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METAL-COMPLEX MEDIATED CATALYSIS OF REDUCTION OF 2-BENZOYLPYRIDINE BY AN NADH-MODEL.

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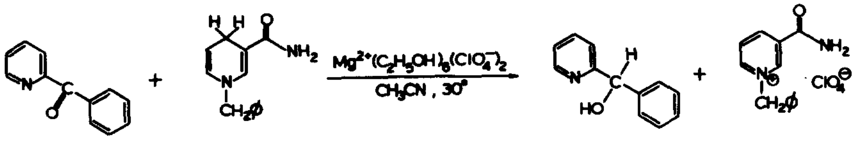
The implication of the active site zinc atom in the mechanism of action of liver alcohol dehydrogenase has prompted nonenzymatic studies of metal ion catalysis of the reduction of carbonyl compounds with NADH models.[1-3] Different interpretations of the role of the metal in the reduction of pyridine-2-carbaldehyde have been, however, recently suggested[2b,c]. The use of the metal halides or perchlorates (of ill-defined water content) in such studies suffers from several serious disadvantages. The former are incompletely dissociated in organic solvents, while the latter have been observed to give insoluble complexes which complicate spectroscopic or kinetic studies. In this communication we describe the application of metal alcoholate complexes, which circumvents the abovementioned complications, in a model reduction reaction. Spectral and kinetic data on the reduction of 2-benzoylpyridine (1, 2-BP) with 1-benzyl-1,4-dihydronicotinamide (2, BNAH) in the presence of magnesiumhexaethanolate perchlorate[4] (3), throw light upon the role of the metal cation.



1 (2-BP) 2 (BNAH) 3 4 5

2-Benzoylpyridine reacted with BNAH (2) in the presence of 1 eq. of the complex 3 (CH_3CN, 30°), to give high yields (> 70%, isolated) of phenyl-2-pyridylcarbinol (4) which was identified by spectral comparison (IR, NMR) with an authentic sample. Analogous results are obtained with $Zn(EtOH)_6(ClO_4)_2$. Particularly relevant to the investigation was the observation that under identical conditions, 3-benzoylpyridine and 4-benzoylpyridine were unaffected. In order to investigate the interaction between the magnesium complex (3) and the reactants, ^1H- and ^{13}C-nmr spectra of the pure compounds and binary and ternary mixtures were examined in CD_3CN. The relevant chemical shift data are presented in Tables I and II. ^{1}H-nmr measurements of mixtures of 2 and 3, containing increasing amounts of the complex 3, indicated that the chemical shifts of the protons did not show a further change after addition of 0.40 equivalents Mg^{++}.

TABLE I

^{1}H-NMR chemical shifts of 1 and 2, in single component, binary and ternary mixtures 0,4 M, in CD_3CN. All chemical shifts are given in ppm downfield from TMS=0

	2-BP(1)	1 + 3 (1:1)	1+2+3 (1:1:1)		BNAH(2)	2+3 (1:1)	1+2+3 (1:1:1)
H-3				H-2	7.02	7.21	7.20
H-4	7.91-8.11	7.95-8.29	7.95-8.22	H-4	3.06	3.06	3.06
H-5				H-5	4.72	4.88	4.68
H-6	8.70	8.84	8.80	H-6	5.83	5.84	5.84

A similar study of mixtures of 1 and 3 showed an analogous effect, although the chemical shift values became constant at a 1 to 3 ratio of 1:1.25. In connection with these results, it is noteworthy that a (2-3) complex containing four molecu of 2 coordinated to a magnesium ion, has been isolated. While 2-benzoylpyridine known to form 2:1 complexes with different metal salts in EtOH, no complex of 2- with Mg^{++} could be isolated, due to unfavourable association equilibrium in CH_3CN. In the ^{1}H-nmr spectrum of 1, the C_6-proton appears as a broad doublet cent at δ 8.70, which sharpens significantly upon addition of 3. This effect can be attributed to the suppression of quadrupole coupling of C_6-H with the neighbouri nitrogen, upon coordination of the latter with the metal. Coupled with the obser downfield shift of the carbonyl carbon of 1, in the binary mixture (^{13}C-nmr, Tab II), the data suggest that the metal is coordinated with both the nitrogen and t oxygen sites. The variation in the shifts of C_2, C_3 and C_5 are also in agreement with a coordination at the carbonyl oxygen. In the case of 2, the ^{13}C-nmr data (Table II) is, again, particularly significant. The strong downfield shifts of C and the carbonyl carbon, and an upfield shift of C_3 suggest strongly that the metal is coordinated at the amide oxygen. A possible coordination of the metal w the 1,4-diene system of BNAH is ruled out by lack of shift of C_6.

