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Reduction by a Model of NAD(P)H. 28. Reduction of an α-Diketone in the Presence of Zinc Ion

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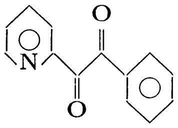
Reduction of 1-phenyl-2-(2-pyridyl)-1,2-ethanedione with 1-benzyl-1,4-dihydronicotinamide in acetonitrile in the presence of zinc perchlorate has been studied. The α-diketone coordinates onto zinc ion through its pyridine-ring nitrogen and benzene-side carbonyl oxygen, whereas the reduction takes place on pyridine-side carbonyl group. It is concluded that an effective ligand to a metal ion is not necessarily a facile substrate of the reduction.

Approaches to elucidate the role of bivalent metal ion in the reduction with an NAD(P)H-model compound have been tried from many aspects.[1–6] In the preceding paper, it was claimed that an effective ligand to a metal ion is not necessarily a facile substrate of the reduction with an NAD(P)H-model compound.[7]

An α-diketone, 1-phenyl-2-(2-pyridyl)-1,2-ethandione (**1**), has two carbonyl groups and can be regarded either as 2-benzoylpyridine (**2**) analog or as methyl benzoylformate (**3**) analog, both of which have been known to be good substrates for metal ion-catalyzed reduction with an NAD(P)H-model compound.[4,5] Therefore, an interest is focused to the point whether **1** acts like **2** or **3** in the metal ion-catalyzed reduction. Note that **2** forms a complex with bivalent metal ion in a considerable amount,[8,9] whereas **3** interacts little with metal ion.[4] In this connection it is interesting to reveal which carbonyl group in **1** is subjected to the reduction and what factor governs the selectivity.



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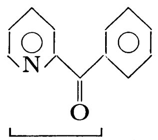

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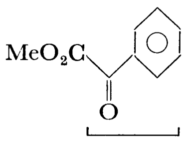

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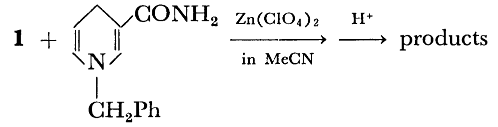
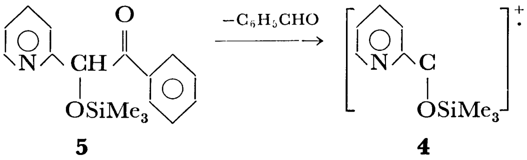
Results and Discussion

Product Analysis. The reaction of **1** with equimolar amount of 1-benzyl-1,4-dihydronicotinamide (BNAH) in the presence of equimolar amount of zinc perchlorate in acetonitrile at 50 °C for 1 h (Eq. 1) afforded a single product besides 1-benzyl-3-carbamoylpyridinium ion (BNA⁺). Unfortunately, however, this product was very unstable under the air. During the procedure to isolate the product from the reaction mixture on preparative TLC, the product was converted smoothly into the starting material **1**. Therefore, the structure of the product was elucidated after protecting the hydroxyl group in the product by trimethylsilylation.



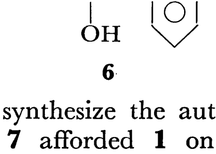
(1)

After treatment of the reaction mixture with 1,1,1,3,3,3-hexamethyldisilazane (HMDS), gas-phase chromatography-mass spectroscopy (GC-MS) gave a fragment at $m/e=179$, which could be assigned to the ion **4** suggesting the structure **5** for the trimethylsilylated product. Consequently, the product from the reduction of **1** with BNAH was identified to be 2-hydroxy-1-phenyl-2-(2-pyridyl)ethanone, **6**. NMR spectrum of the product also confirmed the structure.



5 **4**

(2)



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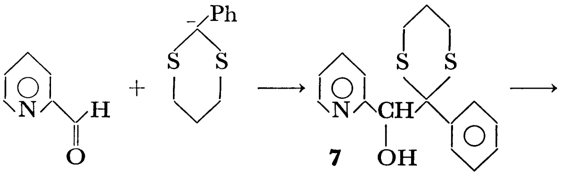
An attempt to synthesize the authentic **6** ended in failure. Instead, **7** afforded **1** on hydrolysis. This observation supports the fact that **6** is oxidized to **1** quite easily. When **1** was allowed to react for 22 h with three equivalences of BNAH in the presence of zinc ion in acetonitrile at 50 °C, the product obtained in poor yield was a mixture of *threo*- and *erythro*-diastereoisomers of 1-phenyl-2-(2-pyridyl)-1,2-ethanediol, **8**.



