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HYDRIDE TRANSFER IN THE REDUCTION OF SUBSTITUTED BENZYLIDENE MALONIC DIESTERS BY COENZYME NAD(P)H MODEL

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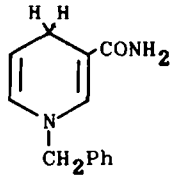
ABSTRACT: The reduction of substituted benzylidene malonic diesters by 1-benzyl-1,4-dihydronicotinamide(BNAH) is catalyzed by magnesium perchlorate. Kinetic isotope effects studies show that the C(4)-H bond cleavage in BNAH is involved in the rate determining step. Spectroscopic investigations have revealed that the ternary complex is formed in the ground state while complexation of substrate with magnesium ion is rate enhancing.

INTRODUCTION

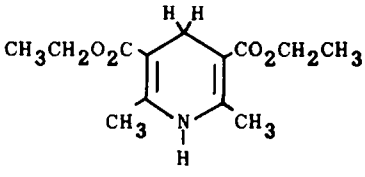
Studies with 1,4-dihydronicotinamide derivatives as the model of coenzyme NAD(P)H have been done extensively. Of continuing interest and debate is the reaction mechanism for the hydride-equivalent transfer from dihydronicotinamides. The pioneering study of Abeles et al[1] on the mechanism of biomimetic reduction of thiobenzophenone with BNAH proposed that the reduction proceeds through one-step hydride transfer. The direct hydride(H^-)transfer mechanism was generally accepted until Chipman[2] and Steffens claimed that stepwise mechanism is responsible for the reduction of trifluoroacetophone by BNAH. On the basis of ESR experiments[3], one-electron transfer has been advocated as the primary step of overall hydride transfer from BNAH to benzil as the substrate. Ohno's work[4] on the studies of kinetics and isotope effects for the reduction of substituted trifluoroacetophenone revealed that reaction proceeds through a multi-step mechanism. Furthermore, photo-induced reduction of many substrates by dihydropyridines have been reported to proceed by multi-step electron-proton-electron transfer processes[5]. However, acceptance of the stepwise mechanism for hydride-equivalent transfer from BNAH is far from being universal. Substituent effect calculations of the charge of the migrating H atom in the reduction of 5-nitro-quinolinium cations by 1,4-dihydro-nicotinamides clearly indicate the hydridic nature of this reaction[6]. Kreevoy and coworkers[7] supported a direct hydride transfer mechanism based on Marcus theory calculations of relative reaction rates and equilibrium

constants for hydride-equivalent reactions employing 10-methylacridan with a series of 1-benzyl-3-cyano-quinolium ions. Verhoeven[8] believes that single electron transfer cannot occur as a primary step in the overall hydride-transfer process except for substrates with very strong one-electron oxidizing properties. The MINDO calculations[9] confirm that hydride transfer mediated by NAD(P)H models under thermal conditions occurs most readily via a concerted pathway. We have reported[10] that the selective reduction of the nitro-group in nitrobenzylidene malonic diester by eosin-sensitized photo-reaction or the C=C double bond by metal ion catalysis in the dark with Hantzsch ester. The results of sensitized[10] and direct[11] photoreduction can be explained by a multi-step mechanism and a direct hydride transfer is proposed for the thermal reaction. In order to obtain further insight into the mechanistic aspects of thermal reaction, the present paper describes the results from spectroscopic and isotope effects studies for magnesium ion catalyzed thermal reaction of NAD(P)H models with substituted benzylidene malonic diesters. The transfer of hydrogen, as a hydride species and the formation of a ground state ternary complex have been demonstrated.

Model Compounds:

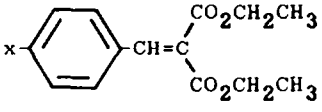


BNAH

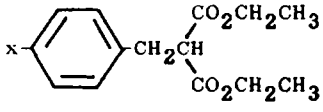


HEH

Substrates:



I. x-BME



II. x-BMEH$_2$

a) x = NO_2, b) x = CN, c) x = Cl, d) x = H, e) x = CH_3, f) x = OCH_3.

