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Study of Mechanism of Reduction of 2-Bromo-1-(p-X-phenyl) ethylidenemalononitrile by 1-Benzyl-1,4-dihydronicotinamide and 10-Methyl-9,10-dihydroacridine

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Abstract: The reduction of 2-bromo-1-(p-X-phenyl) ethylidenemalononitrile (X -BPM: X=H, F, Cl, Br, CN) by NADH models BNAH and $AcrH_2$ has been investigated. Based on product analysis, kinetic isotope effect, and free energy relationship, a direct hydride transfer and an electron transfer-hydrogen abstraction mechanism is proposed, respectively.

The reduced form of nicotinamide adenine dinucleotide (NADH) is a typical coenzyme which plays a vital role in many biological redox reactions. The mechanism of hydrogen transfer from NADH model compounds to a variety of substrates has been extensively studied and continues to be of interest. An issue of particular interest and controversy is the experimental distinction between one-step hydride transfer and multi-step mechanism involving an initial electron transfer[1-4].

The most widely used model compounds for NADH are the 1,4-dihydropyridines such as 4-benzyl-1, 4-dihydronicotinamide (BNAH, 1) and 10-methyl-9, 10-dihydroacridine ($AcrH_2$, 2).

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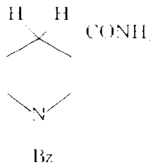
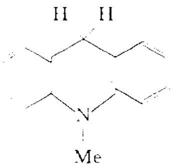


BNAH 1



$AcrH_2$ 2

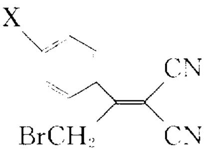
Since typical unsaturated groups which are reduced by NADH dependent enzymes include the C = N, the C = O, and the C = C functionalities, various mechanistic probes have been developed which enable the differentiation between reduction processes which proceed by direct hydride transfer or by the sequential transfer of an electron and a hydrogen atom, or by the sequence of electron-proton-electron transfer. Among these probes, the α-haloacetophenones[5] and cyclopropane ring[6] have been well studied.

In a previous communication[7] we have reported the reduction of 2-bromo-1-phenylethylidenemalononitrile (BPM, 3a), which is another probe, by NADH models BNAH and $AcrH_2$. Product analysis and kinetic studies revealed that the reaction proceeded by one step hydride transfer to give 2-phenylcyclopropane-1, 1-dicarbonitrile (4a) when BNAH was used as the reducing agent but proceeded according to a multistep mechanism to yield 2-phenylethylidenemalononitrile (5a) when $AcrH_2$ was used as the reducing agent. In this paper we wish to report the study of the reduction of five 2-bromo-1-X-phenylethylidenemalononitriles carrying different para substituents on the phenyl group (X-BPM: X=H, F, Cl, Br, CN) (3a—e) by BNAH and $AcrH_2$, respectively, and the substituent effects on the rates of reaction.

Results and Discussion

Reaction of X-BPM and BNAH: X-BPM was readily reduced by BNAH in acetonitrile at 25°C. The oxidation product of BNAH, BNA^+Br^-, precipitated from the reaction mixture within about ten minutes after the mixing of the reactants. The sole reduction product of X-BPM was identified as the cyclopropane derivatives (4a-e) by ^{1}HNMR and mass spectrometry. 2-Phenylcyclopropane-1, 1-dinitrile was reported before[8] by the reduction of 2-bromo-1-phenylethylidenemalononitrile with sodium borohydride.

In order to ascertain the site of transfer of hydrogen from BNAH to X-BPM, 4-deuterated-1, 4-dihydronicotinamide, BNAH-4, 4-d_2, was used as the reducing agent for the reduction of BPM and the position of deuterium incorporated in the product determined by ^{1}HNMR. The results showed that the triplet at δ 3. 3 ppm for the tertiary hydrogen disappeared and the doublet at δ 2. 3 ppm for methylene hydrogen changed to a singlet. This indicates that the deuterium is located on the benzylic position and β-carbon atom to the nitrile group.



