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Redox-Photosensitized Reactions. XIV.[1] Photochemistry of 4-Alkylated NADH Models, 1-Benzyl-4-(1-hydroxyalkyl)-1,4-dihydronicotinamides

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There were investigated photochemical behaviors of 4-alkylated 1-benzyl-1,4-dihydronicotinamides (**1a—c**) having $R^1R^2C(OH)$ as the substituent (a: R^1=Ph and R^2=H; b: R^1=Ph and R^2=CF_3; c: R^1=*p*-NC-C_6H_4 and R^2=H). The direct photolysis of **1a—c** gave R^1R^2CO and the dimers of the dihydronicotinamide (BNA) fragment along with a minor amount of $[C_6H_5CH(OH)]_2$, being thus interpreted in terms of the homolysis between the $R^1R^2(OH)$ and BNA moieties. In the $[Ru(bpy)_3]^{2+}$-photosensitized reactions, it is suggested that **1a—c**$^{+\cdot}$ was generated as a key intermediate by electron transfer to excited $[Ru(bpy)_3]^{2+}$, undergoing a bond cleavage to give R^1R^2CO and the BNA· dimers. In the case of **1c**, however, $R^1R^2CH(OH)$ was formed, being attributed to a product from **1c**$^{-\cdot}$ that is formed by electron transfer from $[Ru(bpy)_3]^+$ to **1c**.

In previous papers,[2,3] we reported that the photosensitized reactions of 1-benzyl-1,4-dihydronicotinamide (BNAH), a typical NADH model, with either olefins or aromatic carbonyl compounds by $[Ru(bpy)_3]^{2+}$ (bpy=2,2′-bipyridine) yielded 1:1 adducts, new classes of 4-alkylated 1,4-dihydronicotinamides. These findings prompted us to investigate chemical behaviors of these adducts, since chemistry of 4-substituted 1,4-dihydronicotinamides has been of synthetic and biological significance.[4—7] We have found that the adducts with carbonyl compounds **1a—c** reveal interesting behaviors in either the direct photolysis or the photosensitization by $[Ru(bpy)_3]^{2+}$.

Experimental

Materials. The preparation and purification of BNAH[8] and $[Ru(bpy)_3Cl_2]\cdot 6H_2O$[9] were carried out according to the literature methods. The 4-alkylated dihydronicotinamides, **1a—c**, were obtained as 1:1 mixtures of the diastereoisomers by the $[Ru(bpy)_3]^{2+}$-photosensitized reactions of BNAH with benzaldehyde, 1,1,1-trifluoroacetophenone, and *p*-cyanobenzaldehyde as previously reported.[1,3] The diastereoisomers were separated by either repeated column chromatography on basic alumina or HPLC.[1] However, we confirmed that the photochemical behaviors of the isolated diastereoisomers are essentially identical with those of 1:1 mixtures. Therefore, we used 1:1-diastereoisomeric mixtures of **1a—c** in the present investigation. The other materials were obtained from Nakarai Chemicals and used after distillation and/or recrystallization.

Analytical Methods. The formation of **2**, **6c**, and 1,2-diphenyl-1,2-ethanediol was followed by GLC, whereas both the disappearance of **1a—c** and the formation of **3—5** were analyzed by HPLC. GLC was carried out on a Shimadzu GC-7A dual column instrument with flame-ionization detectors, and HPLC analysis were done on a Chemicosorb 7-ODS-H column using a Toyosoda CCPD dual pump coupled with a Yanaco M-315 spectromonitor working at 355 nm. A Hitachi 850 spectrofluorometer was used for luminescence-quenching experiments; deaerated solutions of the ruthenium complex (0.25 mM†) were photoexcited at 550 nm and intensities of the luminescence were monitored at 610 nm. Polarographic measurements were carried out for N_2-saturated water-free methanolic solutions containing **2a—c** (1 mM) and $NaClO_4$ (0.1 M) as the supporting electrolyte using an Ag/$AgNO_3$ reference electrode, a dropping mercury working electrode, and a Yanagimoto P-1100 potentiostat.

Direct Photolysis. A 3 cm^3-methanolic solution containing **1a—c** (50 mM) was bubbled with a gentle stream of Ar for 15 min and then irradiated with a high-pressure mercury lamp using a uranil glass filter (>330 nm) under cooling with water. The progress of the photoreactions was followed by GLC and HPLC.

