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MECHANISM OF Co(SALEN)-CATALYZED OXYGENOLYSIS OF INDOLE RING AS A MODEL FOR THE TRYPTOPHAN-2,3-DIOXYGENASE REACTION

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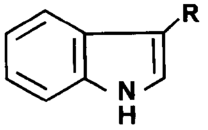
In the Co(Salen)-catalyzed oxygenolysis of 3-methylindole giving rise to o-formylaminoacetophenone, the actual active catalyst species has been found to be the Co(III)-(Salen) complex of an anion of the product. The catalysis involves activation of the substrate but not molecular oxygen. The activation of the substrate involves the rate determining proton transfer from the substrate to the product anion in the coordination sphere of the catalyst.

The oxygenolysis of the heterocyclic ring of 3-substituted indoles related to tryptophan catalyzed by transition metal complexes such as Co(Salen),[1] Co(TPP),[2] Mn(Pc),[3] and CuCl(Py)[4] have been reported as chemical models for the tryptophan-2,3-dioxygenase reaction. With respect to the mechanism of these reactions, involvement of a ternary complex intermediate comprising of the substrate, molecular oxygen, and the catalyst complex has been suggested on the basis of kinetic and spectroscopic data.[1-3] Details of the mechanism of these interesting model reactions have, however, been remained obscure, although the catalysis with the CuCl(Py) complex seems to involve a redox process, $Cu(II) \rightleftharpoons Cu(I)$.[5]

We now find that in the Co(Salen)-catalyzed oxygenolysis of 3-methylindole (**1a**) in CH_2Cl_2, the real catalytically active species is the Co(III)(Salen) complex of an anion of the product, o-formylaminoacetophenone (**2a**), and that the oxygenolysis involves the rate determining proton transfer from the substrate to the product anion in the coordination sphere of the catalyst without the redox process, $Co(III) \rightleftharpoons Co(II)$, which is normally seen in the cobalt ion-catalyzed autoxidation of hydrocarbons.

When oxygen was bubbled through a solution of **1a** (10 mmol) and Co(Salen) (2 mmol) in CH_2Cl_2 (50 ml) at room temperature for 3.5 h, nearly quantitative formation of **2a** was observed with



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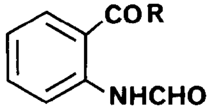

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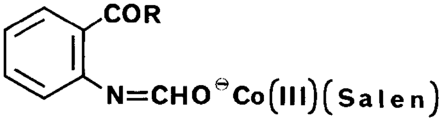
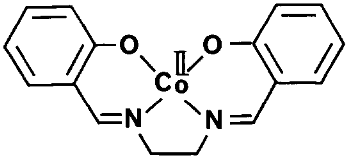


3

a ; R = CH_3 **b ; R = CH_3CH_2**

c ; R = $(CH_3)_2CH$ **d ; R = $(CH_3)_3C$**



Co(Salen)

an 80% conversion of 1a. After the mixture was cocentrated to a half volume, addition of ether gave the Co(III)(Salen) complex of an anion of the product, complex **3** as brown fine crystals (58-70% isolated yield), whose analytical and spectral data are in good agreement with the structure.[6] Filtration of a solution of 3 in CH_2Cl_2 through a short column of silica gel gave **2a** (70-75% isolated yield).

Unexpectedly, when complex 3 was added to a solution of 1a in CH_2Cl_2 under oxygen free conditions, no oxidation of **1a** took place, but if allowed an exposure to oxygen, the oxygenolysis of **1a** occured much faster than the Co(Salen)-catalyzed reaction (Figure 1). These results clearly indicate that the real catalyst is **3**, whose catalytic activity is not due to its redox nature but rather to its basic property as observed in the Co(II)-Schiff bas complex-catalyzed oxygenation of hindered phenols.[7]

