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Mechanistic Studies on the Reduction of 2-Bromo-1-phenylethylidenemalononitrile by NADH Models BNAH and $AcrH_2$

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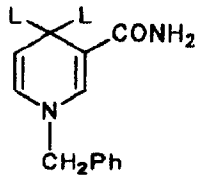
Abstract: Reduction of 2-bromo-1-phenylethylidenemalononitrile (BPM) by coenzyme NADH models BNAH and $AcrH_2$ to give 2-phenyl-1, 1-cyclopropanedicarbonitrile (PCN) and 1-phenylethylidenemalononitrile (PM), respectively, was rationalized in terms of a direct hydride transfer with BNAH and an initial electron transfer with $AcrH_2$.

The reduced form of nicotinamide adenine dinucleotide (NADH) is a typical coenzyme which plays important role in biological redox reactions. The mechanism of hydride-equivalent transfer from NADH models continues to attract considerable interest[1]. The focus of current interest and controversy is the experimental distinction between one-step hydride transfer and stepwise mechanism involving an initial single electron transfer. The pioneering study of Abeles and Westheimer[2] on the reduction of thiobenzophenone by 1-benzyl-1,4-dihydronicotinamide (BNAH) through one step hydride transfer had been accepted until Steffens and Chipman[3] showed that stepwise mechanism existed in the reduction of trifluoroacetophenone by BNAH. Evidences supporting the electron transfer mechanism for reactions involving photochemical[4,5], thermal[6] and electrochemical[7] reactons have been reported. In all these cases, strong one-electron oxidants with minimal hydride-acceptor properties were involved. On the other

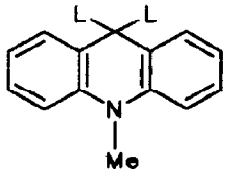
hand, evidences for direct hydride transfer mechanism were put forward for the reduction of NAD^+ models[8], 5-nitroquinolinium cation[9] and carbon-carbon double bond[10,11] by NADH model compounds. Verhoeven and co-workers[12] have pointed out that single electron transfer cannot occur as a primary step, in the overall hydride transfer process, except for substrates with strong one-electron oxidizing properties. It seemed desirable that, if a probe compound with two reducible sites is used, more useful information on the reaction mechanism may be obtained. This idea led us to examine the reaction of NADH models with 2-bromo-1-phenylethylidenemalononitrile (BPM) which meets such requirements.

Here we present the results of the title reaction. It appeared that the products of the reaction varied with the NADH model used. The product analysis and kinetic study revealed that the reaction proceeded by one step hydride transfer with BNAH, but by stepwise reaction with initial electron transfer with 10-methyl-9,10-dihydroacridine ($AcrH_2$) as NADH model.



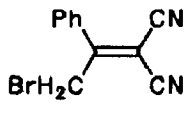
BNAH

(L = H,D)



$AcrH_2$

(L = H,D)



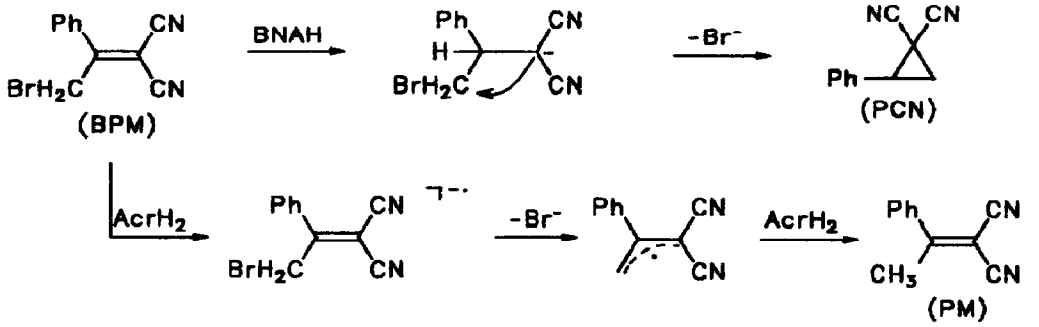
BPM

A mixture of BPM (0.40 mmol) and BNAH (0.45 mmol, L= H)in acetonitrile (10 ml) purged with argon was thermostated at 25℃ for 4 hours in the dark. The product was isolated by t.l.c. with petroleum ether-ethyl acetate as eluent to give 2-phenyl-1,1-cyclopropanedicarbonitrile (PCN) in 88% yield. Analysis: $C_{11}H_8N_2$, C, 79.2; H, 4.9; N, 16.3. Calcd: C, 78.6; H, 4.7; N, 16.6. M/z: 168(M^+). δ^1H (400 MHz, $CDCl_3$): 3.29 (1H, t, J=9 Hz), 2.23 (2H, d, J=9 Hz), 7.38(5H, s) ppm, which were consistent with that reported in the literature[13]. Kinetic studies with BNAH-d_2 (BNAH, L=D) showed a primary kinetic isotope effect (K_H/K_D= 4.3).

A mixture of BPM (0.40 mmol) and $AcrH_2$(0.45 mmol, L=H) in acetonitrile (10

ml) was thermostated at 65℃ for 72 hours in the dark. The product 1-phenylethylidenemalononitrile (PM) was isolated by t. l. c. with petroleum ether-ethyl acetate as eluent in 65% yield. m. p. 93-94℃ (94℃ reported by Mowry[14]). Analysis: $C_{11}H_8N_2$, C, 78.9; H, 4.8; N, 16.4. Calcd: C, 78.6; H, 4.7; N, 16.6. δ^1H (400 MHz, $CDCl_3$): 7.5 (5H, s), 2.6 (3H, s) ppm. No kinetic isotope effect was observed with $AcrH_2$-d_2($AcrH_2$, L=D) under similar reaction conditions.

In the reduction of BPM by BNAH, the three-membered ring product PCN was formed. It is reasonable to propose that an intramolecular nuclophilic substitution took place following an initial hydride attack, which is in accord with the results of reduction of BPM by $NaBH_4$[13]. On the other hand, reduction of BPM by $AcrH_2$ showed that an initial rate determining electron transfer occured. The elimination of bromide ion from the resulting BPM radical anion gave a neutral radical which further reacted with $AcrH_2$ by hydrogen abstraction to give PM (Scheme 1).



(Scheme 1)

It is of mechanistic interest to note that reduction of BPM by BNAH took a pathway different from that by $AcrH_2$. This indicates that the nature of the NADH model as well as that of the substrate has to be taken into consideration in discussion on the mechanisms. The reaction pathways may be related not only to the reduction potential of the substrate, as pointed out by Verhoeven and co-workers[12], but also to the redox properties of the NADH models.

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