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Redox-Photosensitized Reactions. XV.1) Photosensitized and Direct Photolytic Isomerizations of the Tetrahydro Dimers of 1-Benzylnicotinamide

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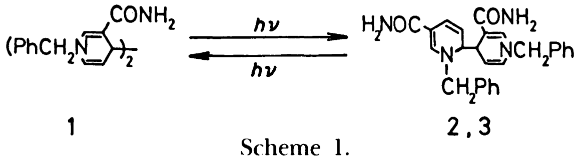
The photosensitization by either [ReBr(bpy)(CO)$_3$] or [Ru(bpy)$_3$]$^{2+}$ (bpy=2,2′-bipyridine) resulted in the isomerization of 1,1′-dibenzyl-1,1′,4,4′-tetrahydro-4,4′-binicotinamide (**1**) and 1,1′-dibenzyl-1,1′,4,6′-tetrahydro-4,6′-binicotinamide (**2**) to give a common mixture of **1**, **2**, and the diastereoisomer of **2** (**3**) in a 2:2:1 ratio at a photostationary state, while either direct photoexcitation or thermal activation effected only the isomerization of **2** to **1** but not at all the retro isomerization.

The pyridine nucleotide coenzymes (NAD(P)$^+$/NAD(P)H) reveal unique redox capabilities of undergoing specific transfer of a hydride equivalent (or two electrons) with a variety of substrates.2) However, one-electron redox reactions can also very often occur with the coenzymes in the absence of oxido-reduction enzymes and particularly with their models in homogeneous solution, giving the corresponding tetrahydrobipyridines (NAD$_2$)3—7) which are considered to be dead-end products incapable of undergoing two-electron redox reactions. Therefore, little has been investigated on chemical properties of NAD$_2$.

Nevertheless, it is certainly of chemical significance to explore chemistry of NAD$_2$ because of the unique dihydropyridyl structures and because of potential electron-donating nature. From this point of view, we have investigated chemical behaviors of NAD$_2$ using 1,1′-dibenzyltetrahydrobinicotinamides (**1**—**3**) which are selectively formed either by one-electron reduction of 1-benzylnicotinamide (BNA$^+$), a typical NAD$^+$ model, or by one-electron oxidation of 1-benzyl-1,4-dihydronicotinamide (BNAH), a typical NADH model. This paper deals with photochemical isomerizations of the 1,1′-dibenzyl-1,1′,4,4′-tetrahydro-4,4′-binicotinamide (**1**) and the diastereomeric isomers of 1,1′-dibenzyl-1,1′,4,6′-tetrahydro-4,6′-binicotinamide (**2** and **3**) (Scheme 1).



Scheme 1.

Results and Discussion

The zinc reduction of 1-benzylnicotinamide gave a mixture of the corresponding tetrahydrobinicotinamides,3) from which one of the 4,4′-bonded diastereomers **1** and one of the 4,6′-bonded diastereomers **2** were obtained in purities enough for the present photochemical investigation, while another diastereomer of **2** (**3**) could be isolated only in a small amount. On the other hand, what appears to be the other isomer of **1**3) was able to be detected by HPLC but not isolated because of its minor formation and difficulties of the isolation. Therefore, we used **1** and **2** as the starting materials and *N*,*N*-dimethylformamide (DMF) as the solvent.

Irradiation of a deaerated solution of **1** (2.5 mM[†]) and [ReBr(bpy)(CO)$_3$] (0.8 mM) at 436 nm resulted in the isomerization of **1** to **2** and **3**, thus giving a 2:2:1 mixture of **1**, **2**, and **3** at a photostationary state (Fig. 1). The photosensitized isomerization of **2** to **1** and **3** again occurred to reach an identical photostationary state. Similarly, [Ru(bpy)$_3$]$^{2+}$ was effectively used as the photosensitizer for the isomerizations while the irradiation was carried at >470 nm. In all the runs, HPLC analyses showed the formation of a few common products in small amounts at retention times identical with those of the minor products in the zinc reduction of BNA$^+$.3) Table 1 summarizes the photostationary-state ratios of **1**, **2**, and **3**.

