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REDUCTION BY A MODEL OF NAD(P)H. REDUCTION OF α-DIKETONES AND α-KETO ALCOHOLS BY 1-BENZYL-1,4-DIHYDRONICOTINAMIDE

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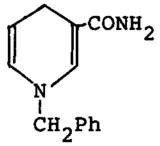
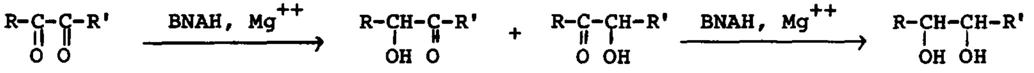
A model reaction of a biochemical process will prove to be of value in the study of biological mechanism and in the practical synthesis. Recently, we have shown the chemical model for NADH-dependent lactate dehydrogenase reaction which α-keto esters are reduced by 1,4-dihydronicotinamides, NAD(P)H-model compounds, in the presence of metal ion, and that chiral α-methylbenzyl group substituted on the carbamoyl nitrogen of a model compound brings about an asymmetric reduction. We wish to report here that under mild condition α-diketones are reduced by an NAD(P)H-model compound in the presence of magnesium perchlorate and that the reaction is accelerated by the irradiation with light. Additionally, we report the finding that α-keto alcohols are also reduced under the same condition.

No reaction was observed when benzil in acetonitrile was treated for a day with 1-benzyl-1,4-dihydronicotinamide (BNAH) alone at 50° in the dark.²⁾ In the presence of an equimolar amount of magnesium perchlorate, however, benzil was converted into benzoin (50%) and meso-1,2-diphenyl-1,2-ethanediol (1%) within 22 hr at this temperature. Longer reaction period or the use of excess BNAH improves the yield of the diol in the sacrifice of benzoin. When benzoin was used as a starting material, the diol was obtained in the presence of this perchlorate, but the yield was poor (3%). Magnesium



(BNAH)

perchlorate in wet acetonitrile or lithium perchlorate was found to be not an effective cofactor. Apparently, the magnesium cation plays an important role in these reductions. Additionally, under the same condition, 1-phenyl-1,2-propanedione afforded acetyl phenyl carbinol (27%), benzoyl methyl carbinol (38%), and meso-1-phenyl-1,2-propanediol (6%). Formation of acetoin and meso-2,3-butanediol from biacetyl was confirmed by vpc.[3)]



$$R\text{-}\underset{O}{\underset{\|}{C}}\text{-}\underset{O}{\underset{\|}{C}}\text{-}R' \xrightarrow{\text{BNAH, } Mg^{++}} R\text{-}\underset{OH}{\underset{|}{CH}}\text{-}\underset{O}{\underset{\|}{C}}\text{-}R' + R\text{-}\underset{O}{\underset{\|}{C}}\text{-}\underset{OH}{\underset{|}{CH}}\text{-}R' \xrightarrow{\text{BNAH, } Mg^{++}} R\text{-}\underset{OH}{\underset{|}{CH}}\text{-}\underset{OH}{\underset{|}{CH}}\text{-}R'$$

R= R'= Ph or Me
R= Ph, R'= Me

Although the rate of the above reduction at room temperature in a dark is very slow,[4)] it was found that the reaction is accelerated by the irradiation with light (≥350 nm)[5,6,7)]: benzil which coexists with BNAH and magnesium ion gave rise to benzoin in 47 % yield in a period of 22 hr, whereas in the absence of magnesium ion the conversion from benzil to benzoin was 8 %. Thus, magnesium ion is contributive to the reduction under photo-irradiation as well as in a dark. The yield of benzoin in acetonitrile containing 10 % of water decreased from 47 to 23 %. It should be noted that photo-irradiation accelerates the reaction regardless the presence of water or absence of magnesium ion

Table 1. Reduction of Carbonyl Compounds with BNAH at 50° in a Dark.

