# A Novel Oxidative Decarboxylation of α-Substituted α-Hydroxy Acids by a Functionalized Oxidation-active Flavin Mimic in the Presence of a Metal Ion in *t*-Butyl Alcohol

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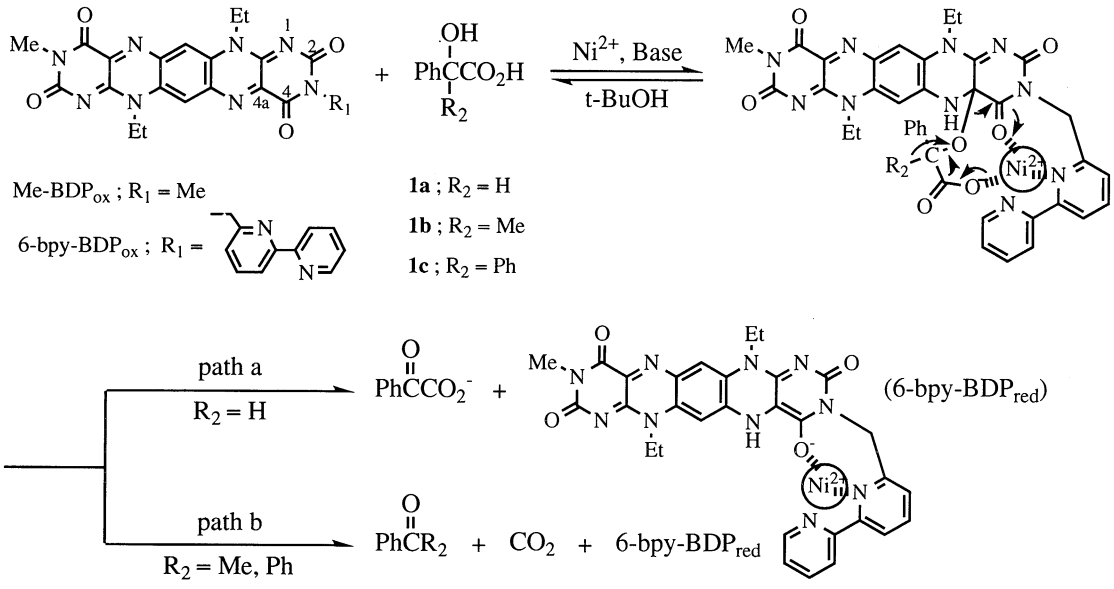
A benzo-dipteridine bearing a bipyridin-6-ylmethyl moiety (6-bpy-BDP$_{ox}$) was found to conduct oxidative decarboxylation of α-methyl mandelic and benzylic acids to give acetophenone and benzophenone and the reduced form (6-bpy-BDP$_{red}$) in the presence of $Ni^{2+}$ and DBU in t-BuOH.

A benzo-dipteridine derivative (Me-BDP$_{ox}$) is a quite useful flavin mimic for model study of flavin-mediated oxidations because of its high oxidation-activity. In particular, Me-BDP$_{ox}$ displays a remarkably high reactivity for the oxidations involving a nucleophilic attack to the C(4a)-position of Me-BDP$_{ox}$.[1] As a rational extension, functionalization of this model would be conceivable for construction of more sophisticated catalytic systems. We have reported that 6-bpy-BDP$_{ox}$ oxidizes α-hydroxy acids such as mandelic and lactic acids to the corresponding keto acids in the presence of metal ions such as $Zn^{2+}$, $Ni^{2+}$, and $Co^{2+}$ and an amine base in t-BuOH or MeCN,[3] which is the first example of a D-lactate dehydrogenase model.[2] We have proposed that the oxidation proceeds via a nucleophilic attack of an alkoxide anion of mandelate to the C(4a) of 6-bpy-BDP$_{ox}$ to form an adduct followed by a base-promoted 1,2-elimination to give benzoylformate and 6-bpy-BDP$_{red}$ as shown in Scheme 1 (path a), and the metal ion bound at the bipyridine moiety (i) increases the oxidation-activity of 6-bpy-BDP$_{ox}$ by interaction with C(2)=O or C(4)=O oxygen, (ii) binds the anionic substrate, and (iii) lowers pKa's of α-OH and α-C-H hydrogens to facilitate both the nucleophilic attack to the C(4a) and the successive elimination. Meanwhile, Me-BDP$_{ox}$ is known to react with $PhCH_2O^-$ to give Me-BDP$_{red}$ and PhCHO,[2] whereas Me-BDP$_{ox}$ forms an adduct with t-$BuO^-$.[3] This suggests that Me-BDP$_{ox}$ reacts with an alkoxide anion to form an adduct, followed by 1,2-elimination when primary and secondary alkoxides are employed (addition-elimination mechanism). This prompted us to examine the reaction of 6-bpy-BDP$_{ox}$ with mandelic acid derivatives having no α-hydrogen such as α-methyl mandelic acid (**1b**) and benzylic acid (**1c**) in the presence of $Ni^{2+}$ and DBU in t-BuOH[4] for detection of the adduct formation.