The efficient photosensitized isomerization of **1** to **2**

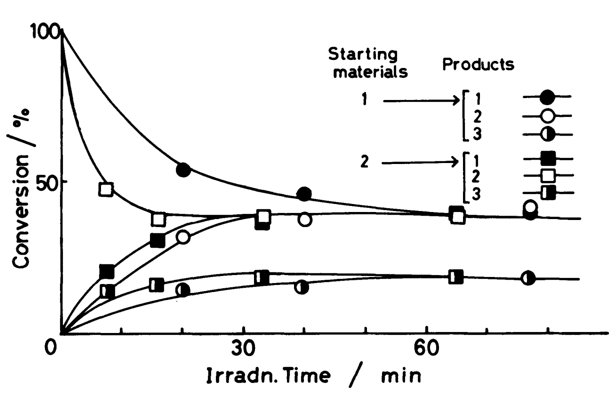


Fig. 1. Time-conversion plots for the [ReBr(bpy)(CO)$_3$]-photosensitized isomerization of **1** and **2** at 436 nm; [**1**] or [**2**]=2.5 mM and [[ReBr(bpy)(CO)$_3$]]=0.8 mM.

[†] 1 M=1 mol dm^{-3}.

Table 1. Photosensitized Isomerization of **1** and **2** by $[\mathrm{ReBr(bpy)(CO)_3}]$ and $[\mathrm{Ru(bpy)_3}]^{2+}$ a)

Starting Material	Sensitizer b)	Irradn. Time/min	Yield c)/%			$k_q\tau$ d) / $\mathrm{M^{-1}}$	k_q e) / $\mathrm{M^{-1}\,s^{-1}}$
			1	**2**	**3**		
1	$[\mathrm{ReBr(bpy)(CO)_3}]$	35	40	40	19	182	3.7×10^9
1	$[\mathrm{Ru(bpy)_3}]^{2+}$	90	25	28	12	1340	1.4×10^9
2	$[\mathrm{ReBr(bpy)(CO)_3}]$	35	36	39	18	571	1.2×10^{10}
2	$[\mathrm{Ru(bpy)_3}]^{2+}$	25	32	29	14	680	7.3×10^8

a) For deaerated DMF solutions containing **1** or **2** (2.5 mM) and the sensitizers (0.8 mM). b) Irradiated at 436 nm for the $[\mathrm{ReBr(bpy)(CO)_3}]$ runs and at >470 nm for the $[\mathrm{Ru(bpy)_3}]^{2+}$ runs. c) Based on the **1** or **2** used. d) Slopes of linear Stern–Volmer plots for quenching of the sensitizer-luminescence by **1** or **2** in deaerated DMF solutions at 20 °C. e) Calculated from the $k_q\tau$ values in DMF using the observed luminescence lifetimes of $[\mathrm{ReBr(bpy)(CO)_3}]$ (49 ns) and $[\mathrm{Ru(bpy)_3}]^{2+}$ (928 ns).

Table 2. Isomerization of **1** and **2** by Direct Photolysis and Thermal Activation a)

Starting Material	Reaction b) Condition	Reaction Time/min	Yield c)/%		
			1	**2**	**3**
1	Photolysis	100	95	Trace	0
2	Photolysis	130	73	11	Trace
1	60°C	960	94	Trace	Trace
1	100°C	300	56	Trace	Trace
2	60°C	960	2	78	1
2	100°C	300	14	2	1

a) For deaerated DMF solutions containing **1** or **2** (2.5 mM). b) "Photolysis" means the reactions by direct photoexcitation at 436 nm, whereas the temperatures indicate the reaction temperatures for the thermal reactions in the dark. c) Based on the **1** or **2** used.