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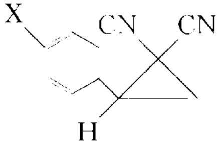

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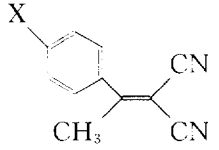

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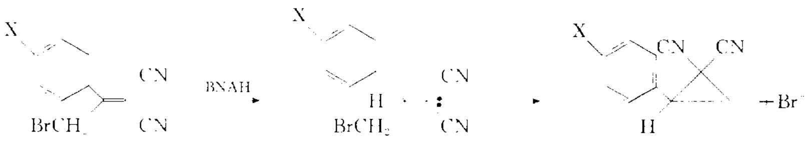
(a)X=H; (b)X=F; (c)X=Cl; (d)X=Br; (e)X=CN

Kinetic determination: Kinetic studies of the reaction were carried out under second-order reaction conditions with equimolar concentrations of BNAH and XBPM. It was found that the reaction was first order with respect to BNAH and first order to XBPM. Kinetic studies were also carried out with BNAH-4, 4-d_2 as the reducing agent. The rate constants as well as the kinetic isotope effects are collected in Table 1.

Table 1. Rate constants (k_B) and kinetic isotope effects for the reactions of XBPM (2.0×10^{-4}M) and BNAH (2.0×10^{-4}M)

X	H	F	Cl	Br	CN
$k_B(10^{-2})M^{-1}s^{-1}$	1.06	1.17	2.19	2.22	5.26
k_H/k_D	3.8	3.5	3.9	3.5	3.2

It is seen from Table 1 that the magnitude of deuterium isotope effect clearly demonstrates primary kinetic isotope effect and that breakage of carbon-hydrogen bond at C—4 of BNAH must be involved in the rate-determining step for the reaction. In view of the fact the 2-X-phenylcyclopropane-1, 1-dinitriles were obtained as the sole products in high yields (86—91%), it is reasonably certain that the reaction takes place by direct hydride transfer mechanism as follows(scheme 1):



Scheme 1

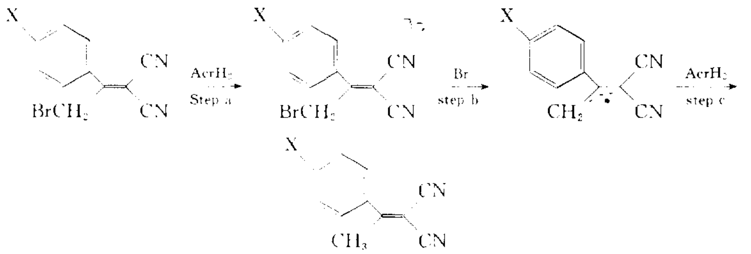
Reaction of XBPM and AcrH₂: The reaction of XBPM with AcrH₂ went slowly at room temperature and it took about 40 hours for completion. The products were identified to be the debrominated compounds with carbon-carbon double bonds intact (5).

Kinetic Studies: Kinetic studies of reaction of XBPM with $AcrH_2$ were carried out under pseudo first-order reaction conditions with XBPM in more than 30-fold excess. The second-order rate constants were obtained by dividing the pseudo first-order rate constants by the concentration of XBPM. The second-order rate constants, kinetic isotope effect, as well as the reduction potentials of 2-bromo-1-(4-X-phenyl) ethylidenemalononitriles (3a-3e) determined by cyclic voltammetry are collected in Table 2.

Table 2. Rate constants (k_A), kinetic isotope effect (k_H/k_D) for the reduction of XBPM by $AcrH_2$, and reduction potentials of XBPM.

X	H	F	Cl	Br	CN
$k_A(10^{-2})M^{-1}s^{-1}$	3.86	4.74	5.36	6.46	1.29
k_H/k_D	1.15	1.37	1.20	1.31	1.42
$E_{red}(V)$	0.32	0.35	0.21	0.12	0.00

It is seen from Table 2 that, albeit kinetic isotope effects k_H/k_D are larger than unity, the absence of primary kinetic isotope effect is obvious. This ruled out direct hydride-transfer mechanism. The reaction probably proceeded according to a multi-step mechanism involving initial electron transfer as follows (Scheme 2):



