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OXYGENATION OF 3-SUBSTITUTED INDOLES CATALYZED BY Co(II)-SCHIFF'S BASE COMPLEXES. A MODEL CATALYTIC OXYGENATION FOR TRYPTOPHAN 2,3-DIOXYGENASE

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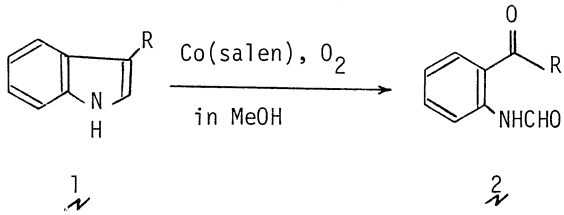
Bis(salicylidene)ethylenediaminatocobalt(II) catalyzes the oxygenation of 3-substituted indoles related to tryptophan in methanol giving rise to oxidative cleavage of the heterocyclic ring of the indoles selectively to give the corresponding o-formylaminoacetophenone derivatives. This provides a nonenzymic model for the reaction of tryptophan 2,3-dioxygenase. Oxidizability of the substrates is correlated with their donor ability.

Tryptophan, at the first step in one of its metabolic pathways, binds molecular oxygen by catalysis of tryptophan 2,3-dioxygenase leading to oxidative cleavage of the heterocyclic ring to give formylkynurenin. Tryptophan 2,3-dioxygenase contains protoheme IX and has been demonstrated to form a transient O_2-complex with the substrate as the reaction intermediate.[1] Activation process of the reaction as well as other reactions of dioxygenases is of current interest.[1,2] Chemical studies on the biological oxidations are focussed on this problem.[3-5] Photosensitized oxygenation of tryptophan and related indoles causes a similar type of degradation providing a chemical model for the enzyme reaction.[6,7] Little has been known about model metal complex-catalyzed oxygenation in which both atoms of molecular oxygen are incorporated into the substrate molecules giving a single product until very recent appearance of works on models for quercetinase[4] and pyrocatechase.[5] In this letter, we wish to report that bis(salicylidene)ethylenediaminatocobalt(II) [Co(salen)] catalyzes the oxygenation of 3-substituted indoles (1) to give the corresponding o-formylaminoacetophenone derivatives (2) in good yield. This provides a nonenzymic model metal complex-catalyzed oxygenation for the reaction of tryptophan 2,3-dioxygenase.

Oxygen was bubbled through a solution of 1 and the catalyst in methanol at ambient temperature. The mixture was evaporated and chromatographed on a silica gel column to give the products (2) (see Table). The structures of the products (2) were confirmed by their spectral data and elemental analyses. Signal pattern of aromatic region in nmr spectra of 2 is so characteristic

and quite similar with each other that it is useful for recognition of o-formylaminoacetophenone derivatives(Figure 1). Thus, although the product (2e) was not obtained as crystalline form because of its strongly hygroscopic property, the structure was reasonably assigned by the nmr spectrum. No oxidation took place without the catalyst.[8] At lowered temperature or low conversion stage, higher



1 2

a; $R=CH_3$
b; $R=CH_2COOMe$
c; $R=CH_2CH_2COOMe$
d; $R=CH_2CH_2NHAc$
e; $R=CH_2-\underset{\underset{NHAc}{|}}{CH}-COOMe$

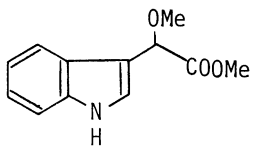


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Table. Co(salen)-catalyzed oxygenation of 1 in methanol at room temperature[a]

1	Reaction time(h)	Conversion (%)	Product 2	Mp(°C)	Yield(%)	δ($CDCl_3$) (ppm)
1a	5	84	2a	79-80[b]	70	2.63(s,3,$COCH_3$), 6.95-8.80(m,6,ArH,NHCHO)
	7	96	2a		70	
	5	30(0°C)	2a		80	
	72	0(-60°C)				
1c	16	95	2c	76-78	72	2.59-3.44(m,4,CH_2CO), 3.70(s,3,OCH_3),
	5	20	2c		96	7.00-8.75(m,6,ArH,NHCHO)
1d	24	96	2d	117-119	44	1.96(s,3,$COCH_3$), 3.00-3.80(m,4,$COCH_2$,NCH_2), 6.35(broad s,1,NH), 7.03-8.83(m,6,ArH,NHCHO)
1e	72	98	2e	——[c]	46	2.08(s,3,$COCH_3$), 3.74(s,3,OCH_3), 3.74(d,2,
	42	40			60	J=8Hz,$COCH_2$), 4.81-5.13(m,1,COCHN), 6.67 (broad,1,NHCHO), 7.02-8.80(m,6,ArH,NHCHO)

[a] Molar ratio, 1 / Co(salen) = 4 / 1. [b] Lit. mp 78-79°C(Ref.9). [c] Syrupy state with stronaly hygroscopic and very soluble in water.

yield of 2 is obtained while with longer reaction time the yield is getting worse, indicating the products (2) being somewhat unstable under the reaction conditions(Table). The reaction proceeds faster in dichloromethane than in methanol and slows down in dimethylformamide due to precipitation of $(DMF)_2Co(salen)_2O_2$ complex.[10] No reaction took place in acetic acid. Longer reaction time is required to complete the reaction with increasing size of R in 1(Table). The reaction rate in CH_2Cl_2 is in order 1a > 1d > 1c > 1b > 1e(Figure 2).

