  Bull. Chem. Soc. Jpn., 53, 2651—2654 (1980)

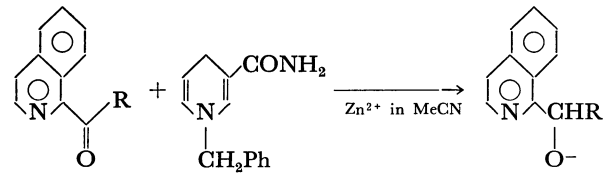
Reduction by a Model of NAD(P)H. 27. Role of Bivalent Metal Ion in the Reduction of 2-Acylpyridines and 1-Acylisoquinolines

Atsuyoshi Ohno,* Shinro Yasui, and Shinzaburo Oka
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611
(Received February 22, 1980)

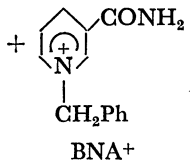
Reductions of 1-acetylisoquinoline (AQ), 1-benzoylisoquinoline (BQ), and isoquinoline-1-carbaldehyde have been studied kinetically and the results are compared with those of 2-acetylpyridine (AP), 2-benzoylpyridine (BP), and pyridine-2-carbaldehyde. Equilibrium constants for complexes between these substrates and zinc ion have also been studied. Kinetic deuterium isotope effects for AQ and BQ are smaller than the corresponding product isotope effects, respectively, whereas those for AP and BP are identical. The results are discussed in terms of stability and reactivity of intermediate radical-ion pair, and it is concluded that strong coordination of a metal ion onto the reaction site of a substrate facilitates the complexation but interferes the reduction.

In a previous paper of this series, it was reported that both substrate–metal ion and coenzyme model–metal ion complexes are reacting species in the zinc ion-catalyzed reductions of 2-acetylpyridine (AP) and 2-benzoylpyridine (BP) with 1-benzyl-1,4-dihydronicotinamide (BNAH).[1] Namely, computor-assisted simulation of the kinetics has revealed a key role of the metal ion-complexes on explanation of unusual behavior of metal ion in the reduction of 2-acylpyridines.[2,3]

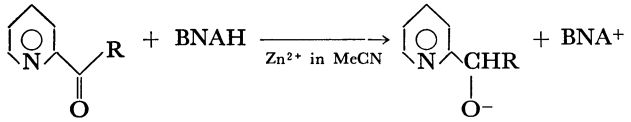
However, relative importance between a substrate–metal ion and BNAH–metal ion complexes has not been discussed yet and the role of metal ion has still remained ambiguous. In order to obtain further insight into relative importance of complexes, we studied kinetics for the reductions of 1-acetylisoquinoline (AQ), 1-benzoylisoquinoline (BQ), and isoquinoline-1-carbaldehyde (QCA) with BNAH in acetonitrile at 50 °C in the presence of zinc perchlorate, and the results were compared with those of the corresponding pyridine derivatives; AP, BP, and pyridine-2-carbaldehyde (PCA).



AQ; R=Me BNAH
BQ; R=Ph
QCA; R=H



(1)



AP; R=Me
BP; R=Ph
PCA; R=H

It is expected that 1-acylisoquinolines and 2-acylpyridines form complexes with zinc ion in a different manner because isoquinoline system has bulky B-ring which would distort the interaction with zinc ion, whereas pyridine system does not. On elucidation of the mechanism of reductions, the difference mentioned above may give a crucial information.