Scheme 2

Substituent Effect on Reaction Rates: For the reduction of XBPM by BNAH, a plot of the logarithm of the second-order rate constants k_B versus Hammett σ_{para}[9] gives a straight line (Figure 1) with slope (ρ) of 2.48. A positive and large value of ρ indicates that the reaction is facilitated by electron-withdrawing substituent and is more sensitive to the electronic properties of the substituent groups.

$$log k_B = \rho\sigma_{para} + A$$

For the reduction of XBPM by $AcrH_2$, a plot of logarithms of rate constantsagainst σ_p values did not give a straight line (Figure 2). This, in conjunction with the absence of primary kinetic isotope effect, indicates that a multi-step mechanism shown in Scheme 2 is probably involved. According to the Scheme, the rate-de-

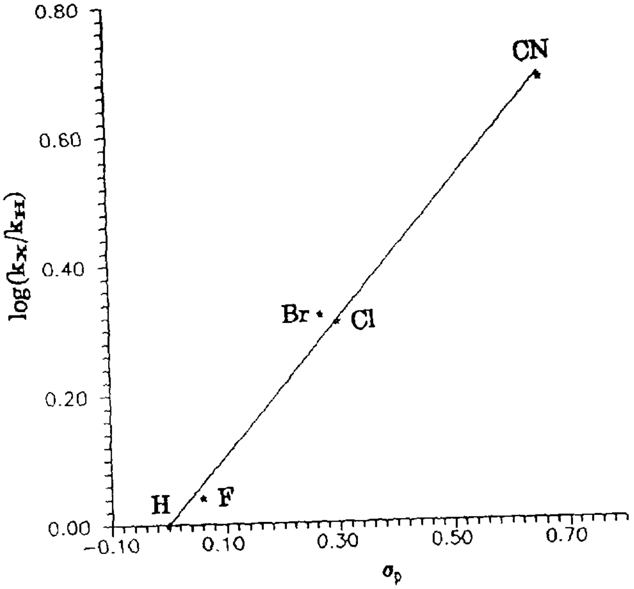


Figure 1. Plot of the logarithm of k_B versus Hammett σ_p values.

termining step for the reaction could either be the electron transfer (step a) or the dissociation of the intermediate radical anion (step b), while the hydrogen abstraction (step c) as the rate-determining step can be eliminated on account of the negligible

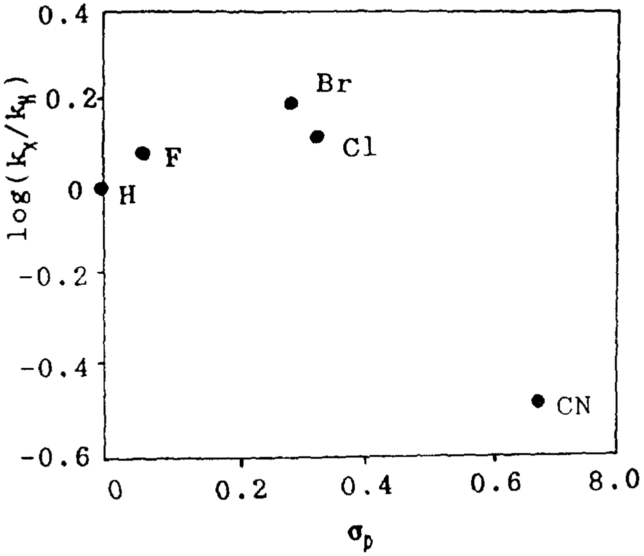


Figure 2. Plot of the rate constants for the reaction of XBPM and $AcrH_2$ versus Hammett σ_p values.

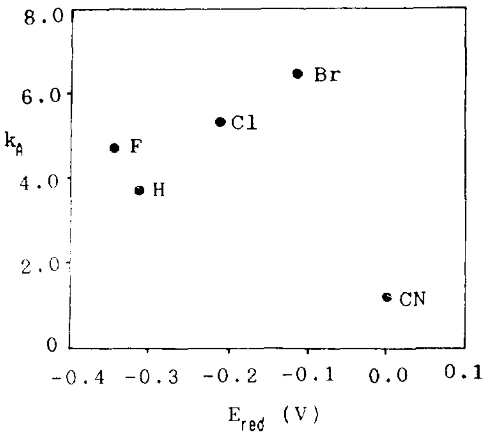
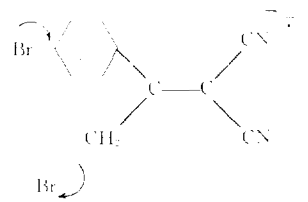
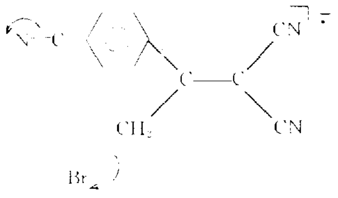