Photosensitized Reactions by $[Ru(bpy)_3]^{2+}$. A 3 cm^3-methanolic solution containing **1a—c** (50 mM) and $[Ru(bpy)_3]^{2+}$ (1 mM) was bubbled with Ar for 15 min and then irradiated with a tungsten-halogen lamp using a solution filter of potassium chromate (20 g dm^{-3}), sodium nitrate (200 g dm^{-3}), and sodium hydroxide (6.7 g dm^{-3})(>470 nm)[2] under cooling with water. The progress of the reactions was followed by GLC and HPLC.

Results and Discussion

Direct Photolysis. Irradiation of a methanolic solution of **1a—c** (50 mM) at >330 nm mainly gave a carbonyl compound (**2a—c**) and the three isomeric dimers of 1-benzyl-3-carbamoyldihydro-4-pyridinyl radical, i.e. the 4,4′-bonded dimer (**3**), 4,6′-bonded dimer (**4**), and the diastereoisomer of **4** (**5**), as shown in Scheme 1. The dimers were isolated and identified by direct comparison with authentic samples,[10] while the other isomers could not be detected. In the case of **1a**, 1,2-diphenyl-1,2-ethanediol was formed in a 12% yield by GLC. Although the diol formation from **1b,c** can be presumed to occur, GLC and HPLC methods could not be used for the analysis.[11] In any case, moreover, we could not detect the alcohols, $R^1R^2CH(OH)$, nor the positional isomers of **1a—c** by extensive GLC and HPLC analyses. Table 1 summarizes yields of **2—5**.

These observations strongly suggest that the photoexcitation of **1a—c** results in a selective homolytic fission to generate a pair of $R^1R^2\dot{C}(OH)$ and the dihydropyridinyl radical (BNA·). The radical

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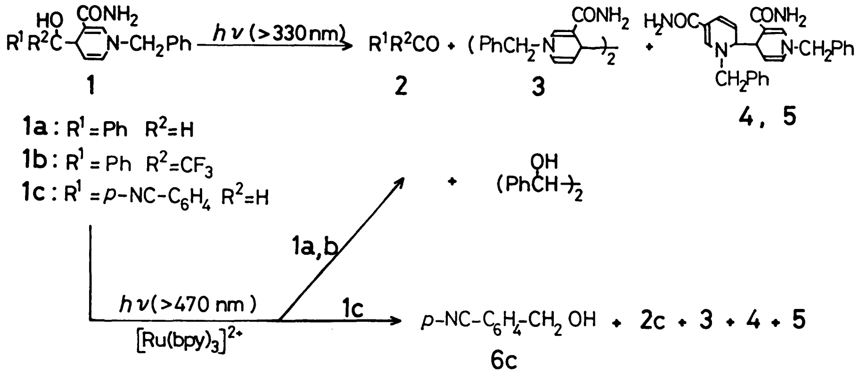
† 1 M=1 mol dm^{-3}.



Scheme 1.

Table 1. Direct Photolysis of **1a**—**c**[a)]

	1		Time	Convn.	Yield/%[b)]			
	R^1	R^2	h	%	**2**	**3**	**4**	**5**
a	Ph	H[c)]	4	47	49	37	26	17
b	Ph	CF_3	12	25	52	80	7	4
c	p-NCC_6H_4	H	10	35	57	43	26	20

a) For 3-cm³ methanolic solutions containing **1a**—**c** (0.05 M) irradiated at >330 nm. b) Based on **1a**—**c** consumed. c) 1,2-Diphenyl-1,2-ethanediol was formed in a 12% yield.

pair might diffuse apart out of a solvent cage in competition with the radical coupling regenerating **1a**—**c**. The free BNA· exclusively dimerizes to give **3**, **4**, and **5** in a kinetic controlled ratio. The predominant formation of **3** in the photolysis of **1b** appears to arise from a consequence of a secondary photoreaction, since irradiation of either **4** or **5** leads to the selective isomerization to **3** though the reverse photoisomerization does not occur.[12)] On the other hand, the $R^1R^2\dot{C}(OH)$ are perhaps oxidized to **2a**—**c** by impurities and/or by unreclaimed reactions in competition with the dimerization. We attempted to detect other possible products arising from the $R^1R^2\dot{C}(OH)$ fragment, since yields of **2a**—**c** are lower than the combined yields of **3**—**5** in each case. However, we could not detect other definite products than those mentioned here. A possible mechanism is shown in Eqs. 1—6.