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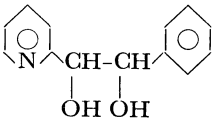

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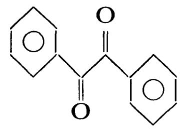
Complexation with Zinc Ion. Complexation of **1** with zinc ion was noted spectrophotometrically. A double reciprocal plot of the stoichiometric concentration of zinc ion present in a solution against the change in absorbance of the solution at 292 nm showed a straight line (correlation coefficient; $r>0.999$), indicating that the complexation obeys Eq. 4;

$$S + M \overset{K_S}{\rightleftharpoons} SM \tag{4}$$

where S and M denote **1** and zinc ion, respectively. The complexation constant, K_S, at 25 °C in acetonitrile was given to be 65 M^{-1} by dividing the intercept with the slope of the straight line.[7] Spectrometry was performed with stoichiometric concentrations of **1** and zinc perchlorate to be 2.87×10^{-5} M and (0.26—1.51)$\times10^{-2}$ M, respectively.

On the other hand, benzil, **9**, showed no change



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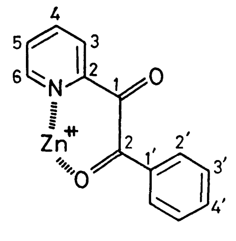
in spectrum even upon the addition of large excess of zinc perchlorate, which indicates that there is little interaction, if any, between **9** and zinc ion. This fact may reveal that a ring nitrogen is prerequisite to the complexation, and may rule out the possibility of bidentate complexation through two carbonyl oxygens.

To elucidate the structure of **1**–zinc ion complex, ^{1}H- and ^{13}C-NMR studies were carried out. Table 1 shows metal ion-induced shifts in ^{1}H- and ^{13}C-NMR spectra of **1** on addition of lithium, magnesium, and zinc perchlorates in CD_3CN. The fact that the shifts induced by lithium ion are the smallest among those induced by three different metal ions can be compared with the previously reported result that both chemical and optical yields in lithium ion-catalyzed reduction of **3** with a chiral NAD(P)H-model compound are remarkably lower than those catalyzed by magnesium or zinc ion.[10,11] Since ionic radii of lithium and magnesium ions are approximately the same,[12] the result indicates that the complexation depends largely on the charge density on the metal ion.

In Table 2, a comparison between zinc ion-induced maximum shifts for **1** and **2** is listed. It should be noted that the shifts of both pyridine-ring and benzene-ring carbons in **1** have similar values to those in **2**. This fact suggests that magnetic environments of pyridine and benzene rings in **1**–zinc ion complex resemble to those in **2**–zinc ion complex, inferring that the carbonyl group in **2**–zinc ion complex corresponds to the benzene-side carbonyl group in **1**–zinc ion complex. Recall that **2** coordinates bidentately onto zinc ion through pyridine-ring nitrogen and carbonyl oxygen.[7] Since **1** cannot behave as a tridentate ligand due to its structural requirement, it is reasonable to conclude that **1** coordinates onto zinc ion bidentately through pyridine ring and benzene-side carbonyl oxygen, **10**.



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Although the sign in shifts of signals from carbonyl carbons are reversed in **1** and **2**, it is important that the shift of signal from benzene-side carbonyl carbon is larger than that from pyridine-side carbonyl carbon.[13]

Table 1. Metal ion-induced shifts ($\Delta\delta$) in ^{13}C- and ^{1}H-NMR spectra of 1-phenyl-2-(2-pyridyl)-1,2-ethanedione (1) on the addition of $M(ClO_4)_n$ in CD_3CN[a,b,c)]
$\Delta\delta=\delta_{complexed}-\delta_{free}$

M^{n+}	Li^+	Mg^{2+}	Zn^{2+}
C=O-1	−0.63	−1.40	−3.80
C=O-2	−0.52	−3.99	−7.16
C-2	−1.04	−4.45	−9.44
C-3	+0.14	+3.36	+7.59
C-4	−0.22	+1.35	+4.06
C-5	−0.35	+0.70	+2.93
C-6	−0.34	−0.35	−0.11
C-1′	−0.81	−1.87	−2.22
C-2′	−0.05	−0.12	+0.95
C-3′	−0.35	−0.29	−0.39
C-4′	−0.17	+0.24	+1.06
H-3,4,5	0.0	+0.1	+0.15—0.25
H-6	+0.05	+0.26	+0.46
Ph-H	0.0	+0.1—0.2	+0.15—0.20

a) In ppm. b) [**1**] = 0.4 M, $[M^{n+}]$ = 2.0 M. c) Corrected by considering the shift of $\overset{*}{C}N$ in CD_3CN ($\Delta\delta$ = +0.52 for Li^+, +0.88 for Mg^{2+}, and +0.64 for Zn^{2+}).