Figure 3. Plot of the rate constants for reaction of XBPM with $AcrH_2$ versus reduction potentials of XBPM's.

isotope effect. If the electron transfer is the rate-determining step, the rate constants for the reaction should show some linear correlation with the reduction potentials of the substrate XBPM. A plot of the rate constants for the reaction of XBPM with $AcrH_2$ versus the reduction potentials of XBPM is illustrated in Figure 3. Although Figure 3 does indicate a linear correlation for the halogen-substituted substrates (except the F-compound), the rate constant for the CN-substituted compound, which has the highest reduction potential, deviates far below the straight line. This seemingly anomalous result can be rationalized by the proposition that the dissociation of the intermediate radical anion is the rate determining step because the substituent effect not only influences the rate of electron transfer leading to the formation of the radical anion, XBPM$^{\cdot-}$, but also the dissociation of the XBPM$\cdot$ leading to the formation of an allylic radical, XBPM$^{\cdot}$, and a bromide anion. Considering the latter step, the transition state for the dissociation of radical anion 3d$^{\cdot-}$ and 3e$^{\cdot-}$ can be represented as follows:



transition state for
the dissociation of 3d$^{\cdot-}$



transition state for
the dissociation of 3e$^{\cdot-}$

It can be visualized that, when the para substituent of the phenyl ring is a halogen, because the electron-donating conjugative effect of halogen substituents facilitates the leaving of the bromide anion from the substrate radical anion and thus lowers the energy of the transition state, the rate of dissociation is enhanced. On the other hand, when the substituent is a cyano group, which possesses an electron-withdrawing conjugative effect and retards the leaving of the bromide anion, it raises the energy of the transition state, hence the rate of dissociation is diminished. Since the order of electron-donating conjugative effect of halogen substituents is Br>Cl>F, it is justifible to conclude that the dissociation of the intermediate radical anion is the rate-determining step for the reaction, which accommodates well the observed order of reactivity of the five XBPM's in their reaction with $AcrH_2$(Table 2):

p-CNBPM<HBPM<p-FBPM<p-ClBPM<p-BrBPM

To sum up, the reaction of 2-bromo-1-(p-X-phenyl)ethylidenemalononitrile and BNAH is clearly shown to proceed via a direct hydride transfer mechanism. On the other hand, the reaction of 2-bromo-1-(p-X-phenyl)ethylidenemalononitrile and $AcrH_2$ goes through a multi-step electron transfer-hydrogen abstraction process.

Experimental

Materials: 1-Benzyl 1,4-dihydronicotinamide (BNAH) was prepared according to the literature[10]. BNAH-4, 4-d_2 was synthesized as described[11]. 10-Methyl-9, 10-dihydroacridine ($AcrH_2$) was prepared according to the literature[12]. 10-Methyl-9, 10-dihydroacridine[9,9-$^2H_2$]($AcrD_2$) was prepared by oxidation of $AcrH_2$ with chloranil and reduction with BNAH-4, 4 d_2[13]. It was shown to contain 93.0% deuterium by 400 MHz ^{1}HNMR spectroscopy. Acetonitrile, analytical grade, was purified and dried according to standard procedure. 2-Bromo-1-phenylethylidenemalononitrile and its derivatives (XBPM) were prepared by condensation of the corresponding ketones with malononitrile[14] followed by bromination with N-bromosuccinimide (NBS) in carbon tetrachloride under UV illumination using dibenzoyl peroxide as initiator.

2-Bromo-1-phenylethylidenemalononitrile (HBPM): yield 50%; mp 120-122°C (recrystallized from CH_3OH); Found: C 53.82, H 2.90, N 11.18, Calc. for $C_{11}H_7BrN_2$: C 54.07, H 2.96, N 11.38; MS: m/z 246/248 (M/M+2); ^{1}HNMR ($CDCl_3$): δ7.6(5H, s), 4.53(2H, s).