Results and Discussion

Complex Formation. AQ, BQ, QCA, and PCA form complexes with zinc ion. The complexation constant, K_S, defined by Eq. 2

$$S + M \overset{K_S}{\rightleftharpoons} SM \qquad (2)$$

S; a substrate, M; zinc ion

was determined in acetonitrile at 50 °C spectrophotometrically[4] for each substrate and the results are summarized in Table 1 together with those of AP and BP.[1,5] It is known that the complexation constant for BNAH, K_B, defined by Eq. 3 is 500 M^{-1} under the same conditions.[1,5]

$$B + M \overset{K_B}{\rightleftharpoons} BM \qquad (3)$$

B; BNAH, M; zinc ion

It has been reported that the pyridine-ring nitrogen and carbonyl oxygen in 2-acylpyridines are oriented in *E* each other in liquid phase.[6] 1-Acylisoquinolines are also expected to have similar conformations. When the isoquinoline-ring nitrogen is oriented in *Z* to the carbonyl oxygen, a large steric repulsion arises between the isoquinoline-B-ring and the R group except for QCA. Examination with CPK molecular models indicates that AP and BP have small repulsion in their *Z* conformers and the magnitude of this repulsion is slightly larger in BP than in AP. It is important that increasing order of repulsion forces (PCA≃QCA≪AP<BP≪BQ<AQ) are just in agreement with decreasing order of the complexation constants. That is, the more stable the *Z*-conformer, the more stable

Table 1. Complexation constant, K_S

Substituent	K_S, M^{-1}	
	Pyridine	Isoquinoline
H	1900	1800
Ph	200[a)]	50
Me	500[a)]	30

a) See Refs. 1 and 5 for detail.

the corresponding complex with zinc ion, which may lead to the conclusion that the complexation demands the *Z*-conformation for the carbonyl compound. The conclusion is also supported by spectroscopic investigations.[7,8] Thus, the distortion angle between the planes of carbonyl group and heterocyclic ring in the complexed substrate increases in the order; PCA≃QCA< AP≲BP<BQ≲AQ. CPK molecular models predict that the angle in PCA-complex is about 0° and that in AQ-complex is nearly 90°.

Kinetics. Pseudo-first-order kinetics at 50 °C in acetonitrile was followed spectrophotometrically by observing the decrease in the intensity of absorption from BNAH at 360 nm unless otherwise indicated in Experimental Section. Each run gave a good first-order relationship (correlation coefficient; $r>0.999$) for more than at least two half-lives. Rate constant for zinc ion-catalyzed auto-decomposition of BNAH (6.94×10^{-5} s^{-1}) was small enough to be neglected.[1] Observed first-order rate constants at appropriate concentrations of reagents are summarized in Tables 2—5.

Similarly to the previous procedure,[1] we obtain a kinetic expression shown in Eqs. 4 and 5 for the present reaction (Eq. 6).

$$k_{obsd}[B]_T = k^H[B][S][M], \quad (4)$$

$$k^H = k_1K_B + k_2K_S, \quad (5)$$

Table 2. Reduction of 1-acetylisoquinoline (AQ)

$[AQ]_T$ $\times10^3$, M	$[Zn^{2+}]_T$ $\times10^3$, M	$[BNAH]_T$ $\times10^4$, M	k_{obsd} $\times10^4$, s^{-1}
1.98	0.401	0.990	1.73
1.98	0.603	0.990	2.01
1.98	1.00	0.990	2.63
1.98	2.01	0.990	4.39
1.98	3.11	1.00	4.74
1.98	4.02	0.990	6.10
2.02	0.601	0.970[a]	0.909
2.02	1.03	0.970[a]	1.37
2.02	2.05	0.970[a]	1.84
2.02	3.00	0.970[a]	1.92

a) BNAH-4,4-d_2 was used.