In this paper, we wish to report a novel oxidative decarboxylation of **1b** and **1c** by 6-bpy-BDP$_{ox}$.[5] Spectroscopic examination for the reaction of 6-bpy-BDP$_{ox}$ with **1b** showed formation of 6-bpy-BDP$_{red}$, indicating two-electron oxidation of **1b**. Product analysis was performed. Formation of PhCOMe and $Ph_2C{=}O$ was confirmed.[6] Furthermore, 6-bpy-BDP$_{ox}$ was found not to react with methyl α-methyl mandelate under the same conditions. These results clearly indicate the oxidative decarboxylation of the α-hydroxy acids as shown in Scheme 1 (path b).

Pseudo-first-order rate constants of the oxidative decarboxylation were determined by following the absorption increase of 6-bpy-BDP$_{red}$ at 610 nm. The rate constants and relative rates are given in Table 1. Table 1 shows that the oxidation of **1a** is a much faster process compared to that of the oxidative decarboxylation of **1b** and **1c**. This may be explained




**Scheme 1.** Reaction scheme for the oxidation of α-hydroxy acids by 6-bpy-BDP$_{ox}$.

**Table 1.** Pseudo-first-order rate constants and relative rates

| substrate | $k_{obs}$ / $min^{-1}$ | rel. rates |
|---|---|---|
| **1a** | $1.6 \times 10^{2}$ | $2.1 \times 10^{3}$ |
| **1b** | $7.5 \pm 0.3 \times 10^{-2}$ | 1.0 |
| **1c** | $6.9 \pm 0.3 \times 10^{-1}$ | 9.2 |

[6-bpy-$BDP_{ox}$] = $1.0 \times 10^{-5}$M, [$Ni(NO_3)_2 \cdot 6H_2O$] = $1.0 \times 10^{-4}$M, [**1**] = $5.0 \times 10^{-4}$M, [DBU] = $1.5 \times 10^{-3}$M, t-BuOH, $N_2$, 25 °C.

in part by that the decarboxylation step is depressed by the metal ion owing to its interaction with the carboxyl anion. In other words, the metal ion acts as a rate-retarding factor for the decarboxylation (path b) whereas a rate-accelerating one for the elimination (path a). It is well known that decarboxylation of carbon acids is facilitated by electron-withdrawing groups at α-carbon.[7] As seen in decarboxylases and their model systems, so called "electron sinks" are necessary to stabilize carbaions formed by decarboxylation.[8] For example, α-hydroxy acid such as α-lactylthiamin is known to be decarboxylated quite easily even in aqueous solutions.[9] Thus, an electron-withdrawing moiety must generate at the α-carbon of **1b** and **1c** for decarboxylation. This could be achieved by formation of the adduct as depicted in Scheme 1. Namely, the electron-withdrawing benzo-dipteridine moiety is introduced at the α-oxygen atom of the substrates by the adduct formation. As the result, the oxidative decarboxylation is facilitated by that the benzo-dipteridine moiety of the adduct acts as an electron sink. The larger rate constant of **1c** than that of **1b** suggests that the decarboxylation is involved in the rate-determining step.

The present study demonstrates a novel oxidative decarboxylation of α-hydroxy acids by a flavin model, and more importantly provides evidence to support the addition-elimination mechanism proposed for the oxidation of mandelic and lactic acids by 6-bpy-$BDP_{ox}$ in the presence of a metal ion.

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## References and Notes

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3 Spectroscopic examination showed that Me-$BDP_{OX}$ (548 nm) changed to a compound absorbing at 530 nm by addition of t-$BuO^-$ in t-BuOH, which regenerated the starting spectrum of Me-$BDP_{OX}$ by adding aqueous HCl and by $O_2$ bubbling. Isolation of the adduct has not yet been successful since Me-$BDP_{OX}$ is formed in separation procedures such as column chromatography and recrystallization. We speculate at present this compound to be a C(4a)-adduct.

4 The reaction conditions were employed since $Ni^{2+}$ showed the largest rate-acceleration for the oxidation of **1a** by 6-bpy-$BDP_{OX}$. DBU; 1,8-diazabicyclo[5.4.0]undec-7-ene. 1 M = 1 mol $dm^{-3}$.

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6 A mixture of 6-bpy-$BDP_{OX}$ ($3.7 \times 10^{-4}$ M), **1b**($1.9 \times 10^{-3}$M), $Ni(NO_3)_2 \cdot 6H_2O$ ($3.7 \times 10^{-4}$ M), and DBU ($5.6 \times 10^{-3}$ M) in t-BuOH (535 ml) containing DMF (20 ml) was stirred for 1 h in the dark. After the solvent was evaporated, $H_2O$ (10 ml) was added to the residue. The aqueous layer was extracted with $CHCl_3$ (10 ml x 3), and the $CHCl_3$ layer was washed with $H_2O$ (10 ml x 2). After dried over $MgSO_4$, the solvent was distilled carefully. Formation of acetophenone was confirmed by GLC (67% yield based on 6-bpy-$BDP_{OX}$) and TLC (silica gel, $CHCl_3$-hexane, 5 : 3 v/v), sprinkled with 2,4-dinitrophenylhydrazine in 3N HCl solution). A blank experiment without 6-bpy-$BDP_{OX}$ revealed no formation of acetophenone. Product analysis of **1c** was performed similarly.

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