Table 2. Comparison of maximum metal ion-induced shifts ($\Delta\delta$) in ^{13}C-NMR spectra of 1-phenyl-2-(2-pyridyl)-1,2-ethanedione (1) and 2-benzoylpyridine (2) on the addition of $Zn(ClO_4)_2$ in CD_3CN[a)]
$\Delta\delta=\delta_{complexed}-\delta_{free}$

Position	**1**[b,c)]	**2**[d)]
C=O-1	−3.80	+2.8
C=O-2	−7.16	—
C-2	−9.44	−9.9
C-3	+7.59	+7.2
C-4	+4.06	+5.1
C-5	+2.93	+2.7
C-6	−0.11	+1.7
C-1′	−2.22	−3.0
C-2′	+0.95	+1.0
C-3′	−0.39	+0.2
C-4′	+1.06	+2.4

a) In ppm. b) [**1**] = 0.4 M, $[Zn^{2+}]$ = 2.0 M. c) Corrected by considering the shift of $\overset{*}{C}N$ in CD_3CN ($\Delta\delta$ = +0.64 ppm). d) [**2**] = 1.67 M, $[Zn^{2+}]$ = 1.50 M. Ref. 8.

It is interesting to point out that **1**–zinc ion complex prefer a six-membered ring structure. Although distorted octahedral geometry has been proposed for a certain pyridine derivative–zinc perchlorate complex,[14,15] the structure of 2-cinnamoylpyridine–zinc ion complex has been determined to be tetrahedral.[16,17] The six-membered ring structure presently proposed for **1**–zinc ion complex may be in accordance with tetrahedral structure, because six-membered ring is less strained in tetrahedral structure than in octahedral one.

Kinetics. Pseudo-first-order kinetics at 25 °C in acetonitrile was followed spectrophotometrically by observing the decrease in the intensity of absorption from BNAH at 370 nm. Each run gave a good first-

Table 3. Reduction of 1-phenyl-2-(2-pyridyl)-1,2-ethanedione (**1**) in acetonitrile at 25 °C

$10^3[\mathbf{1}]_\mathrm{T}$ M	$10^3[\mathrm{Zn}^{2+}]_\mathrm{T}$ M	$10^4[\mathrm{BNAH}]_\mathrm{T}$ M	$10\,k_\mathrm{obsd}$ s^{-1}
1.99	1.00	1.01	0.281
1.99	2.00	1.01	0.446
1.99	4.00	1.01	0.566
1.99	6.00	1.01	0.585
1.99	10.1	1.01	0.549
1.99	15.3	1.01	0.465
1.99	20.8	1.01	0.414
8.01	0.412	2.00	0.765
8.09	0.824	2.00	1.18
8.01	1.64	2.00	1.64
7.91	3.30	2.00	1.18
8.06	4.94	2.00	2.13
7.87	8.02	2.00	2.38
7.87	12.2	2.00	2.37
7.98	16.3	2.00	2.02
7.98	20.1	2.00	1.83
7.98	28.1	2.00	1.43
7.98	36.1	2.00	1.33

order relationship (correlation coefficient; $r > 0.999$) for more than at least two half-lives. The results are listed in Table 3. Obviously, the rate constant-zinc ion concentration profile has a maximum similarly to those of **2** and other 2-acylpyridines.[1,7)] Computer-assisted simulation of the profile gave a numerical value for a constant $k_1K_\mathrm{B}+k_2K_\mathrm{S}$ to be $2.65\times10^4\ \mathrm{M}^{-2}\ \mathrm{s}^{-1}$,[1)] where K_B, k_1, and k_2 are defined by Eqs. 5 and 6;

$$\mathrm{B} + \mathrm{M} \overset{K_\mathrm{B}}{\rightleftharpoons} \mathrm{BM} \tag{5}$$

$$\left.\begin{array}{l} \mathrm{BM} + \mathrm{S} \xrightarrow{k_1} \\ \mathrm{SM} + \mathrm{B} \xrightarrow{k_2} \end{array}\right\} \text{products} \tag{6}$$

and B, S, and M denote BNAH, **1**, and zinc ion, respectively.

Role of Zinc Ion. Both kinetics and reaction site indicate that **1** behaves like **2** rather than like **3**. More striking fact revealed by the present study is that the carbonyl group which coordinates onto zinc ion is different from the one subjected to the reduction. Although reasonable explanation for this fact has not been given yet, stereochemical requirement for the carbonyl groups at the transition state should be taken into account as one of controlling factors.[18)] 2-Cinnamoylpyridine is an example of a substrate where the reaction and coordination sites are different each other.[16)] However, since these positions are conjugated, the result from 2-cinnamoylpyridine is not surprising.