Table 3. Reduction of 1-benzoylisoquinoline (BQ)

$[BQ]_T$ $\times10^3$, M	$[Zn^{2+}]_T$ $\times10^3$, M	$[BNAH]_T$ $\times10^4$, M	k_{obsd} $\times10^4$, s^{-1}
1.99	1.01	1.02	4.64
1.99	2.01	1.02	7.12
1.99	3.02	1.02	8.15
1.99	5.04	1.02	9.19
1.98	6.22	1.02	9.09
1.98	7.76	1.02	9.51
1.99	10.1	1.02	9.15
1.99	12.1	1.02	8.71
1.99	15.1	1.02	8.48
1.99	5.01	0.970[a]	3.17
1.99	8.01	0.970[a]	3.28
1.99	10.0	0.970[a]	3.36
1.99	15.0	0.970[a]	3.11

a) BNAH-4,4-d_2 was used.

$$\left.\begin{matrix} BM + S \xrightarrow{k_1} \\ SM + B \xrightarrow{k_2} \end{matrix}\right\} \text{products}, \quad (6)$$

where B, S, and M denote BNAH, a substrate, and zinc ion, respectively, and the subscript T means stoichiometric concentration. Computor-assisted analysis of kinetic data[1] gave numerical value of k^H as listed in Table 6.

Although k^H's are composite constants, there is no doubt that their relative magnitudes are in the same order as those of rate-constants for rate-determining

Table 4. Reduction of isoquinoline-1-carbaldehyde (QCA)

$[QCA]_T$ $\times10^3$, M	$[Zn^{2+}]_T$ $\times10^3$, M	$[BNAH]_T$ $\times10^4$, M	k_{obsd} $\times10$, s^{-1}
1.99	0.501	1.03	4.46
2.00	1.00	1.03	4.78
1.99	1.50	1.03	5.42
2.00	2.00	1.03	6.19
1.99	2.51	1.03	6.40
2.00	3.01	1.03	5.88
1.99	3.99	1.03	6.11
2.00	4.51	1.03	5.59
1.99	4.99	1.03	4.63
1.99	5.98	1.03	4.19

Table 5. Reduction of pyridine-2-carbaldehyde (PCA)

$[PCA]_T$ $\times10^2$, M	$[Zn^{2+}]_T$ $\times10^2$, M	$[BNAH]_T$ $\times10^4$, M	k_{obsd} $\times10$, s^{-1}
1.00	0.204	1.01	4.95
1.00	0.297	1.01	5.14
1.00	0.306	1.01	3.91
1.00	0.503	1.01	6.13
1.00	0.621	1.01	7.57
1.01	0.689	0.980	7.41
1.00	0.836	0.980	7.16
1.01	1.19	0.980	5.78
1.00	1.50	1.01	4.55
1.00	1.52	0.980	4.19
1.00	2.01	0.980	3.05
1.00	2.03	1.01	3.84
1.00	2.54	1.01	2.65

Table 6. Computed third-order rate constant, k^H

Substituent	k^H, M^{-2} s^{-1}		Ratio[b]
	Pyridine[a]	Isoquinoline[a]	
H	3.32×10^5	1.33×10^6	4.01
	(1.72×10^4)	(6.89×10^4)	
Ph	2.37×10^2 [c]	4.05×10^2	1.71
	(1.22×10)	(2.10×10)	
Me	1.93×10[c]	2.25×10^2	11.7
	(1.00)	(1.17×10)	

a) Numbers in parentheses are relative values. b) Ratio of k^H for a 1-acylisoquinoline to that for the corresponding 2-acylpyridine. c) Data reported in Ref. 1.

proton (or hydrogen atom) transfer from BNAH to the substrates. Namely, the reduction is associated by large kinetic deuterium isotope effect, whereas no deuterium isotope effect is observed on complexation constant, as will be descibed below in detail. Variation in complexation constants is much smaller than that in rate constants, which means that relative magnitude of k^H is determined mainly by kinetic term.

