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REDUCTION OF METHYL BENZOYLFORMATE BY REDUCED NICOTINAMIDE ADENINE DINUCLEOTIDE MODEL IN THE PRESENCE OF RHODIZONIC ACID

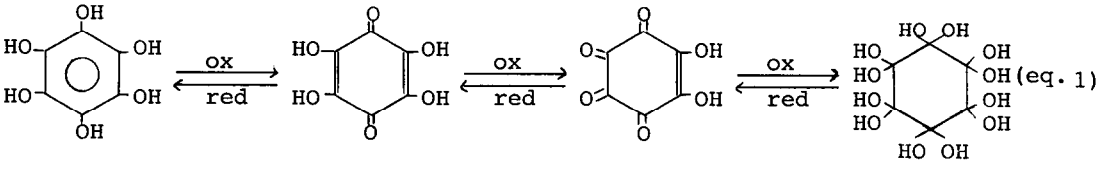
Takeshi Endo,* Tadayoshi Takada, and Makoto Okawara

Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan

Summary: The reduction of rhodizonic acid(RA) with 1-benzyl-1,4-dihydronicotinamide(BNAH; NADH model) was carried out at room temperature to obtain tetrahydroxy-p-quinone(THQ) and hexahydroxybenzene(HHB) by two-electron and four-electron reductions, respectively. The reduction of methyl benzoylformate with BNAH proceeded smoothly in the presence of RA, although it could not be reduced at all without RA.

The reduction by use of 1-alkyl-1,4-dihydronicotinamide derivatives as a model for the reduced nicotinamide adenine dinucleotide(NADH) have been widely studied in relation to the biomimetic reaction[1]. 1-Benzyl-1,4-dihydronicotinamide(BNAH), a model of NADH, has ability to reduce thiobenzophenone[2] and activated carbonyl compounds[3] such as hexachloroacetone and 2,2,2-trifluoroacetophenone. It has been also reported[4] that α-ketoesters can be easily reduced by BNAH in the presence of metal ions such as magnesium(II) and zinc(II).
Further, we have reported[5] that vicinal tricarbonyl compounds such as alloxan and ninhydrin can be reduced by BNAH to isolate the radical anion salt of alloxan and dialuric acid obtained by one- and two-electron reductions, respectively.

Rhodizonic acid(RA), which is known as an example of oxocarbons, can be reduced with some reducing agents initially to tetrahydroxy-p-benzoquinone(THQ) and later to hexahydroxybenzene(HHB). The reduction has been studied potentiometrically; it takes place in successive two-electron steps and essentially reversible[6](eq.1).



(eq. 1)

Hexahydroxybenzene (HHB) | Tetrahydroxy-p-benzoquinone(THQ) | Rhodizonic acid(RA) | Triquinoyl octahydrate(TQO)

In this communication, we report the reduction of RA with BNAH and electron-transport systems mediated by RA in the reduction of methyl benzoylformate.

It was found that methyl benzoylformate could be easily reduced with BNAH by adding a catalytic amount of RA as a catalyst,

although the reduction of it with BNAH alone did not proceed at all. The results of the reduction carried out at room temperature and 50°C are shown in Table 1.

Table 1. Reduction of Methyl benzoylformate by BNAH in the Presence of RA

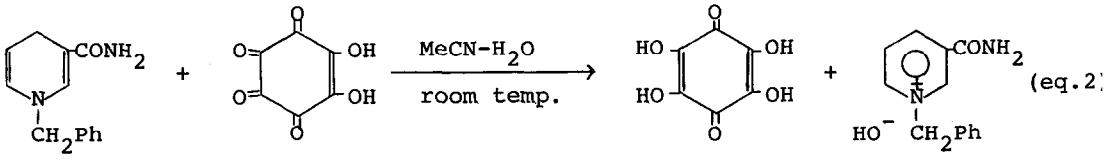
RA/BNAH (mole ratio)	methyl mandelate(%) 25°C	50°C	turn over of RA 25°C	50°C
0.1[a)]	77.6	90	7.7	9
0.01	54.2	38.7	54.2	38.7
0.001	15.8	7.5	158	75

BNAH; 3 mmol. PhCOCOOMe; 3.6 mmol. reaction time; 5 days solvent; MeCN-H_2O(9:1,v/v):20 mL. a) MeCN-H_2O(1:1):40 mL.

The yield in the reduction increased as the amount of RA increased. The catalytic effect(turn over) of RA increased as the concentration of RA decreased.