2-Bromo-1-(p-bromophenyl)ethylidenemalononitrile (BrBPM): yield 60%; mp 82-84°C (recrystallized from CH_3OH); Found: C 40.51, H 1.92, N 8.44; Calc. for $C_{11}H_6Br_2N$: C 40.74, H 1.85, N 8.64; MS: m/z 324/326/328 (M/M+2/M+4); ^{1}HNMR ($CDCl_3$): δ7.7 (2H, d, J=12.0Hz), 7.48 (2H, d, J=12.0Hz), 4.62 (2H, s).

2-Bromo-1-(p-chlorophenyl)ethylidenemalononitrile (ClBPM): yield 65%; mp 95-97℃ (recrystallized from CH_3OH); Found: C 47.03, H 2.29, N 9.88; Calc. for $C_{11}H_6BrClN_2$: C 47.14 H 2.14, N 10.00, MS: m/z 280/282 (M/M+2); ^{1}HNMR δ7.5 (4H,s),4.49(2H,s).

2—Bromo—1—(p—fluorophenyl)ethylidenemalononitrile (FBPM): yield 43%; mp 48—50℃ (recrystallized from CH_3OH); Found: C 49.87, H 2.30, N 10.41, Calc. for $C_{11}H_6BrFN_2$: C 50.0, H 2.27, N 10.60, MS: m/z 264/266 (M/M+2); ^{1}HNMR δ7.6(2H,d,J=12.0Hz), 7.3(2H,d,J=12.0Hz),4.5(2H,s).

2-Bromo-1-(p-cyanophenyl) ethylidenemalononitrile (CNBPM) yield 2.5%; mp 118-120℃ (recrystallized from CH_3OH); Found: C 52.98, H 2.33, N 15.27, Calc. for $C_{11}H_6BrN_3$: C 53.13, H 2.21, N 15.51, MS: m/z 271/273 (M/M+2); ^{1}HNMR ($CDCl_3$):δ7.7(2H,d,J=11Hz), 7.5(2H,d,J=11Hz),4.62(2H,s).

Reduction of XBPM by BNAH and $AcrH_2$: A mixture of X-BPM (0.4 mmol) and BNAH (0.45 mmol) in 10 ml deaerated acetonitrile was thermostated at 25℃ for 4 hours in the dark. The solvent was removed in a rotary evaporator under reduced pressure. The products were separated by t. l. c. giving 2-(p-X-phenyl)-1, 1-cyclopropanedicarbonitrile (XPCN) in high yield. Meanwhile, a mixture of XBPM (0.4mmol) and $AcrH_2$(0.45mmol) in 10 ml deaerated acetonitrile was thermostated at 65℃ for 48 hours in the dark. The product 1-(p-X-phenyl)ethylidenemalononitrile (XPM) was isolated by column chromatography on silica gel with petroleum ether-ethyl acetate as eluant. The structure of XPCN and XPM were determined by ^{1}HNMR and mass spectrometry.

HPCN yield: 88%; Found: C 78.32, H 4.84, N 16.55; Calc for $C_{11}H_8N_2$: C 78.57, H 4.76, N 16.67; MS: m/z 168(M^-);^{1}HNMR ($CDCl_3$): δ7.38(5H,s),3.30 (1H,t,J=9.0Hz), 2.23(2H,d,J=9.0Hz).

FPCN yield: 91%; Found: C 71.22, H 3.76, N 15.00; Calc. for $C_{22}H_7N_2F$: C 70.97, H 3.89, N 15.05; MS: m/z 186(M^-); ^{1}HNMR ($CDCl_3$): δ7.30(2H,d,J=11Hz),7.05(2H,d,J=11Hz), 3.25(1H,t,J=8.0Hz), 2.25(2H,d,J=11Hz).

