A Model Catalytic Oxygenation for the Reaction of Quercetinase

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Summary Bis(salicylidene)ethylenediaminatocobalt(II) catalyses the oxygenation of 3-hydroxyflavones in dimethylformamide giving rise to oxidative cleavage of the heterocyclic ring of the flavones to give the corresponding depsides in excellent yield; this provides a nonenzymic model for the reaction of quercetinase.

BASE-CATALYSED oxygenation of 3-hydroxyflavones has previously been demonstrated to be a nonenzymic model for the reaction of quercetinase, a dioxygenase produced by *Aspergillus flavus*, which catalyses the total insertion of O into the substrates quercetin and related 3-hydroxyflavones, resulting in oxidative cleavage of the heterocyclic ring to give the corresponding depsides of type (II) and carbon monoxide.[1] However, base catalysis gives complicated results with an OH group at the 7-position.[1] Quercetinase contains the Cu^{2+} ion which is considered to participate at the reaction site.[2] Little is known about metal ion-catalysed oxygenation as a model for the reaction of dioxygenases.[3]

We now find that bis(salicylidene)ethylenediaminatocobalt(II) [Co(salen)] catalyses the oxygenation of 3-hydroxyflavones (I) to give the corresponding depsides (II) in excellent yield even with an OH group at the 7-position. O_2 was bubbled through a solution of (I) and the catalyst in dimethylformamide (DMF) at ambient temperature. The mixture was diluted with water and extracted with ether; evaporation then gave the crystalline products (II) (see Table). The structures of the products (II) were confirmed

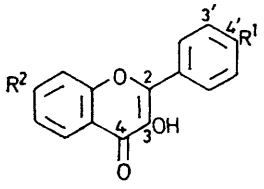
TABLE. The Co(salen)-catalysed oxygenation of 3-hydroxyflavones (I) in DMF at room temperature.[a]

		Product (II)		
	$t_{1/2}$ h[b]	Yield (%)[c]	M.p./°C	ν_{CO}/cm^{-1}
(Ia)	18	97	130—131	1745, 1700
(Ib)	4·2	98	141—142	1740, 1695
(Ic)	2·5	97	183—183·5	1725, 1700
(Id)	15	61[d]	122—123	1730, 1690
(Ie)	9·3	72[d]	155—156	1710, 1700
(If)	1·5	36[d]	192—193	1700, 1690

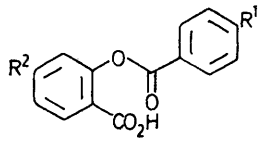
[a] 0·2 mol. equiv. of Co(salen) was used. [b] Time required for half conversion of (I). [c] Isolated yield after complete oxygenation. [d] Hydrolysed products were obtained.

by their spectral data and elemental analyses and also by the fact that alkaline hydrolysis quantitatively gave the known hydrolysates. Substitution by an oxygen-containing function results in acceleration of the reaction rate in the order OH > OMe, 4′-OH > 7-OH; a similar effect has been observed in the enzyme reaction[2] and base-catalysed oxygenation of (I).[1,4] An oxygen-containing function at

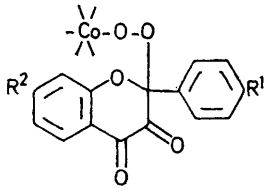
the 7-position promotes hydrolysis of ester group in (II), lowering the yield of (II). After passing through the solution, the gas contained CO_2 together with CO resulting from C-3 of (I). The yield of CO_2 increased and that of CO decreased when the mixture was left in a closed system. A



(I)



(II)



(III)

a; $R^1 = R^2 = H$
b; $R^1 = OMe$, $R^2 = H$
c; $R^1 = OH$, $R^2 = H$
d; $R^1 = H$, $R^2 = OMe$
e; $R^1 = H$, $R^2 = OH$
f; $R^1 = R^2 = OH$

separate experiment showed that CO_2 is formed by Co (salen)-catalysed oxygenation of CO in DMF. These facts suggest that CO_2 is formed in the catalytic oxygenation of (I) by further oxidation of the CO primarily formed.

The catalytic oxygenation of (I) is rationalized by assuming an intermediate (III) formed through an electron-transfer process, analogous to those in the oxygenation of substituted phenols catalysed by Co^{II}–Schiffs base complexes.[5] The oxygenation is affected by solvent: catalysis takes place in Me_2SO as well as DMF but not in MeOH, tetrahydrofuran, or CH_2Cl_2, corresponding to the dependence on solvent of the formation of O_2 complexes with Co(salen).[6] This suggests that a Co–O_2 complex is the active species in the catalytic oxygenation of (I). Oxygenation in pyridine, which forms a 1:1 complex with Co(salen)[6] indicates that the 1:1 (Co:O_2) complex is less reactive. This is supported by the fact that di-(3-salicylidene-aminopropyl)aminecobalt(II), which is known to form a 1:1 complex[6] is also less reactive in the oxygenation.

Oxygenation of (I) is also catalysed by $CuCl_2$ where the active species is most probably a Cu^{II}-chelate complex with (I), which are formed easily, but the catalysis is less effective than that by Co(salen).

Oxygenation of quercetin catalysed by Co(salen) gave a complex mixture containing the corresponding depside of type (II) which is not easily isolable; simultaneous oxidation of the aromatic ring with OH groups at 3′- and 4′-positions causes complications.

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