EXPERIMENTAL

Materials -- Benzylidene malonic diesters were prepared according to the literature[12] and purified by recrystallization from aqueous alcoholic solution. Ia--m.p.91 °C(lit.,92 °C), Ib--m.p.73 °C, Ic--m.p.25 °C(lit.,72 °C/1mm), Id--b.p.132 °C/2mm(lit.,164 °C/6mm), Ie--m.p. 49 °C(lit.,44 °C), If--b.p. 195 °C/3mm(lit.,180 °C/1mm). 1-benzyl-1,4-dihydronicotinamide(BNAH) was prepared by published method[13]. BNAH-4-d_1 and BNAH-4,4-d_2 were synthesized as

described[14], the NMR spectra were consistent with the deuterium only at the 4-position. Hantzsch ester(HEH) was prepared by known method[15]. Deuterated solvents were commercially available(Beijing Chemical Factory). Acetonitrile was purified by drying over phosphorous pentoxide and then distilled. Magnesium perchlorate was dried by heating at 120 °C for 8 hrs.

Instruments and Methods -- Electronic absorption spectra were measured on Hitachi 340 spectrometer. ^{1}H and ^{13}C-NMR were recorded on a Varian FT-80A spectrometer. ^{1}H spectrum resonance frequency 79.5MHz, spectrum width 800 Hz, TMS as internal standard. ^{13}C spectrum resonance frequency 20.0 MHz, spectrum width 4000 Hz, pulse width 2 μ(25 °C), pulse repetition time 1.2 s, using the method of modulated noise decoupling. Mass spectra were obtained on a Finnigan 4021 quadruple GC-MS, 70 eV electron bombardment, direct insertion. Redox potential was recorded by a cyclic voltammeter with L-23-204 XY function recorder(Shanghai Automatic Instrument No.2 Factory). Three electrodes system was applied. The reference electrode was Ag/AgCl, saturated with KCl solution. Pt was used as counter electrode saturated by KCl as well. Pyrolytic graphite was chosen as working electrode. 0.1M Et_4NClO_4 as supporting electrolyte.

Thermal Reduction -- A mixture of BNAH(2.5×10^{-2}M), x-BME(1.25×10^{-2}M), and magnesium perchlorate(1.25×10^{-2}M) was refluxed in 9:1 acetonitrile-methanol. After reaction the solvent was removed. The residue was dissolved in chloroform and washed several times with 1N HCl, then with water. The chloroform layer was separated and evaporated to dryness in a rotary evaporator. The products were separated by column chromatography on silica gel and their structures were determined by ^{1}H-NMR and mass spectroscopic analysis.

Kinetic Studies -- Kinetics were followed spectrophotometrically by observing the decrease in the intensity at 380 nm which is the absorption peak of BNAH of a 9:1 acetonitrile-methanol solution containing BNAH(2.0×10^{-4}M)/ or BNAH-4,4-d_2, x-BME(1.0×10^{-2}M), $Mg(ClO_4)_2$(5×10^{-3}M). Reaction rate constants, kinetic isotope effect(k_H/k_D) are determined. Deuterium content in the reduced product obtained by the reduction with BNAH-4-d_1 is the isotopic ratio(Y_H/Y_D) which can be determined by ^{1}H-NMR and mass spectroscopic analysis.

RESULTS AND DISCUSSION

Products of Thermal Reduction -- Reduced products x-$BMEH_2$ of thermal reaction were subjected to ^{1}H-NMR analysis and the results show doublet peaks around δ 3.3 ppm which are characteristics of α-methylenes[16] of the product, indicated that the C=C double bond has been reduced. The molecular ion peaks in mass spectra of reduced products are as follows: IIa--m/z 295(M^+,40%), IIb--m/z 275(M^+,42%), IIc--m/z 284(M^+,47%), IId--m/z 250(M^+,50%), IIe--m/z 264(M^+,55%), IIf--m/z 280(M^+,35%). The yields of the products are listed in Table 1. Table 1 shows that the olefinic double bonds of x-BME are reduced by BNAH in very good yields in the presence of magnesium ion. It is also indicated that electron withdrawing group in the benzene ring of x-BME enhanced the reaction rate. Magnesium ion catalyzed the reaction and played a specific role in the reduction. Without the aid of magnesium ion the reaction is limited to the reduction of very electron-deficient C=C double bonds. The results are similar with HEH as the reducing agent.

Table 1.

Product yields for the reduction of x-BME(1.25×10^{-2}M) with BNAH(2.5×10^{-2}M), $Mg(ClO_4)_2$(1.25×10^{-2}M) in 9:1 CH_3CN-CH_3OH.

x-BME	Time(hr.)		Yield(%)*	
x	without Mg^{++}	with Mg^{++}	without Mg^{++}	with Mg^{++}
NO_2	12.0	5.0	83.4	91.4
CN	11.0	5.5	75.4	90.1
Cl	--	6.0	--	98.0
H	--	6.5	--	82.3
CH_3	--	8.5	--	88.9
OCH_3	--	9.5	--	92.8

*. Isolated yields of reduced products of x-$BMEH_2$.