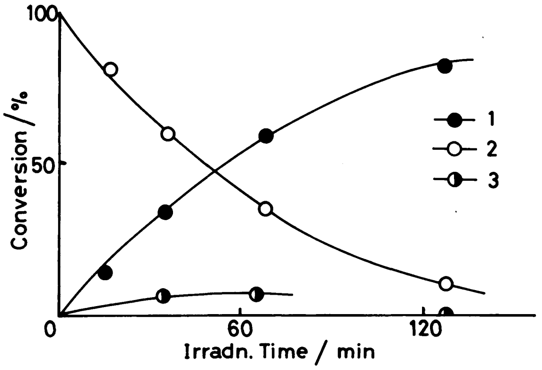


Fig. 2. Time-conversion plots for the direct photolytic isomerization of **2** at 436 nm; [**2**]=2.5 mM.

and **3** is of synthetic and mechanistic interest, since either thermal[3)] or direct photoexcitation can effect the one-way isomerization from **2** to **1** for the most part. Upon heating a DMF solution of **2** at 60 or 100 °C, a reaction proceeded to give **1** only in poor yields along with substantial amounts of untractable materials, while little isomerization of **1** to either **2** or **3** occurred at 60 °C and even at 100 °C being accompanied by substantial consumption of **1**, as shown in Table 2. This means that the isomerization of **1** and **2** is only a negligible or minor pathway in the ground-state reactions. On the other hand, direct photoexcitation of **2** in DMF at 436 nm resulted in the isomerization to **1** along with very minor formation of **3** (Fig. 2), while **1** was found to be quite stable under the irradiation at 436 nm. In the excited state(s), **2** might cross to a reactive state or might give reactive intermediates while physical and chemical decays to the original ground state should predominantly occur with **1**.

For mechanistic elucidation, it shoud be noted that either chemical or electrochemical one-electron reduction of $\mathrm{BNA^+}$ affords a mixture of **1**, **2**, and **3** in comparable amounts along with the other minor isomers in ratios depending on reaction conditions.[3)] We also observed that a 2:2:1 mixture of **1**, **2**, and **3** is quantitatively formed by the photosensitized one-electron reduction of $\mathrm{BNA^+}$ with triethylamine.[8)] It is therefore conceivable that the formation of mixtures of **1**, **2**, and **3** should arise as the consequences of kinetic-controlled dimerization of the 1-benzyl-3-carbamoyldihydropyridyl radicals (BNA·), since BNA· is certainly a common intermediate in the chemical, electrochemical, and photochemical one-electron reductions of $\mathrm{BNA^+}$.

These arguments strongly suggest that the photosensitized isomerizations of **1** and **2** involve BNA· as a key intermediate. In this regard, it should be noted that the luminescence of $[ReBr(bpy)(CO)_3]$ or $[Ru(bpy)_3]^{2+}$ is efficiently quenched by **1** and **2** at the rate constants listed in Table 1. In a previous paper,[9] we demonstrated that the luminescence of $[Ru(bpy)_3]^{2+}$ is quenched by BNAH at $2.0\times10^8\ M^{-1}\ s^{-1}$ in DMF by way of electron transfer from the quencher to the ruthenium(II) complex. Therefore, it is reasonable to assume that electron transfer from **1** and **2** to the luminescent excited-state sensitizers occurs to initiate the isomerizations, since **1** and **2** have the dihydronicotinamide chromophores. The dimeric structures of **1** and **2** imply that these compounds should be stronger electron donors compared with BNAH, a presumption being in accord with the greater quenching rate constants for **1** and **2**. Furthermore, the observation that the luminescence quenching is more efficient for $[ReBr(bpy)(CO)_3]$ than for $[Ru(bpy)_3]^{2+}$ can be reasonably understood according to the electron-transfer mechanism, since the excited-state reduction potential of $[ReBr(bpy)(CO)_3]$ is more positive by ca. 0.24 eV than that of $[Ru(bpy)_3]^{2+}$.[10,11] An alternative mechanism involving triplet-energy transfer from the sensitizers to **1** and **2** is unlikely to operate in the photosensitized isomerizations, since such organic triplet photosensitizers as coronene and chrysene were found to be totally ineffective.