Isotope Effects. Kinetics were also followed with BNAH-4,4-d_2 to obtain rate constants, k^D. Thus calculated deuterium isotope effects, k^H/k^D, are listed in Table 7. Reproducibility of two or three experiments was satisfactory. Errors in rate constants for PCA and QCA were, however, too large to obtain precise kinetic isotope effects. In Table 7 product isotope effect, Y^H/Y^D, for AP and AQ are also listed. The product isotope effect is defined as the ratio of isotope content at the particular position of the product alcohol obtained by the reduction with BNAH-4-*d*. For the other substrates, Y^H/Y^D could not be obtained because of thermal unstability of the corresponding alcohols on VPC. Y^H/Y^D's in the reduction with an NAD(P)H-model compound have been reported to be larger than 3.0 for many substrates.[9-14] The results indicate clearly that a hydrogen nucleus is transferred from BNAH to a substrate in the rate-determining step of the reduction.

Table 7. Kinetic and product isotope effects

Substituent	Pyridine		Isoquinoline	
	k^H/k^D	Y^H/Y^D	k^H/k^D	Y^H/Y^D
H	—	—	—	—
Ph	3.28[a)]	—	2.79	—
Me	3.21[a)]	3.2	2.45	3—5

a) Data from Ref. 1.

It should be noted that k^H/k^D's are appreciably smaller than Y^H/Y^D's for AQ and BQ, whereas both isotope effects are identical for AP and BP. The discrepancy between k^H/k^D and Y^H/Y^D reveals the existence of at least one intermediate prior to the rate-determining step of the reduction.

Reactivity of the Substrates. For certain substrates it has been established that the reduction proceeds through transfer of an electron, a proton, and an electron (or an electron and a hydrogen atom) in this order.[9,15-17] Therefore, the present reduction can also be proposed to proceed similarly, on the basis of the results described above.[18] That is, the facility of a substrate toward the reduction can be substituted by the stability of substrate-originated anion-radical counterpart of the radical-ion pair intermediate, becasue the cation-radical counterpart originates from BNAH and is common to all reductions.

It has been established that zinc ion catalyzes the initial electron-transfer process.[10,17] Zinc ion would also contribute to stabilize the anion radical by neutralizing the negative charge. Such stabilization is expected to be the largest in the anion radicals formed from PCA and QCA, because these substrates can interact with zinc ion most effectively as indicated by large complexation constants. The effect of zinc ion on the stabilities of anion radicals from AP and BP are expected to be a little smaller but still significant. On the other hand, anion radicals from AQ and BQ are supposed to be much less stabilized by zinc ion, because the interaction of AQ or BQ with zinc ion forces to distort stable conformations of these substrates as discussed in the previous section.

However, contribution of an aryl group to the stability of anion radicals should also be taken into consideration. Since the plane of benzene ring in the BQ–Zn^{2+} complex can be coplanar with the plane of carbonyl group where negative charge of the anion radical appears mainly, the benzene ring can delocalize the negative charge and contribute to the stability of anion radical. It should be noted that the negative charge on anion radicals of AP, BP, PCA, and QCA can also delocalize into pyridyl or isoquinolyl moiety. Since the distorted AQ-complex has no moiety that can delocalize the negative charge, no factor is pointed out at all to stabilize the corresponding anion radical. Consequently, stability of the radical-ion pair intermediate will increase in the order: AQ<BQ<BP<AP<PCA$\simeq$QCA as a result of participation of substituent and zinc ion.

On the other hand, ratios of k^H's listed in Table 6 indicate that the value for AQ *vs.* AP is much larger than those for other substrates. The large ratio should be accounted for by unexpectedly high reactivity of AQ against other substrates, becasue the similarity of structures of 2-acylpyridine complexes cannot predict the low reactivity only for AP.

It has been predicted that an unstable radical-ion pair intermediate requires higher free energy of transition for the electron-transfer step than that for the proton (or hydrogen atom)transfer step resulting in large discrepancy between k^H/k^D and Y^H/Y^D.[10] The present result agrees with this prediction. That is, the most unstable AQ-complex is associated by the largest discrepancy.