In order to ascertain the site of transfer of the hydrogen from BNAH to x-BME. BNAH-4,4-d_2 was employed as the reducing agent. The position of the deuterium atom in the reduced products were established by ^{1}H-NMR and mass spectrometry. Upon incorporation of a deuterium atom in the benzylic methylene group masses of the fragments carrying the latter moiety will be augmented by one unit. This was observed in the mass spectra of IIa - IIf. It is apparent that the deuterium atom is located at the β -carbon to the dicarboxylic group giving the reduced product Ar-CH(D)-CH($CO_2CH_2CH_3$)$_2$. When the reduction was carried out in 4:1 acetonitrile-methanol-O-d and/or methanol-d_4, it has been found in all cases the deuterium atom is incorporated to the α-carbon resulting in the formation of reduced products Ar-CH_2-CD($CO_2CH_2CH_3$)$_2$.

Kinetics and Isotope Effects -- It has been found that the reaction is pseudo-first order in BNAH in the range of concentration employed. The values of observed rate constants $k_{obs.}$, $k_{corr.}=(k_{obs.}-k_{dec.})$ where $k_{dec.}$ is the rate constant for the magnesium ion catalyzed decomposition of BNAH at $C_{x\text{-BME}}=0$ M, together with second-order rate constants k_x calculated by dividing $k_{corr.}$ by the concentration of x-BME, are listed in Table 2. Kinetics was also studied with BNAH-4-d_1 and BNAH-4,4-d_2 and the kinetic isotope effects k_H/k_D were calculated. Table 2 lists the calculated kinetic isotope effects as well as isotopic ratios in the product Y_H/Y_D. Table 2 indicates that the values of k_H/k_D are around 3. It is believed that hydride transfer often exhibits modest deuterium isotope effects, many in the range of 2-5[17]. The magnitude of the kinetic isotope effects are nearly consistent with the isotopic ratios in the reduced products. Some of the values of k_H/k_D are smaller than Y_H/Y_D due to isotope scrambling in

the products[18] and can no longer be considered in support of a stepwise hydride transfer mechanism. In Table 2 the rate constant with NO_2-BME as substrate is smaller than the rate constant with CN-BME as substrate. This is due to the complex formation between the nitro group of NO_2-BME and BNAH[19], the C=C double bond reduction is hindered to a certain extent.

Table 2.

Rate constants*, isotope effects(k_H/k_D) and deuterium ratios(Y_H/Y_D) in the reduced product for the reduction of x-BME(1.0×10^{-2}M) with BNAH(2.0×10^{-4}M), $Mg(ClO_4)_2$(5.0×10^{-3}M) in 9:1 CH_3CN-CH_3OH at 16 °C.

x	$10^3 \times k_{obs.}$ (min^{-1})	$10^3 \times k_{corr.}$ (min^{-1})	$10 \times k_x$ ($M^{-1}.min^{-1}$)	k_H/k_D	Y_H/Y_D NMR	Y_H/Y_D MS
NO_2	10.80	10.10	10.10	3.34	2.33	2.33
CN	17.52	16.82	16.82	2.23	3.00	2.79
H	4.42	3.73	3.73	2.55	3.42	3.12
CH_3	4.08	3.38	3.38	3.56	3.63	3.49
OCH_3	3.55	2.85	2.85	2.02	3.50	2.93

*. $k_x = (k_{obs.} - k_{dec.})/[x\text{-BME}]$, where $k_{dec.} = 0.70 \times 10^{-3}$ min^{-1}.

Mechanism of Metal Ion Catalyzed Thermal Reduction -- Using BNAH-4,4-d_2 as the reducing agent, it was found that the deuterium of C-4 position of BNAH-4,4-d_2 is directly transferred to the β -carbon in x-BME giving Ar-CHD-$CH(CO_2CH_2CH_3)_2$, demonstrating that the reaction occurs by a hydride transfer mechanism. Calculations[20] showed that the β -carbon in x-BME is more electron deficient than the α -carbon and should be the site susceptible to nucleophillic attack. When the reactions were performed in deuterated solvent, methanol-O-d and/or methanol-d_4, the deuterium is exclusively incorporated to the α -carbon giving Ar-CH_2-$CD(CO_2CH_2CH_3)_2$, indicated that the hydroxylic proton of methanol is predominantly involved in the reduction pathway.

Interaction of Magnesium Ion with Benzylidene Malonic Diesters and BNAH -- The UV-VIS absorption of BNAH in CH_3CN shifted from 344 nm to 352 nm on the addition of magnesium perchlorate indicating complex formation. The UV-VIS spectra of benzylidene malonic diesters in dry CH_3CN were hardly affected by added magnesium ion. On the other hand, magnesium ion remarkably affected the cyclic voltammetric behavior of BNAH[21] and x-BME as shown in Table 3.