According to the above discussion, we propose a possible mechanism for the photosensitized isomerizations in Eqs. 1—5. The key mechanistic sequence is the fragmentation of $BNA_2^{+\cdot}$ ($\mathbf{1}^{+\cdot}$ and $\mathbf{2}^{+\cdot}$) to BNA· and BNA^+ (Eq. 3) followed by back electron transfer from $S^{-\cdot}$ ($[ReBr(bpy)(CO)_3]^{-\cdot}$ or $[Ru(bpy)_3]^+$) to BNA^+ to generate BNA· (Eq. 4). It can be predicted that electron transfer from $S^{-\cdot}$ to BNA^+ (Eq. 4) rapidly occurs since the reduction potentials of $[ReBr(bpy)(CO)_3]$ (−1.35 V vs. SCE in acetonitrile)[12] and $[Ru(bpy)_3]^{2+}$ (−1.36 V)[13] are substantially more negative than that of BNA^+ (ca. −1.0 V).[14] The final products are thus formed by free-radical coupling of BNA· (Eq. 5). Since material balances are excellent in the photosensitized isomerizations, the fragmentation of $BNA_2^{+\cdot}$ (Eq. 3) appears to be efficient, thus predominating over Eq. 2.

$$S + BNA_2 \overset{h\nu}{\rightleftarrows} S^{-\cdot} + BNA_2^{+\cdot} \tag{1}$$

$$BNA_2^{+\cdot} \longrightarrow \text{Others} \tag{2}$$

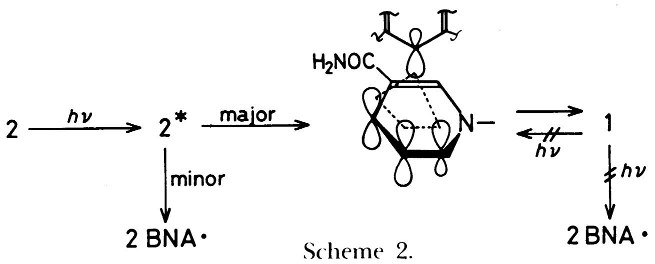
$$BNA_2^{+\cdot} \longrightarrow BNA^+ + BNA^\cdot \tag{3}$$

$$S^{-\cdot} + BNA^+ \longrightarrow S + BNA^\cdot \tag{4}$$

$$2BNA^\cdot \longrightarrow \mathbf{1} + \mathbf{2} + \mathbf{3} \tag{5}$$

$(S=[ReBr(bpy)(CO)_3]$ or $[Ru(bpy)_3]^{2+}$; $BNA_2=\mathbf{1}—\mathbf{3})$

On the other hand, the participation of BNA· appears to be negligible or minor in the isomerizations of ground-state and excited-state BNA_2, since only the one-way isomerization from **2** to **1** can occur. Furthermore, the free-radical mechanism disagrees with the negligible formation of **3** from **2** upon either thermal activation or direct photoexcitation, since the isomerization of **2** to **3** should comparably occur, at least at an early stage of the reactions, by this mechanism. Presumably, the photoisomerization of **2** might mainly proceed via 1,3-sigmatropic migration of the 1,4-dihydropyridinyl moiety from the 6′ position to the 4′ position of the 1,6-dihydronicotinamide ring, which is an orbital-symmetry-allowed process in the excited state (Scheme 2).[15] The reverse sigmatropic migration (i.e. **1** to **2**) would be thermodynamically unfavorable. According to this mechanism, it can be reasonably understood that the thermal isomerization of **2** occurs only in poor yields, since a suprafacial 1,3-sigmatropic rearrangement is forbidden in the ground state.



Scheme 2.

Summary

It was found that the isomerizations of **1** and **2** occur upon photosensitization by $[ReBr(bpy)(CO)_3]$ or $[Ru(bpy)_3]^{2+}$ to give a common 2:2:1 mixture of **1**, **2**, and **3** at a photostationary state. On the other hand, direct photoexcitation resulted in the one-way isomerization from **2** to **1** along with only minor formation of **3**; **1** was found to be photostable. Although **2** was reported to isomerize to **1** by thermal activation,[3] we confirmed that the isomerization can occur only as a minor pathway in the ground-state reactions.