Conjugation of two carbonyl groups in **1** is not efficient, because a canonical form with a positive charge on an oxygen is unstable. Therefore, **1** may be the first example of a substrate which has different reaction site from the coordination site. In addition, a comparison of calculated rate constants for rate-determining proton (or hydrogen atom)-transfer step shows that non-coordinated carbonyl group in **1** has larger reactivity than coordinated carbonyl group in **2**.

The present result confirms the idea that an effective ligand to a bivalent metal ion is not necessarily a facile substrate of the reduction with an NAD(P)H-model compound.

It seems likely that zinc ion plays a role to enhance the encounter of a model compound and substrate by coordinating onto both reagents. Another role of zinc ion is to catalyze the initial electron-transfer step,[19)] but it interferes the following transfer of a proton (or hydrogen atom).

Experimental

1-Phenyl-2-(2-pyridyl)-1,2-ethanedione, **1** (mp; 70.5—71 °C), was prepared according to a literature procedure.[20,21)] Other materials were obtained and purified as described in the preceding paper.[7)] Procedures for determining rate and complexation constants were also described in the preceding paper.[7)]

Product Analysis. A solution of 6.3 mg (0.030 mmol) of **1**, 6.7 mg (0.031 mmol) of BNAH, and 9.0 mg (0.034 mmol) of zinc perchlorate in 0.5 ml of acetonitrile was allowed to react at 50 °C under nitrogen atmosphere in the dark for 1 h. A 10 μl aliquot was mixed with 10 μl of 1,1,1,3,3,3-hexamethyldisilazane (HMDS), then the mixture was analyzed on a Shimadzu LKB-9000S GC-MS Spectrometer equipped with a PACK 300DG-b Computing System. Reproducibility from three times experiments was satisfactory.

The mass spectrum obtained showed a fragment at $m/e=179$ with fragments of small intensities at $m/e=180$ and 181. Such a fragmentation pattern is common to moieties that contain a silicon atom.[22)] Therefore, this fragment was assigned to the cation radical **4**. Other fragments appeared at $m/e=135$, 105, and 77.

The production of 1-phenyl-2-(2-pyridyl)-1,2-ethanediol, **8**, from **1** on the reduction with BNAH was confirmed as following: a solution of 52.7 mg (0.250 mmol) of **1**, 159.9 mg (0.747 mmol) of BNAH, and 69.2 mg (0.262 mmol) of zinc perchlorate in 10 ml of acetonitrile was allowed to react at 50 °C under nitrogen atmosphere in the dark. After 22 h, complete consumption of **1** was confirmed on TLC. Then, aqueous sodium carbonate was added to the solution and the mixture was extracted three times with benzene. The organic layer was washed once with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* remaining 150 mg of solids. The solids were separated into four fractions on preparative TLC with ethyl acetate as an eluent. A NMR spectrum of each product was recorded. The first product (with the largest R_f-value) was identified to be **1** generated during the procedure of isolation (15 mg; 28% yield). The structure of the third product was determined as **8** based on comparison of its NMR spectrum with that of the authentic sample (*ca.* 5 mg; 10% yield). Unfortunately, the second (17 mg) and the fourth (10 mg) products could not be identified.

NMR Spectroscopy. Proton and carbon-13 NMR studies were carried out in $\mathrm{CD_3CN}$. The concentration of **1** employed was 0.4 M for each run.[23)]

The signals in ^{13}C-NMR spectrum of **1** were assigned as following: in the proton-decoupled spectrum, four signals at 134.03, 152.23, 196.73, and 197.56 ppm had low intensities. Moreover, these four signals did not split in the off-resonance spectrum, then these are attributed to C-2, C-1′, C=O-1, and C=O-2 carbons. By comparing with the chemical shifts of 2-benzoylpyridine, **2**, the signals at 134.03 and

152.23 ppm could easily be assigned to C-1′ and C-2 carbons, respectively.[8] In the non-decoupled spectrum of **1**, the signal at 197.56 ppm showed more complex coupling pattern than the signal at 196.73 ppm, indicating that the signal at 197.56 ppm was attributable to C=O-2 carbon. Long-range coupling of C=O-1 carbon with four protons on the pyridine ring would be simpler than that of C=O-2 carbon with five protons on the benzene ring. Other signals could be assigned on the basis of comparison with those of **2**,[8] benzophenone,[24] and benzil, **9**.[25]

Correlation of Physical Unit. A unit used for temperature is correlated with the SI-unit by the following equation

$$t/°\mathrm{C} = T/\mathrm{K} - 273.15.$$

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