Table 3.

Effect of the magnesium ion(5×10^{-3}M) on the reduction potential of x-BME(1×10^{-2}M) in CH_3CN.

	x	NO_2	CN	H	CH_3	OCH_3
$-E_R$ (in volts*)	without Mg^{++}	0.97	1.26	1.63	1.67	1.69
	with Mg^{++}	0.54	0.69	0.64	1.04	1.09

*. Relative to the saturated calomel electrode at RT.

It is believed that the presence of magnesium ion caused the reduction potential shift for the reduction of x-BME is due to the ion pairing interaction[22]. ^1H and ^{13}C-NMR spectra of BNAH and/or H-BME single components and binary and ternary mixtures were examined in 1:1 $CDCl_3$-CD_3OD. The relevant chemical shift data are presented in Tables 4 and 5.

Table 4.

^1H-NMR chemical shifts* of H-BME(1) and BNAH(2) in single component, binary and ternary mixtures containing magnesium ion(3) in 1:1 $CDCl_3$-CD_3OD at room temperature. All chemical shifts are given in ppm downfield from TMS=0 ppm.

	H-BME	1 + 3 (1:1)	1 + 2 + 3 (1:1:1)		BNAH	2 + 3 (1:1)	1 + 2 + 3 (1:1:1)
CH_3	1.30	1.30	1.30	H-2	7.02	7.15	7.08
	1.36	1.36	1.36	H-4	3.08	3.08	3.08
		1.00	1.00	H-5	4.70	4.90	4.80
CH_2	4.30	4.30	4.30	H-6	5.75	5.83	5.70
	4.33	4.36	4.36	CH_2	4.30	4.30	4.30
		3.90	3.90				
C_6H_5	7.35	7.35	7.35	C_6H_5	7.25	7.25	7.25
		7.27	7.27				
CH	7.69	7.69	7.69				

*. [H-BME] = [BNAH] = $[Mg^{++}]$ = 0.2 M

In ^1H-NMR spectrum of H-BME, new peaks of CH_3, CH_2 and C_6H_5-protons at 1.00, 3.90, 7.27 ppm appear respectively upon addition of magnesium ion, coupled with the observed downfield shift of one of the carbonyl carbon in the binary mixture (^{13}C-NMR in Table 5) suggesting that magnesium ion is coordinated both with the carbonyl oxygen and the benzene moiety.

Table 5.

^{13}C-NMR chemical shifts of H-BME and BNAH in single component, binary and ternary mixtures. Measurement conditions see Table 4.

	H-BME	1 + 3 (1:1)	1 + 2 + 3 (1:1:1)		BNAH	2 + 3 (1:1)	1 + 2 + 3 (1:1:1)
CH_3	13.7	12.8	12.9	C-2	140.6	141.6	143.3
	14.0	13.1	13.0	C-3	99.1	98.3	95.5
CH_2	61.4	60.9	60.9	C-4	22.1	22.5	24.0
C=O	163.8	163.0	163.0	C-5	103.9	104.5	103.0
	166.0	168.0	168.0	C-6	129.1	129.1	--
				C=O	170.0	171.3	171.0
				CH_2	56.7	56.7	56.7

The ^{1}H-NMR spectrum of BNAH shows downfield shifts of H-2, H-5, H-6 together with downfield shift of C-2 and the carbonyl carbon and upfield shift of C-3 indicating that magnesium ion is coordinated both at the amide oxygen and onto the dihydropyridine moiety[23]. The ^{1}H-NMR and ^{13}C-NMR spectra of the ternary mixture by adding(2) to (1)+(3), indicating that the shifts for (1) are identical to those found in the binary mixture of (1)+(3), showing that the formation of the complex of (1)+(3) even though in the presence of (2). While the ^{1}H and ^{13}C-NMR spectra of the ternary mixture by adding(1) to (2)+(3), show strong downfield shift of C-2 and upfield shift of C-3 of (2) in comparison with those found in the binary mixture of (2)+(3) and the shifts of H-2 and H-5 are intermediate between those for the free BNAH and binary of (2)+(3), indicating the presence of a ground state ternary complex as shown in Fig.1.