The reactivity of the indoles (1) in the Co(salen)-catalyzed oxygenation can be correlated with their donor ability. Indoles are known to form donor-acceptor complexes with 1,3,5-trinitrobenzene.[11]

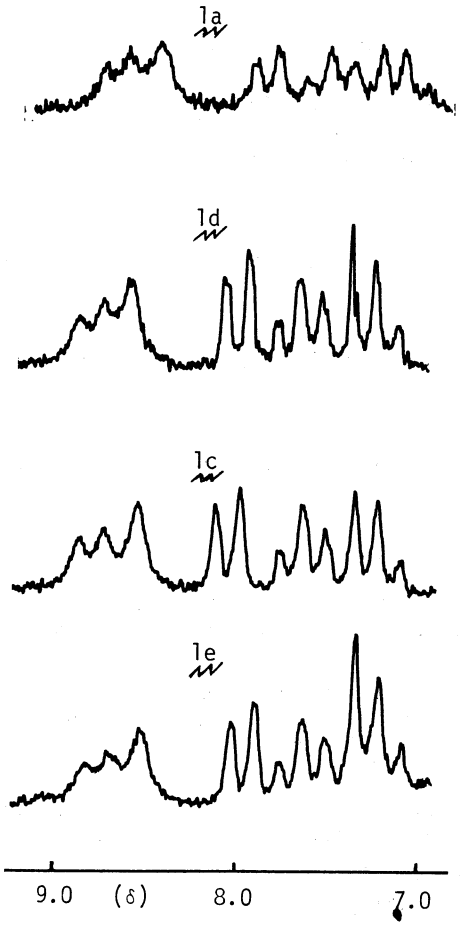

Figure 1. Aromatic region in nmr spectra of 2.

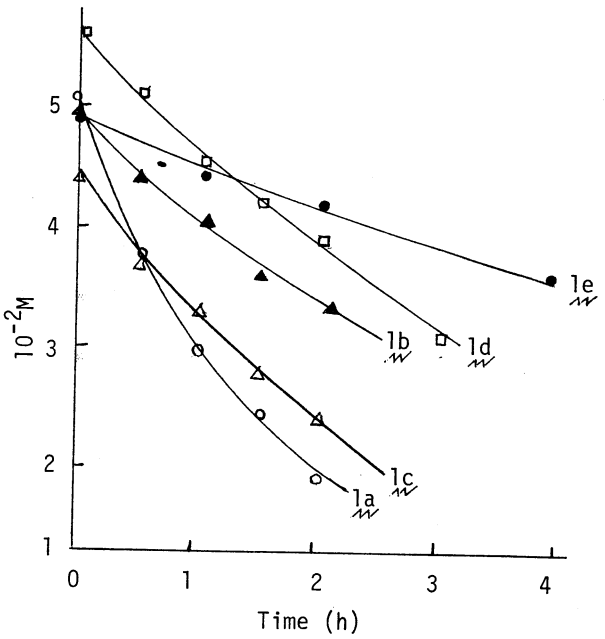

Figure 2. Time course of the conversion of 1 in the Co(salen)-catalyzed oxygenation in CH_2Cl_2 at 14°C; molar ratio of 1/Co(salen)=3/1.

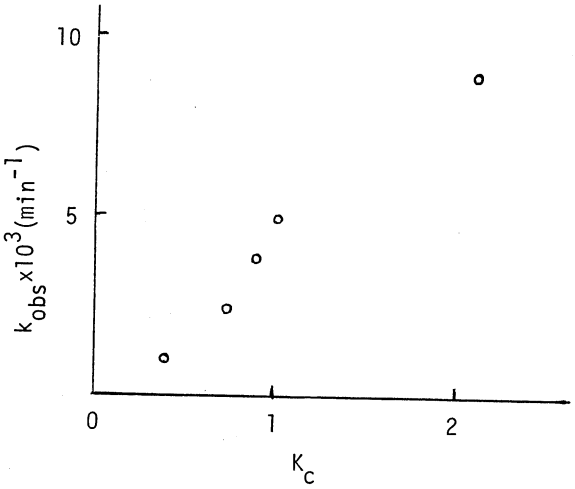

Figure 3. Plots of the rate constants for the conversion of 1 under the conditions given in Figure 2 against K_c values.