Conclusion. From the above discussion, it may be concluded that factors which govern the facility for complexation and for reduction are independent. Rather, a corbonyl group which weakly coordinates onto metal ion has large reactivity toward the reduction within a limited framework of substrate structure. In other words, strong coordination of a metal ion onto the reaction site of a substrate facilitates the complexation but interferes the reduction. This is in contrast to the idea previously proposed; a substrate is activated by metal ion upon the coordination onto the reaction site.[2,3,19-21]

Experimental

Materials. Acetonitrile was distilled three times on phosphorus pentaoxide and once on potassium carbonate, then kept in a bottle filled by dry argon and capped by a silicone-rubber stopper. 2-Acetylpyridine (AP; bp 95 °C/34 mmHg), 2-benzoylpyridine (BP; mp 42—44 °C), pyridine-2-carbaldehyde (PCA; bp 75 °C/22 mmHg), and zinc perchlorate were commercially available (Nakarai Chem. Co. and Merck & Co., Inc.). These acylpyridines were purified

by recrystallization or distillation prior to the use. Zinc perchlorate was dried at 120 °C *in vacuo* for 15 h and kept in a desiccator over calcium chloride.

1-Benzyl-1,4-dihydronicotinamide (BNAH),[14] BNAH-4-*d*, BNAH-4,4-d_2,[10] 1-acetylisoquinoline (AQ; purified by column chromatography),[22] 1-benzoylisoquinoline (BQ; mp 74.5—75 °C),[22] and isoquinoline-1-carbaldehyde (QCA; mp 53—54 °C)[23] were prepared according to literature procedures. Deuterium contents in BNAH-4-*d* and BNAH-4,4-d_2 were 99.0±1.0% for both.

Product Analysis. Each 1 mmol of a substrate, BNAH, and zinc perchlorate was dissolved into 10 ml of acetonitrile, and the solution was kept at 50 °C for 1 d under nitrogen atmosphere in the dark. An aqueous EDTA was added to this mixture and the product was extracted with dichloromethane. The organic layer was concentrated *in vacuo*. After the purification on column chromatography, the product was identified to be the corresponding alcohol by NMR and IR spectra. The spectra were identical to those of authentic samples. Other products except for the pyridinium salt were not detected on TLC and NMR. The yields of the isolated products were 60—70%.

In the case of QCA, the product alcohol was not stable under the air and could not be isolated. The quantitative production of the corresponding alcohol, however, was confirmed on VPC.

Complexation Constant. A series of acetonitrile solutions containing zinc perchlorate, the concentrations of which varied from 20 to 200 times excess against appropriate concentration of the substrate, were prepared. Each solution was placed in a UV-cell (1 cm) equipped with a silicone-rubber stopper, and the cell was kept for at least 5 min in the cell-compartment of a Union Giken SM-401 Spectrophotometer which was kept at 50.0±0.1 °C. The reference cell was filled with acetonitrile. The substrate in acetonitrile was added to the sample cell, then the spectrum was recorded. Reproducibility was satisfactory for each run.

Kinetics. For AQ and BQ, an acetonitrile solution for kinetics was prepared and placed in a UV-cell (1 cm) equipped with a silicone-rubber stopper. Kinetics was followed spectrophotometrically with a Union Giken SM-401 Spectrophotometer, the cell-compartment of which was kept at 50.0±0.1 °C. The reference cell was filled with acetonitrile, then BNAH in acetonitrile was added to the sample cell. It was confirmed that the order of incubation of reagents did not affect the kinetics.

For PCA and QCA, the reaction was so rapid that stopped-flow method was employed on a Union Giken RA-401 Rapid Reaction Analyzer equipped by a Union Giken Kinetic Data Processer System 71. An acetonitrile solution of a substrate containing zinc perchlorate and that of BNAH were placed in two reservoirs separately. The reservoirs and UV-cell were kept at 50.0±0.1 °C under argon atmosphere. After a few minutes of incubation, both solutions were mixed and the reaction was followed spectrophotometrically.