ClPCN yield: 90%; Found: C 65.22, H 3.51, N 13.53; Calc. for $C_{11}H_7N_2Cl$: C 65.35, H 3.46, N 13.86; MS: m/z 202(M^-); ^{1}HNMR ($CDCl_3$): δ7.45(2H,d,J=8.0Hz),7.20(2H,d,J=8.0Hz), 3.25(1H,t,J=10.0Hz), 2.25(2H,d,J=10.0Hz).

BrPCN yield: 90%; Found: C 53.39, H 3.04, N 11.20; Calc. for $C_{11}H_7N_2Br$: C 53.66, H 2.84, N 11.38; MS: m/z 246/248(M^+/M+2);^{1}HNMR ($CDCl_3$): δ7.55 (2H,d,J=8.0Hz), 7.20(2H,d,J=8.6Hz).

CNBPM yield: 86%; Found: C 74.68,H 3.60, N 21.44; Calc. for $C_{12}H_7N_3$: C 74.61, H 3.63, N21.76; MS:m/z 193(M^+);^{1}HNMR: δ7.60(2H,d,J=7.8Hz), 7.45 (2H,d,J=7.8Hz), 3.25(1H,t,J=9Hz), 2,25(2H,d,J=9Hz).

HPM yield: 65%; Found: C 78.43, H 4.80, N 16.48; Calc. for $C_{11}H_8N_2$: C

78. 57, H 4. 76, N 16. 67; MS: m/z 168(M^+); ^{1}HNMR ($CDCl_3$): δ7. 5(5Hz,s), 2. 6 (3H,s).

FPM yield: 72%; Found: C 70. 81, H 3. 93, N 14. 97; Calc. for $C_{11}H_7N_2F$: C 70. 97, H 3. 89, N 15. 05; MS: m/z 168(M^-); ^{1}HNMR: δ7. 35(2H,d,J=10Hz), 7. 00 (2H,d,J=10Hz), 2. 5(3H,s).

ClPM yield: 69%; Found: C 65. 17, H 3. 53, N 13. 71; Calc. for $C_{11}H_7N_2Cl$: C 65. 35, H 3. 46, N 13. 86; MS: m/z 202(M^+); ^{1}HNMR ($CDCl_3$): δ7. 45(4H,s), 2. 56 (3H,s).

BrPM yield: 78%; Found: C 53. 46, H 2. 91, N 11. 25; Calc. for $C_{11}H_7N_2Br$: C 53. 66, H 2. 84, N 11. 38; MS: m/z 246/248($M^+/M+2^+$); ^{1}HNMR ($CDCl_3$): δ7. 65 (2H,d,J=9Hz),7. 45(2H,d,J=9Hz), 2. 65(3H,s).

CNPM yield: 70%; Found: C 74. 66, H 3. 75, N 21. 51; Calc. for $C_{11}H_7N_3$: C 74. 61, H 3. 63, N 21. 76; MS: m/z 193(M^-); ^{1}HNMR: δ7. 6(2H,d,J=8. 0Hz),7. 40 (2H,d,J=8. 0Hz), 2. 6(3H,s).

Kinetic Measurements: Kinetic measurements were carried out using a Hitachi 557 UV-visible spectrophotometer connected to a superthermostat circulating bath to regulate the temperature of cell compartments. For the reduction of XBPM by BNAH, reaction rates were monitored by the decay of the absorption band due to BNAH (λ = 365nm) of an acetonitrile solution containing BNAH (2x10^{-4}M) and XBPM (2x10^{-4}M) at 25℃. For the reduction of XBPM by $AcrH_2$, measurements were carried out at 60℃ under pseudo first-order conditions with XBPM in at least 30-fold excess. Reaction rates were monitored by the increase of the absorption band due to $AcrH^+$(λ=413nm)

Cyclic Voltammetry: Reduction potentials of XBPM were determined by cyclic voltammetry in acetonitrile containing 0. 1M($n-Bu)_4NClO_4$ at scan rates 50mV. s^{-1}. The measurements were performed using a B. A. S. CV-27 Electrochemical Analyzer (Bioanalytical System, Inc. West Lafayette, Indiana) with a glassy carbon working electrode, which had been polished and dried before use, and a SCE reference electrode. The scan range was within +0. 2 to −1. 0 V and the cyclic voltammograms of XBPM show an irreversible reductive peek. The cyclic voltammetric data reported are the average of three separate runs.

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