The donor-acceptor complex formation constants (K_c) in CH_2Cl_2 at 35°C estimated by nmr technique[12] were 2.1,[11] 0.96, 0.90, 0.78, and 0.40 kg·mol^{-1} for 1a, 1d, 1c, 1b, and 1e, respectively. Plots of the association constants (K_c) against observed rate constants for the conversion of 1 under the conditions given in Figure 2(8.4, 4.9, 3.6, 2.3, and 1.2x10^{-3} min^{-1} for 1a, 1d, 1c, 1b, and 1e, respectively) show nearly linear relationship(Figure 3) suggesting that the oxidizability of 1 is directly referred to their donor ability. On the other hand, Co(salen) reversibly interacts with O_2

in the presence of an axial donor ligand where activation process of the O_2-binding is described as an electron transfer from Co(II) to the oxygen molecule.[10] These results suggest that the present attempted catalytic oxygenation involves an electron transfer process through transient formation of Co-O_2 complex with 1 as axial ligand and that bulky substituent nullifies the electronic advantage for the formation of the complex. Similar substituent effect on the formation of donor-acceptor complexes with substituted indoles has been reported.[11]

Unexpectedly, the Co(salen)-catalyzed oxygenation of 1b in methanol did not cause the oxidative cleavage of the heterocyclic ring but the oxidation of the side chain to afford 3 (54 % yield), mp 127-129°C: δ(DMSO-d_6) 3.28(s,3,CH_3), 3.63(s,3,CH_3), 5.14(s,1,OCH), and 6.92-7.68(m,6,indole ring)ppm. N-Alkylindoles and 1 (R=CHO, $COCH_3$, or $COOCH_3$) were unreactive to the catalytic oxygenation.

Bis(3-methoxysalicylidene)ethylenediaminatocobalt(II) and bis(salicylidene)-o-phenylenediaminatocobalt(II) also catalyze the oxygenation of 1 whereas $Co(OAc)_2$, $CoCl_2$, Co(acac), Fe(salen), and Cu(salen) were not reactive indicating that complexes being able to form O_2-complex are effective for the catalysis.

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References and Notes

1) Y. Ishimura, M. Nozaki, O. Hayaishi, T. Nakamura, M. Tamura, and I. Yamazaki, J. Biol.Chem., 245, 3539 (1970); T. Tanaka and W. E. Knox, ibid., 234, 1162 (1959); H. Maeno and P. Feiglson, ibid., 242, 596 (1967).

2) K. Bloch and O. Hayaishi, "Biological and Chemical Aspects of Oxygenases," Maruzen Company, Ltd. 1966, p.347; H. Fujisawa, K. Hiromi, M. Nozaki, M. Uyeda, and O. Hayaishi, J. Biol. Chem., 246, 2320 (1971); 247, 4422 (1972); H. H. Tai and C. J. Sih, ibid., 245, 5072 (1970); G. A. Hamilton, Adv. Enzymol., 32, 55 (1969).

3) A. E. Martell and M. M. Tagui Khan, "Inorganic Biochemistry," ed. by G. L. Eichorn, Elsevier, Amsterdam-London-New York (1973), p. 654; G. A. Hamilton, Adv. Enzymol., 32, 55 (1969).

4) A. Nishinaga, T. Tojo, and T. Matsuura, Chem. Commun., 896 (1974).

5) J. Tsuji and H. Takayanagi, J. Amer. Chem. Soc., 96, 7349 (1974).

6) W. E. Savige, Aust. J. Chem. 24, 1285 (1971), and references therein.

7) I. Saito, M. Imuta, and T. Matsuura, Chem. Lett., 1173, 1197 (1972).

8) Base-catalyzed oxygenation of 1 took place only with strong base (e.g. t-BuOK-DMSO) affording a complex mixture of products in which no compound 2 was detected except the case of 1a. Products in the base-catalyzed oxygenation of 1a contained much amount of colored material besides 2a. Results will be published elsewhere.

9) L. J. Dolby and D. L. Booth, J. Amer. Chem. Soc., 88, 1049 (1966).

10) R. G. Wilkins, Advan. Chem. Ser., 100, 111 (1971), and references therein; D. V. Stynes, B. R. James, and J. A. Ibers, J. Amer. Chem. Soc., 95, 1796 (1973); G. N. Schrauzer and L. P. Lee, ibid., 92, 1551 (1970); R. Nakon and A. E. Martell, Inorg. Chem. 11, 1002 (1972); E. Ochiai, J. inorg. nucl. Chem., 35, 1727, 3375 (1973).

11) 2.4 kg mol^{-1} for 1a (in $CHCl_3$) has been reported; R. Foster and C. A. Fyfe, J. Chem. Soc. (B), 926 (1966).

12) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, London and New York (1969), p. 140.

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