Since the solution of substrate including a high concentration of zinc perchlorate had an absorption near 360 nm, the decrease in the intensity of the absorption from BNAH was monitored at longer wavelength (370—400 nm).

Product Isotope Effect. A product obtained by the reduction with BNAH-4-*d* was analyzed for deuterium contents by mass spectrometry on a Shimadzu LKB-9000S GC-MS Spectrometer equipped with a PACK 300DG-b Computing System and areas of appropriate peaks were measured.

Spectroscopy. NMR spectra were recorded on a Varian T-60 Spectrometer or a JASCO JNM-FX 100 FT NMR Spectrometer. IR spectra were obtained with a Hitachi EPI-S2 Spectrometer.

Correlation of Physical Units. Physical units used in this report are correlated with SI-units by the following relationship.

1 M=1 mol dm^{-3}, t/°C=T/K−273.15,

p mmHg=13.5951×980.665×10^{-2} p Pa.

References

1) A. Ohno, S. Yasui, R. A. Gase, S. Oka, and U. K. Pandit, *Bioorg. Chem.*, in press.

2) R. A. Gase, G. Boxhoorn, and U. K. Pandit, *Tetrahedron Lett.*, **1976**, 2889.

3) M. Hughes and R. H. Prince, *J. Inorg. Nucl. Chem.*, **40**, 703 (1978).

4) D. J. Creighton, J. Hajdu, and D. S. Sigman, *J. Am. Chem. Soc.*, **98**, 4619 (1976).

5) These compounds form complexes of two different types, SM and S_2M. Only first complexation constants, K_{S1}, are listed in Table 1. See Ref. 1 for detail.

6) J. Barassin, G. Queguiner, and H. Lumbroso, *Bull. Soc. Chim., Fr.*, **1967**, 4707.

7) a) Y. Kidani, M. Noji, and H. Koike, *Bull. Chem. Soc. Jpn.*, **48**, 239 (1975); b) R. R. Osborn and W. R. McWhinnie, *J. Chem. Soc., A*, **1967**, 2075.

8) a) R. A. Gase and U. K. Pandit, *J. Am. Chem. Soc.*, **101**, 7059 (1979); b) R. A. Gase, Ph. D. Thesis, Uiniv. of Amsterdam, Amsterdam, The Netherlands (1979).

9) A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi, *Chem. Lett.*, **1978**, 65.

10) A. Ohno, S. Yasui, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, **51**, 294 (1978).

11) J. Hajdu and D. S. Sigman, *J. Am. Chem. Soc.*, **98**, 6060 (1976).

12) J. J. Steffens and D. M. Chipman, *J. Am. Chem. Soc.*, **93**, 6694 (1971).

13) R. H. Abels, R. F. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957).

14) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955).

15) E. M. Kosower, A. Teuerstein, H. D. Burrows, and A. J. Swallow, *J. Am. Chem. Soc.*, **100**, 5185 (1978).

16) a) Y. Ohnishi and A. Ohno, *Chem. Lett.*, **1976**, 697; b) N. Kito, Y. Ohnishi, M. Kagami, and A. Ohno, *ibid.*, **1974**, 353; c) A. Ohno and N. Kito, *ibid.*, **1972**, 369.

17) A. Ohno, H. Yamamoto, T. Shio, and S. Oka, unpublished results which will be submitted elsewhere.

18) *Cf.* also D. J. Creighton, J. Hajdu, G. Mooser, and D. S. Sigman, *J. Am. Chem. Soc.*, **95**, 6855 (1973).

19) M. Hughes and R. H. Prince, *Chem. Ind. (London)*, **1975**, 648.

20) S. Shinkai and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 8258 (1972).

21) D. J. Creighton and D. S. Sigman, *J. Am. Chem. Soc.*, **93**, 6314 (1971).

22) A. Kaufmann, P. Dändliker, and H. Burkharodt, *Ber.*, **46**, 2934 (1913).

23) R. S. Barrows and H. G. Lindeall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).