The photosensitized isomerzations of **1** and **2** were discussed in terms of the following chemical sequences; (1) electron transfer from **1** or **2** to the luminescent excited state sensitizers, (2) bond cleavage of $\mathbf{1}^{+\cdot}$ and $\mathbf{2}^{+\cdot}$ to generate BNA· and BNA^+, (3) back electron transfer from the one-electron reduced sensitizers to BNA^+, and (4) the free-radical dimerization of BNA· to give a mixture of **1**, **2**, and **3** for the most part. According to this mechanism, a significant point is that both $\mathbf{1}^{+\cdot}$ and $\mathbf{2}^{+\cdot}$ are chemically reactive to undergo the fragmentation to BNA· and BNA^+. On the other hand, a 1,3-sigmatropic mechanism was suggested for the direct photolytic isomerization of **2** to **1**.

Experimental

Materials. The sensitizers, $[ReBr(bpy)(CO)_3]$[16] and $[Ru(bpy)_3]Cl_2\cdot6H_2O$,[17] were prepared and purified according to the literature methods. The preparation and isolation of **1**, **2**, and **3** was carried out according to the Ohnishi's method[3] utilizing the reduction of 1-benzyl-3-carbamoylpyridinium chloride with activated zinc powder in the presence of copper(II) sulfate. The isolated tetrahydrobipyridines, particularly **2** and **3**, were carefully recrystallized from deaerated DMF–H_2O solution below room temperature in order to avoid the contamination of untractable materials due to thermal decomposition and oxidation. The ^1H NMR spectra of the isolated samples were essentially identical with the published data.[3]

Analytical Methods. Both the disappearance and the formation of **1**, **2**, and **3** were followed by HPLC, which was carried out on a Chemicosorb 7-ODS-H column with a Yanaco M-315 spectromonitor working at 355 nm. The mobile phase was a 6:4 (v/v) mixture of methanol and an NaOH–KH_2PO_4 buffer solution (pH 7) at a flow rate of 0.8 $cm^3 min^{-1}$. A Hitachi 850 spectrofluorometer was used for luminescence-quenching experiments; the ruthenium complex (0.25 mM) in DMF was excited at 550 nm and intensities of the luminescence were monitored at 610 nm, whereas the luminescence of the rhenium complex (0.75 mM) excited at 420 nm was monitored at 600 nm.

Photoreactions. Deaerated DMF solutions of **1** or **2** (2.5 mM) in the presence or absence of the sensitizers (0.8 mM) were irradiated under cooling with water (20±2 °C), and the progress of the reactions was followed by HPLC. It was confirmed that no reaction of **1** and **2** occurred in the dark under the conditions. The $[Ru(bpy)_3]^{2+}$-photosensitized reactions were run by the irradiation with a tungsten–halogen lamp (300W) using a 1-cm pathlength filter solution of K_2CrO_4 (20 g dm^{-3}), $NaNO_3$ (200 g dm^{-3}), and NaOH (6.7 g dm^{-3}) which cuts off the light shorter than 470 nm.[9] In both the $[ReBr(bpy)(CO)_3]$-photosensitized runs and the direct photolyses, an Eikosha high-pressure mercury arc (300W) was used; the 436-nm resonance line was isolated by the passage through a 1-cm pathlength solution of $CuSO_4$ in 28% ammonium hydroxide.[18] In the $[ReBr(bpy)(CO)_3]$-photosensitized reactions, contributions of reactions due to direct light absorption of the reactants are negligible, since the optical density of the sensitizer at 436 nm is 7—8 times greater than that of each reactant and since the photosensitized reactions are much more efficient than the direct photolyses.

Thermal Reactions. Deaerated DMF solutions of **1** or **2** (2.5 mM) were heated at 60±0.5 °C or at 100±0.5 °C in a dark room. The progress of the reactions was followed by HPLC. All the procedures were done with care in order to avoid exposure of the reactant solutions to scattering light.

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