source of fine structure.

The low coupling constant for the o-NH_2 moiety (0.83 G) in radical III is presumably due to coordination of the NH_2 group in an axial position of the cobaloxime catalyst, which strongly hinders interaction (conjugation)

of the nitrogen lone pair with the π-system of the ring. The sequence of steps required to rationalize the observed behavior is given in Scheme 1, where for simplicity, $Co(Hdmg)_2$ has been replaced by Co^{II}. The catalytic activity is due to the ability of cobaloxime(II) to form a superoxo complex $Co^{III}O_2$ with dioxygen.

The free radical intermediates detected show that the overall reaction (1) occurs via a series of oxidative dehydrogenation and addition steps brought about by $Co^{III}O_2$. The first H-atom abstraction step leading to free radical I takes place within the superoxocobaloxime IV. *o*-Benzo-

Table 1. ESR Parameters (G) of the Free Radicals Detected (T = 25°C)

Radical	Solvent	g	a_N	a_H (NH_2)	a_H (*ortho*)	a_H (*para*)	a_H (*meta*)
I	CH_3OH	2.0041	4.54	6.50(2)	2.10	4.20	0.76(2)
I	CD_3OD	2.0047	4.54	1.00(2)	2.10	4.20	0.76(2)
I[a]	H_2O	2.0037	4.76	5.30(2)	2.94	4.31	1.01; 0.1
III	CH_3OH	2.0044	0.83	0.83(2)	8.94	--	--
III	CD_3OD	2.0047	0.83	--	8.17	--	--

[a] Data from ref. 5

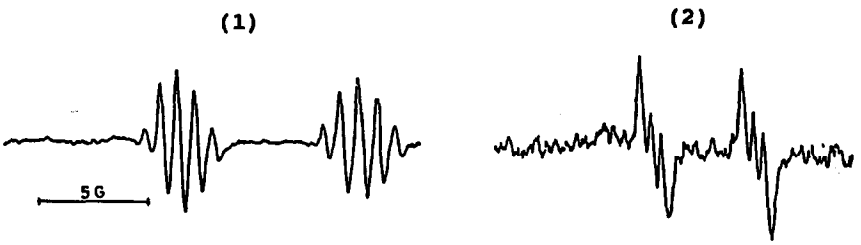
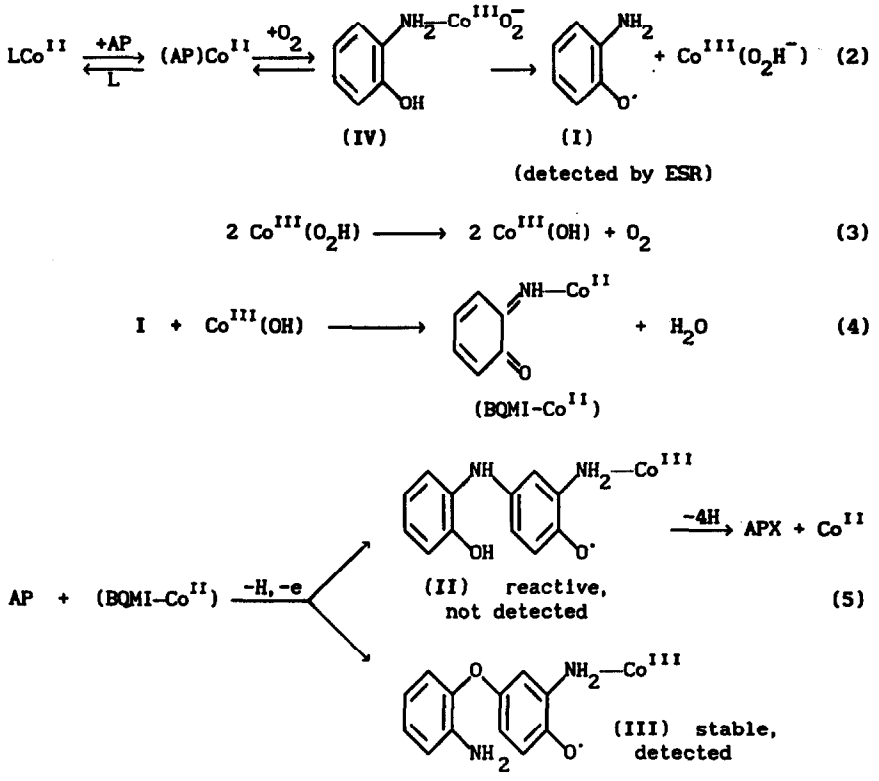


Fig. 1. ESR spectra of radical III recorded in CH_3OH (1) and CD_3OD (2)

quinonemonoimine (BQMI) coordinated to cobaloxime(II) is a key intermediate, ensuring the observed excellent selectivity. Its formation is supported by the structure of radical III. The latter is an isomer of radical II, which could not be detected owing to its high reactivity.

A step of special importance is the reduction of $Co^{III}(OH)$ by radical I, eq.(4), which is the path for the regeneration of Co^{II}. Significantly, the other possibility, *viz.* reduction by AP, is very slow as shown experimentally using a synthetic hydroxocobaloxime(III) species.

Scheme 1



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