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BIOMIMETIC REDUCTIONS OF BENZALDEHYDE AND ACETOPHENONE BY MODELS OF NAD (P) H

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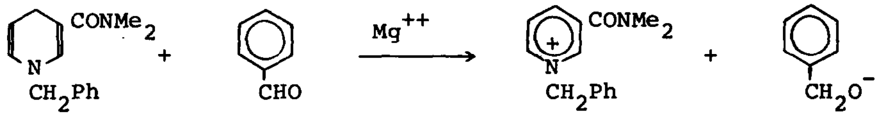
With respect to enzymatic reductions of carbonyl compounds by reduced pyridine nucleotides, NAD(P)H, we described previously chemical reduction, assisted by a divalent metal ion such as Mg^{++} or Zn^{++}, of α-keto esters with 1-benzyl-1,4-dihydronicotinamide(BNAH) as a model of NAD(P)H[2]. This mimicry has been extended to the reduction of α-diketones, α-hydroxy ketones[3], and 2-acylpyridines[4]. Magnesium ion also promoted largely the reduction of α,α,α-trifluoroacetophenone in non-aqueous media[5], but the reduction of benzaldehyde has not yet been effected under similar conditions because of low reactivity of BNAH for it. Recently, Shirra and Suckling described that benzaldehydes afforded the benzyl alcohols by 1-heptyl-3-morpholinosulfonyl-1,4-dihydropyridine(HMSPH) in the presence or absence of lithium ion at 20°C[6]. However, in our re-examination using *m*- or *p*-chlorobenzaldehyde and HMSPH, the yields of the alcohols were less than 0.5% at even 50°C[7]. In this communication, we wish to report that using a large excess of a more reactive model compound and raising reaction temperature benzaldehydes and acetophenone underwent a Mg^{++}-assisted reduction.



When we treated benzaldehyde(0.5 mg, 0.09 mmol) with 1-benzyl-N,N-dimethyl-1,4-dihydronicotinamide(BMNAH)(242 mg, 1.00 mmol) and $Mg(ClO_4)_2$ (238 mg, 1.07 mmol) in 13 ml of dry acetonitrile at 82°C for 61 hr, there was obtained benzyl alcohol in 9% yiled. Conversion of acetophenone to 1-phenylethanol was also observed under similar conditions, but the yield was only 2%. Furthermore, we attempted the reduction of substituted benzaldehydes with BNAH and BMNAH, and obtained the results summarized in Table 1. All samples were degassed and sealed in a high vacuum prior to reaction. Yields, based on the amount of benzaldehydes weighed, were determined by vapour phase or high pressure liquid chromatography.

Table 1 shows that the order of reactivities is BMNAH > BNAH > HMSPH[8] and that the yield of alcohols increased with increasing electron-withdrawing power of the substituents on benzaldehyde, the electronic effect being consistent with that observed in the reduction of benzaldehydes with NADH in the presence of horse liver alcohol dehydrogenase[9]. In the absence of a metal ion, the reduction

Table 1. Reduction of Benzaldehydes by NADH-Model in the Presence of Magnesium Perchlorate[a)]

Substituent	Yields of the alcohol, %		
	with BMNAH	with BNAH	with HMSPH
H	9	2	—
p -Cl	30	6	—
m -Cl	52	29 (14)[b)]	<1(<1)[c)]
m $-NO_2$	76	29	—
p $-NO_2$	91	56	—

a) A solution of 0.1 mmol of an aldehyde, 1.0 mmol of a model compound and 1.0 mmol of magnesium perchlorate in 13 ml of acetonitrile was heated at 82°C for 61 hr. b) At room temperature for 14 days. c) In the absence of a metal ion.

of *m*- or *p*-chlorobenzaldehyde with BNAH was negligible(less than 0.5%).

Thus, the Mg^{++}-assisted reduction was extended to include that of normal carbonyl compounds such as benzaldehyde and acetophenone, indicating that carbonyl compounds in general can be reduced chemically by a 1,4-dihydropyridine. Considering the wide scope and stereoselectivity of the Mg^{++}-assisted reduction, it is evident that this mimicry is an excellent model system for biological reduction of carbonyl compounds of metabolic importance by alcohol dehydrogenases and is especially well suited for studying the essential chemical steps and stereospecificity in enzymatic reactions involving NAD(P)H. It may be that a zinc ion located in the active site in the biological system behaves as a magnesium ion does in the mimetic system[10)], that is, the metal ion plays an accelerating role in the primary electron-transfer process from NAD(P)H to a substrate.

References and footnote

1) Reduction by a model of NAD(P)H. Part XXIV.

2) a) Y. Ohnishi, M. Kagami, and A. Ohno, J. Amer. Chem. Soc., **97**, 4799(1975): b) A. Ohno, T. Kimura, S. G. Kim, H. Yamamoto, S. Oka, and Y. Ohnishi, Bioorg. Chem., **6**, 21(1977): c) A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, Chem. Comm., 328(1978).

3) Y, Ohnishi, M. Kagami, and A. Ohno, Tetrahedron Letters, 2437(1975).

4) Y. Ohnishi, T. Numakunai, and A. Ohno, ibid., 2699(1975).

5) A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi, Chem. Letters, 65(1978).

6) A. Shirra and C. J. Suckling, Tetrahedron Letters, 3323(1975) and J. Chem. Soc. Perkin II, 759(1977).

7) As re-examination, a solution of a benzaldehyde (0.11 mmol) and HMSPH (0.21 mmol) with or without $LiClO_4$ (0.2 mmol) in 4 ml of dry and peroxide-free THF was stirred for 3 days at 50°C under atomosphere of argon.

8) This order was also supported by the following results; when BMNAH, BNAH and HMSPH were used, conversion of ethyl benzoylformate to the mandelate were 90, 60, and 4%, respectively, and pseudo-first order rate constants in the reduction of 2,6-dichlorophenol indophenol in MeOH-H_2O (1:1 v/v) at 30°C were 537, 204, and 8 $M^{-1}min^{-1}$, respectively. Furthermore, peak potentials in anodic voltammograms were found to be 0.58, 0.65 and 0.85 V(vs. SCE), respectively, in acetonitrile with a glassy carbon electrode.

9) C. H. Blomquist, Acta Chem. Scand., **20**, 1747(1966).

10) A. Ohno, S. Yasui, H. Yamamoto, S. Oka, and Y. Ohnishi, Bull. Chem. Soc. Japan, **50**, 294 (1978) and references cited therein.

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