

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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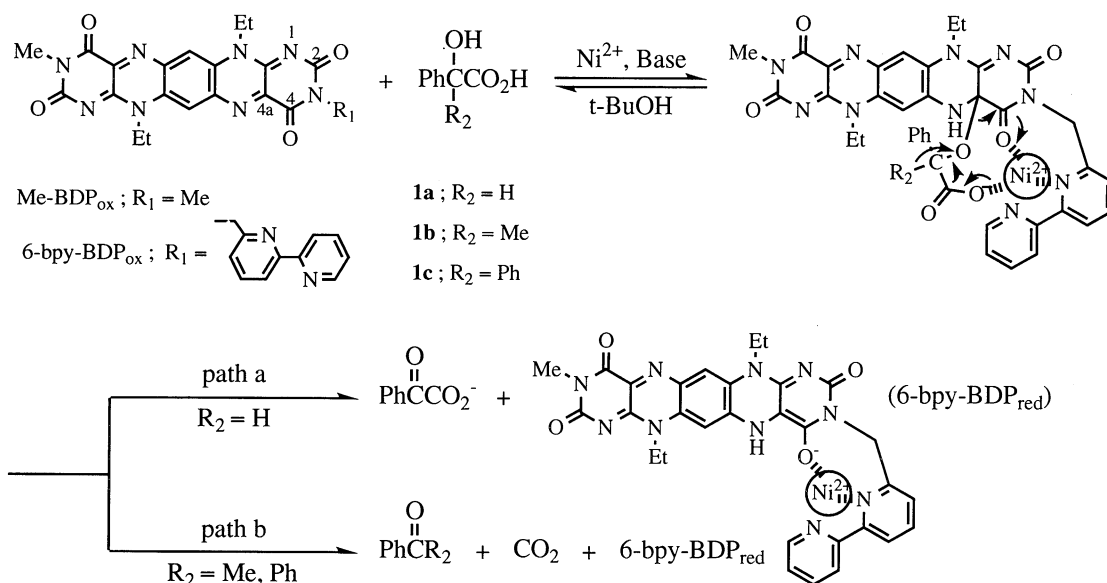
A benzo-dipteridine bearing a bipyridin-6-ylmethyl moiety (6-bpy-BDP_{ox}) was found to conduct oxidative decarboxylation of α -methyl mandelic and benzylic acids to give acetophenone and benzophenone and the reduced form (6-bpy-BDP_{red}) in the presence of Ni²⁺ and DBU in *t*-BuOH.

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 Zn²⁺, Ni²⁺, and Co²⁺ 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 pK_a'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 PhCH₂O⁻ 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 Ni²⁺ and DBU in *t*-BuOH⁴ 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 Ph₂C=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	$k_{\text{obs}} / \text{min}^{-1}$	rel. rates
1a	1.6×10^2	2.1×10^3
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}] = 1.0×10^{-5} M, [Ni(NO₃)₂·6H₂O] = 1.0×10^{-4} M, [1] = 5.0×10^{-4} M, [DBU] = 1.5×10^{-3} M, t-BuOH, N₂, 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 carbanions 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-dipiperidine 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-dipiperidine 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 O₂ 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 Ni²⁺ 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} (3.7×10^{-4} M), **1b** (1.9×10^{-3} M), Ni(NO₃)₂·6H₂O (3.7×10^{-4} M), and DBU (5.6×10^{-3} M) in t-BuOH (535 ml) containing DMF (20 ml) was stirred for 1 h in the dark. After the solvent was evaporated, H₂O (10 ml) was added to the residue. The aqueous layer was extracted with CHCl₃ (10 ml x 3), and the CHCl₃ layer was washed with H₂O (10 ml x 2). After dried over MgSO₄, the solvent was distilled carefully. Formation of acetophenone was confirmed by GLC (67% yield based on 6-bpy-BDP_{ox}) and TLC (silica gel, CHCl₃-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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