TABLE II

^{13}C-NMR chemical shifts of 1 and 2 in single component, binary and ternary mixtures, 0,7 M, in CD_3CN. All chemical shifts are given in ppm downfield from TMS = 0

2-BP(1)	1	1 + 3 (1:1)	1+2+3 (1:1:1)	BNAH(2)	2	2+3 (1:1)	1+2+3 (1:1:1)
C-2	154.6	149.8	151.2	C-2	138.5	142.3	142.3
C-3	123.9	128.6	127.1	C-3	99.4	96.4	96.2
C-4	137.0	139.6	138.9	C-4	22.1	21.7	21.7
C-5	126.1	129.0	128.4	C-5	102.5	104.4	104.6
C-6	148.2	149.8	149.4	C-6	128.6	128.6	128.6
C=O	193.4	197.0	195.8	C=O	169.7	171.3	171.5
C-1'	136.3	134.6	134.8	CH_2	56.4	56.8	56.8

The spectral data [^{1}H-nmr, ^{13}C-nmr] of the ternary mixtures of 1, 2 and 3 (1:1:1), under the reaction conditions, are relevant to the mechanism of the reaction. While the ^{1}H-nmr and ^{13}C-nmr spectra of the ternary mixture both indicate that the shifts for the dihydropyridine 2 are identical to those found in the binary mixture of 2 and 3, those for the ketone 1 are intermediate between those for the free ketone and the 1:1 mixture. Although a detailed picture of the equilibria involved in the complex formation is not yet available, the following two mechanisms for the reduction process may be considered.

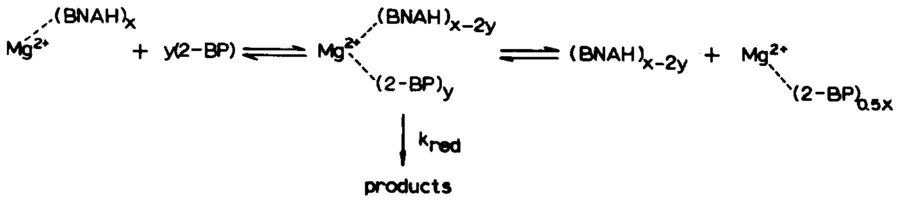
Mechanism A

$$m\,\mathrm{BNAH} + \mathrm{Mg}^{2+} \overset{k_1}{\rightleftharpoons} \mathrm{Mg}^{2+}\text{--}(\mathrm{BNAH})_m$$

$$n\ \text{2-BP} + \mathrm{Mg}^{2+} \overset{k_2}{\rightleftharpoons} \mathrm{Mg}^{2+}\text{--}(\text{2-BP})_n$$

$$\mathrm{BNAH} + \mathrm{Mg}^{2+}\text{--}(\text{2-BP})_n \xrightarrow{k_{red}} \text{products}$$

Mechanism B



To develop evidence which would bear upon the proposed mechanisms, the influence of the concentration of the complex 3, upon the rate of the reduction reaction, was investigated. A plot of the initial 2nd order rate constants versus concentration of 3 measured by following decrease of 2, is presented in Fig. 1. The catalytic effect of 3 first increases till about 0.40 eq. of the complex has been added and then rapidly drops off with further addition. Both the results of the kinetic measurements and the nmr-spectroscopic studies can be rationalized on the basis of a mechanism in which the uncoordinated dihydropyridine derivative 2 reacts with the coordinated (activated) form of the carbonyl derivative 1 (Mechanism A). The transfer of a hydrogen, as a hydride species, would be suppressed due to the electron-withdrawing effect of a coordinated metal. The presence of a reactive ternary complex in low concentrations (Mechanism B), so as to be undetectable cannot, however, be excluded. The kinetic results in the latter case may be explained by assuming that the reactive ternary complex is critically dependent upon metal concentration.and dissociates at high concentrations of magnesium perchlorate. It should, however, be emphasized that thusfar no evidence exists, which makes the involvement of a ternary intermediate obligatory. Further studies related to the mechanism of the reaction and the details of the complexes involved, are currently in progress.

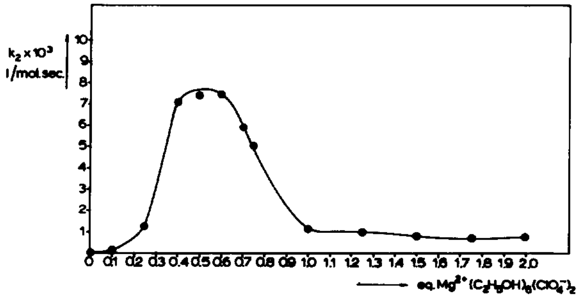


Fig. 1
Initial rate of reaction of 2-benzoylpyridine with 1-benzyl-1,4-dihydronicotinamide (CH_3CN, 30°) versus concentration of magnesium salt.

1. D.J. Creighton, D.S. Sigman, J.Amer.Chem.Soc., 93, 6314 (1971).
2. (a) M. Shirai, T. Chishina, M. Tanaka, Bull.Chem.Soc. Japan, 48, 1079 (1975); (b) M. Hughes, R.H. Prince, Chem.Ind., 1975, 648.
3. Y. Ohnishi, T. Numakunai, A. Ohno, Tetrahedron Lett. 1975, 3813 and references cited therein.
4. P.W.N.M. van Leeuwen, Recl. Trav.Chim. Pays-Bas, 86, 247 (1967).