Figure 1 shows the time course of oxygen absorption in the catalytic oxygenation of **1a** under various conditions. With Co(Salen), an induction period is observed, whereas no induction period is obtained in the oxygenation with Co(III) species. Therefore, the induction period obtained in the former case can be interpreted as the time required for the formation of the active Co(III) species.[8] Addition of N-methylimidazole (MeIm) in amounts equivalent with the catalyst retarded the reaction remarkably. With an excess of MeIm, no reaction took place at all, strongly suggesting that the coordination of the substrate to the catalyst complex is essential for the present catalysis in accord with the earlier observations.[1] Steric effect of the 3-substituent R in 1 on the reaction rate was also observed: a larger size of R decreases the reaction rate, as observed relative rates 1.00, 0.98, 0.28, and 0.18 for **1a, 1b, 1c,** and

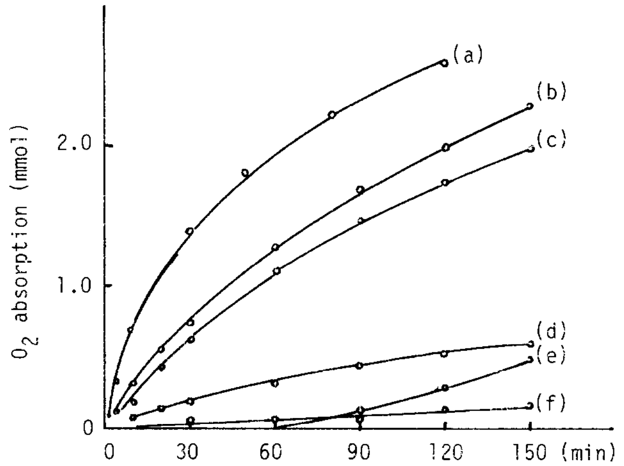


Figure 1. Time course of oxygen absorption in the catalytic oxygenation of 3-methylindole (**1a**). [**1a**] = 0.1 M, [Co]=0.01 M, PO_2 = 790 mm Hg, 5 °C in CH_2Cl_2 (50 ml).
(a); Co(III)(t-BuO⁻).[11] (b); Co(III)(t-BuOO⁻).[10] (c); Complex **3**. (d); Co(III)(t-BuOO⁻) in MeOH (50 ml). (e); Co(Salen). (f); Co(III)(t-BuOO⁻) with MeIm (0.01 M). Co(III) = Co(III)(Salen).

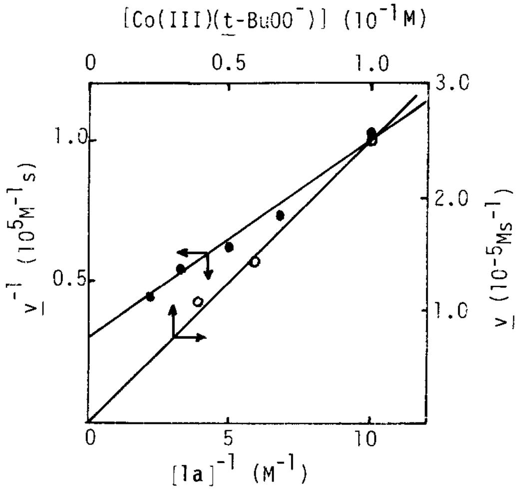


Figure 2. Relationship between initial rates and concentration of the substrate and the catalyst in the Co(III)(Salen)(t-BuO⁻)-catalyzed oxygenation of **1a**.
(a); [Co(III)] = 0.01M, PO_2 = 790 mm Hg, CH_2Cl_2 = 50 ml, 5 °C.
(b); [**1a**] = 0.15 M, PO_2 = 790 mm Hg, CH_2Cl_2 = 50 ml, 5 °C.

1d, respectively.[12] Bulkiness of the substituent R therefore hinders the coordination of **1** to the catalyst. The fact that the reaction with Co(III)(Salen)(t-BuO⁻) is faster than that with Co(III)(Salen)(t-BuOO⁻) (Figure 1) suggests that the catalyst functions as a base, the reaction rate depending on the basicity of the anionic fifth ligand.