Substrate[a)]	BNAH, mmol	Metal Ion,[b)] mmol	Addendum	Reaction Time, hr	Isolated Yield, %		
					Benzil	Benzoin	Diol[c)]
Benzil	1.04	none		22	97	0	0
	1.05	Mg^{++}, 1.20		22	48	50	1
	1.15	Mg^{++}, 1.18	0.13 mmol p-hydroquinone	22	50	48	1
	1.07	Mg^{++}, 1.28	5% water	22	99	0.2	0
	1.06	Mg^{++}, 1.27		66	38	42	8
	2.05	Mg^{++}, 1.23		22	34	42	16
	1.05	Li^{+}, 2.49		22	100	0	0
Benzoin	1.04	none		22	--	100	0
	1.04	Mg^{++}, 1.01		22	--	94	3

a) 1 mmol in 20 ml of acetonitrile. b) perchlorate salt.
c) meso-1,2-diphenyl-1,2-ethanediol.

Table 2. Reduction of Carbonyl Compounds by BNAH under Photo-Irradiation at Room Temparature.

Substrate[a]	BNAH, mmol	$Mg(ClO_4)_2$, mmol	Addendum	Irradiation Time, hr	Isolated Yield, %		
					Benzil	Benzoin	Diol[b]
Benzil	1.16	none		22	72	8	1
	1.11	1.16		22	53	47	1
	1.11	1.11		44	18	75	1
	1.04	0.99	0.82 mmol *p*-hydroquinone	22	56	41	1
	1.16	1.17	10% water	22	64	23	1
Benzoin	1.16	1.20		44	--	81	1

a) 1 mmol in 20 ml of acetonitrile. b) *meso*-1,2-diphenyl-1,2-ethanediol.

(Compare Tables 1 and 2).

Even under the photo-irradiating condition the presence of *p*-hydroquinone (0.82 mol percent) in this system did not disturb the reduction. This fact shows that the present reductions with and without light do not involve a free-radical process. Unfortunately, it was unsuccessful to prove the direct hydrogen transfer, which characterizes biological reduction, from BNAH to benzil in the reduction with and without light, because of the enolization of benzoin in the presence of metal ion. The results summarized in Tables 1 and 2 are similar to that obtained previously in the reduction of α-keto esters which has been proved to be paralell to enzymatic hydrogen transport. This similarity and the experiment with *p*-hydroquinone support that the present reductions may be regarded as for biological reductions with NAD(P)H. However, the identity of the mechanism for reactions with and without light is not yet confirmed.

Biologically, α-diketones such as biacetyl[10)] and benzil[11)] are reduced to α-keto alcohols and, subsequently, to 1,2-diols. The conversion of α-keto alcohol to 1,2-diol is also very significant in biological systems as is seen in reduction of glyceraldehyde. The present non-enzymatic reduction may be essencially close to the reduction catalyzed by metalloenzyme[12)] and the followings should be considered as the role of magnesium ion; the activation of (i) the substrate and (ii) 1,4-dihydronicotinamide, and (iii) the stabilization of the transition state. Considering the asymmetric induction of α-keto esters reported previously,1) the third contribution seems to be particularly important. Although the mechanism for photo-activation of BNAH is not clear,5) in enzymatic systems there is a possibility that the action of metalloenzyme brings about the similar activating species of the 1,4-dihydronicotinamide moiety of NAD(P)H.

The mechanistic details of the model reduction and the scope of this type is currently under investigation.

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2) Under a vigorous condition (172°, 24 hr), benzil is reduced by Hantzsch ester to benzoin in 23 % yield, see E. A. Braude, B. J. Hannah, and S. R. Linstead, *J. Chem. Soc.*, 3257 (1960).

3) Because of difficulty in isolation of products, no quantitive analysis was done.

4) For 21 days at room temperature in a dark, benzil afforded benzoin (18%) and the diol (1%).

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6) Light of shorter wave length than 350 nm is cutted away by a solution of 2,3-dihydro-5,7-dimethyl-1,4-diazepine perchlorate, see G. Schwarzenbach and K. Kutz , *Helv. Chim. Acta*, **23**, 1139 (1940).

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