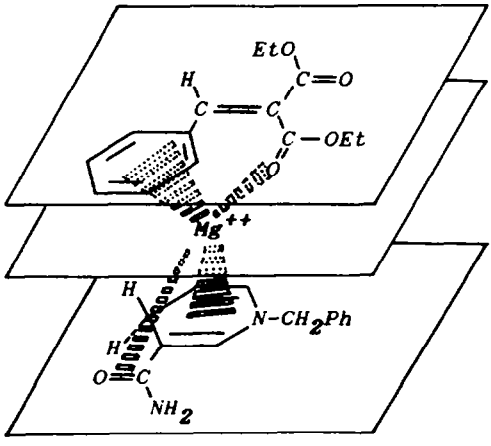
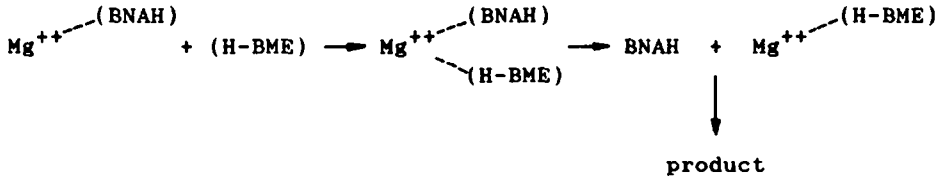


Fig.1 Schematic representation of the ground state ternary complex

The above spectroscopic studies have revealed the formation of a ground state ternary complex in equilibrium with other dimeric complexes. A mechanism by which the coordination of electron withdrawing magnesium ion with the carbonyl group of substrate(1), resulted in alternating the electron density of C=C double bond to make it more susceptible to nucleophillic attack by the uncoordinated(3)(Scheme 1) is proposed, because complexation of substrate carbonyl group with electron withdrawing magnesium ion would be rate enhancing, but inhibitory with BNAH for the hydride transfer.

Scheme 1.



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References

1. R. H. Abeles; F. W. Westheimer. J. Am. Chem. Soc. 1957, *79*, 712.
2. J. J. Steffens; D. M. Chipman. J. Am. Chem. Soc. 1971, *93*, 6694.
3. Y. Ohnishi; A. Ohno. Chem. Lett. 1976, 696.
4. A. Ohno; H. Yamamoto; S. Oka. J. Am. Chem. Soc. 1981, *103*, 2041.
5. (a) F. M. Martens; J. W. Verhoeven. J. of Royal Neth. Chem. Soc. 1981, *100*, 228.
   (b)C. Pac; Y. Miyauchi; O. Ishitani; M. Ihama; H. Sakurai. J. Org. Chem. 1984, *49*, 26.
6. J. W. Bunting; S. Sindhuatmadja. J. Org. Chem. 1981, *46*, 4211.
7. M. M. Kreevoy; I-S. H. Lee. J. Am. Chem. Soc. 1984, *106*, 2550.
8. J. W. Verhoeven; W. van Gerresheim; F. M. Martens; S. M. van der Kerk. Tetrahedron. 1986, *42*, 495.
9. M. C. A. Donkersloot; H. M. Buch. J. Am. Chem. Soc. 1981, *103*, 6554.
10 H. J. Xu; G. Deng; Q. Yu. J. Chem. Soc., Chem. Commun. 1987, 916.
11. G. Deng; H. J. Xu. J. Chem. Soc., Perkin Trans. *II*. 1990(in press).
12. J. Zablicky. J. Chem. Soc. 1961, 683.
13. D. Mauzerall; F. H. Westheimer. J. Am. Chem. Soc. 1975, *77*, 2261.
14. W. S. Caughey; K. A. Schellenberg. J. Org. Chem. 1966, *31*, 1978.
15. Org. Synth. Coll. Vol. II, 214.
16. S. Shinkai; Y. Kusano; T. Ide; T. Sone; O. Manabe. Bull. Chem. Soc. Jpn. 1978, *51*, 3544.
17. R. Srinivasan; H. F. Fisher. J. Am. Chem. Soc. 1982, *104*, 807.
18. M. F. Powell; T. C. Bruice. J. Am. Chem. Soc. 1982, *104*, 5834.
19. G. Deng. in Advances in Photochemistry (B. W. Zhang *et al.* ed) Pergamon Press, Beijing, 1989, 126.
20. T. Shen. Dyes and Pigments. 1978, 8, 375
21. S. Fukuzumi; N. Nishizawa; T. Tanaka. J. Chem. Soc. Perkin Trans. *II*. 1985, 371.
22. M. D. Ryan; D. H. Evans. J. Electroanal. Chem. 1976, *67*, 333.
23. A. Ohno; T. Kimura; H. Yamamota; S. Oha; Y.Ohnoshi. Bull. Chem. Soc. Jpn. 1977, *50*, 1535.