Kinetic studies have been carried out by measuring the initial rate in the Co(III)(Salen)-(t-BuO⁻)-catalyzed oxygenation of **1a** in CH_2Cl_2 at 5 °C. Plots of $\underline{v}^{-1}$ vs. $[\mathbf{1a}]^{-1}$ at a given concentration of the Co(III) catalyst and $\underline{v}$ vs. [Co(III)] at a given concentration of the substrate gave straight lines (Figure 2), and the reaction rate was independent upon the O_2 pressure ($\underline{v}$ = 1.08, 1.17, and 1.06 x 10^{-5} M sec^{-1} at PO_2 = 470, 792, and 1205 mm Hg, respectively).[13] Furthermore, when the NH group of **1a** and **1d** was deuterated, isotope effect on the reaction rate was observed (v_H/v_D = 1.43 and 1.39 for **1a** and **1d**, respectively).[14] Therefore, the mechanism of the present catalysis is reasonably considered to involve the coordination of the substrate to the catalyst Co(III) complex in the first step[15] followed by the rate determining deprotonation from the NH group of the substrate in the coordination sphere giving rise to

Co(III)(Salen)(1^-), into which dioxygen is incorporated rapidly to form complex 3 and the successive catalytic cycles are established as depicted in the following scheme.

$$\mathbf{1} + \mathrm{Co(III)(X^-)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Co(III)(X^-)(\mathbf{1})} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{Co(III)(\mathbf{1}^-)} + \mathrm{HX}$$

$$\underset{\mathbf{4}}{\mathrm{Co(III)(\mathbf{1}^-)}} + O_2 \xrightarrow{\text{fast}} \underset{\mathbf{3}}{\mathrm{Co(III)(\mathbf{2}^-)}} \overset{\mathbf{1}}{\rightleftharpoons} \mathrm{Co(III)(\mathbf{2}^-)(\mathbf{1})} \xrightarrow{\nearrow \mathbf{4}} \mathbf{2}$$

where Co(III) = Co(III)(Salen), X^- = t-BuOO$^-$, t-BuO$^-$, and k_1, k_{-1} > k_2, k_{-2}.

In conclusion, the model catalytic oxygenation of 3-substituted indoles with Co(Salen) requirs the activation of the substrate by way of deprotonation through coordination to the catalyst, but no activation of molecular oxygen.

The present results as well as those obtained in the oxygenation of hindered phenols with Co(II)-Schiff base complexes[7] suggest that the similar activation process may be involved in reactions catalyzed by dioxygenases.[16]

References and Notes

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6) Anal. Calcd for $C_{25}H_{22}N_3O_4Co\cdot1/2\ H_2O$: C, 60.49; H, 4.67; N, 8.46; Co, 11.87. Found: C, 60.32; H, 4.25; N, 8.53; Co, 9.06. IR(Nujol); 1640, 1610, 1545 cm^{-1}. The electronic spectrum of 3 was superposed upon that of Co(III)(Salen)(t-BuOO$^-$)[10] in the range of about 300 nm to 700 nm. Indolenyl-3-peroxy Co(III)(Salen) is not the case, because no reduction of 3 took place with PPh_3 which can reduce peroxy Co(III) complexes to give the corresponding alcohols.
7) A. Nishinaga, H. Tomita, K. Nishizawa, and T. Matsuura, J. Chem. Soc. Dalton Trans., 1504 (1981).
8) In addition to the induction period, the reaction in the catalytic cycles was considerably slower than that with Co(III) species. This is due to the formation of catalytically inactive Co(III)(Salen)(Cl$^-$) by the oxidation of Co(Salen) with the solvent.[9]
9) L. G. Marzilli, P. A. Marzilli, and J. Halpern, J. Am. Chem. Soc., 92, 5752 (1970).
10) A. Nishinaga, H. Ohara, and H. Tomita, to be published elswhere: The complex was obtained by the oxidation of Co(Salen) with t-BuOOH in dichloromethane.
11) This compound was obtained by the reduction of Co(III)(Salen)(t-BuOO$^-$) with PPh_3 in quantitative yield, as confirmed by the isolation of $OPPh_3$ quantitatively.
12) In this experiment, the corresponding products 2 were obtained in nearly quantitative yield.
13) [1a] = 0.1 M, [Co(III)(Salen)(t-BuOO$^-$)] = 0.01 M in CH_2Cl_2 at 5 °C.
14) The considerably small isoptope effect is probably due to a charge-transfer nature of the coordination of the substrate.[1]
15) According to the kinetic data, cis-coordination of the substrate is reasonably considered.
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