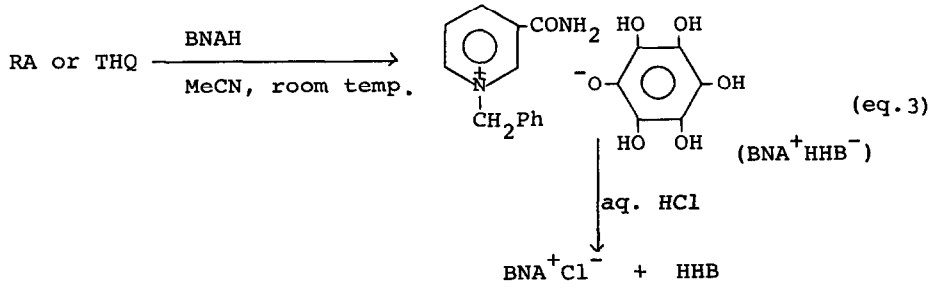
A typical procedure is as follows; A solution of 1.64g(3 mmol) of BNAH, 0.56g(3.6 mmol) of methyl benzoylformate and a certain amount(10 mol%-0.1 mol% for BNAH) of disodium rhodizonate in 20 mL of MeCN-H_2O was stirred at room temperature or 50°C for 5 days. After the solvent was removed in vacuo, 20 mL of water was added to the reaction mixture. The solution was extracted with ether three times. The organic layer was dried over anhydrous magnesium sulfate. Ether was removed in vacuo. The reduction yield in the residue was determined by NMR[proton ratio of methine proton(5.13 ppm) of methyl mandelate and total methyl proton(1.4 ppm) of methyl benzoylformate and methyl mandelate].

Reduction of RA with BNAH. The equimolar reaction of RA with BNAH was carried out at room temperature in MeCN-H_2O to give THQ in 70% yield by two-electron reduction(eq.2). Further, the reduction of THQ with BNAH was carried out at room



(BNAH) (RA) (THQ) (BNA^+OH^-)

temperature in MeCN-H_2O to obtain the pyridinium salt(BNA^+HHB^-, mp.147-148°C) of HHB in 65% by two-electron reduction. The obtained salt was treated with aq. HCl to give HHB and pyridinium salt(BNA^+Cl^-) qauntitatively(eq.3).



The reduction of methyl benzoylformate with BNAH was also tried in the presence of THQ, which was obtained by two-electron reduction of RA. The results are indicated in Table 2. THQ acted effectively as a catalyst in the reduction of methyl benzoylformate with BNAH.

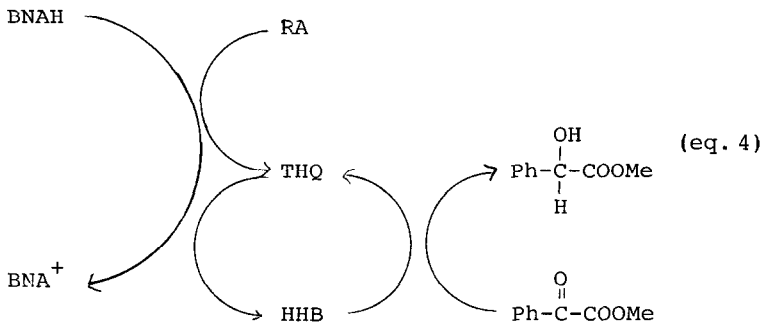
Table 2. Reduction of Methyl benzoylformate by BNAH in the Presence of THQ

THQ/BNAH (mole ratio)	product(%) (methyl mandelate)	turn over of THQ
0.1	93.9	9
0.01	41.1	41
0.001	12.5	125
0	0	-

BNAH; 3 mmol. PhCOCOOMe; 3.6 mmol. reaction time; 5 days. temp.; 50°C. solvent; MeCN-H_2O(1:1,v/v): 40 mL.

It was observed by uv spectroscopy that the amount of HHB(λmax; 314 nm) decreased in MeCN-H_2O when methyl benzoylformate was added at room temperature, whereas the oxidized form(THQ)(λmax; 525 nm) of HHB increased. On the other hand, the amount of RA(λmax; 485 nm) or THQ do not change at all by adding methyl benzoylformate. These observations suggest that only HHB can reduce methyl benzoylformate. Further, the reduction of methyl benzoylformate by HHB was subsequently achieved in the preparative scale to give methyl mandelate(40%) and THQ(37%), respectively.

These findings suggested that HHB was the active species in the reduction system. In addition, these results demonstrated that THQ has played the role of a catalyst for the reduction of methyl benzoylformate with BNAH(eq.4)



(eq. 4)

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