$$R^1R^2C(OH)\text{-}BNA \overset{h\nu}{\rightleftarrows} \overline{R^1R^2\dot{C}(OH)\quad BNA\cdot} \tag{1}$$

$$\overline{R^1R^2\dot{C}(OH)\quad BNA\cdot} \longrightarrow R^1R^2\dot{C}(OH) + BNA\cdot \tag{2}$$

$$R^1R^2\dot{C}(OH) \xrightarrow[-H\cdot]{} R^1R^2C{=}O \tag{3}$$

$$2R^1R^2\dot{C}(OH) \longrightarrow R^1R^2C(OH)C(OH)R^1R^2 \tag{4}$$

$$R^1R^2\dot{C}(OH) \longrightarrow \text{Others} \tag{5}$$

$$2BNA\cdot \longrightarrow \mathbf{3} + \mathbf{4} + \mathbf{5} \tag{6}$$

It is of interest to note that the radical pair can be regarded as a mechanistic equivalent to a key intermediate that is involved in an ECE mechanism[13)] proposed for the reduction of carbonyl compounds by BNAH in the dark as shown in Eqs. 7 and 8. According to this mechanism, BNA· could donate an electron to $Ph\dot{C}(OH)CF_3$ and p-$NCC_6H_4\dot{C}H(OH)$ since the reductions of trifluoroacetophenone and p-cyanobenzaldehyde by BNAH do occur in the dark to give the corresponding alcohols. However, the photolysis of either **1b** or **1c** did not afford the corresponding alcohols, thus indicating that BNA· is incapable of undergoing one-electron reduction of $R^1R^2\dot{C}(OH)$.[1,14)]

Furthermore, the lack of the BNAH formation in the photolysis of **1a**—**c** suggests that transfer of a hydrogen-atom equivalent from $R^1R^2\dot{C}(OH)$ to BNA·, the reverse pathway of Eq. 7, is very unlikely to occur.

$$R^1R^2C{=}O + BNAH \rightleftarrows$$
$$\overline{R^1R^2CO^{-\cdot}\quad BNAH^{+\cdot}} \rightleftarrows \overline{R^1R^2\dot{C}(OH)\quad BNA\cdot} \tag{7}$$

$$\overline{R^1R^2\dot{C}(OH)\quad BNA\cdot} \rightleftarrows \overline{R^1R^2\bar{C}(OH)\quad BNA^+} \xrightarrow{H^+}$$
$$R^1R^2CH(OH) + BNA^+ \tag{8}$$

Photosensitization by $[Ru(bpy)_3]^{2+}$. The photosensitized reactions of **1a**—**c** were carried out by the irradiation at >470 nm in order to achieve the selective photoexcitation of $[Ru(bpy)_3]^{2+}$. In the cases of **1a**,**b**, the results are similar to those of the direct photolysis with some differences in product ratios. The major products are again **2a**,**b**, and the BNA· dimers without the formation of BNAH and $R^1R^2CH(OH)$, and 1,2-diphenyl-1,2-ethanediol was also formed in a 13% yield in the case of **1a**.[11)] Prominently, the photosensitized reaction of **1c** yielded p-cyanobenzyl alcohol (**6c**) in a 50% yield along with **2c** and the BNA· dimers, showing a sharp contrast to the lack of the alcohol formation in the direct photolysis. In this case, moreover, it is notable that the combined yield of **3**—**5** is significantly lower than that of **2c** and **6c** though BNAH is not formed, an observation contrary

Table 2. $[Ru(bpy)_3]^{2+}$-Photosensitized Reactions[a)]

	1		Time	Convn.	Yield/%[b)]				
	R^1	R^2	h	%	**2**	**3**	**4**	**5**	**6**
a	Ph	H[c)]	8	67	67	56	30	10	0
b	Ph	CF_3	16	10	30	50	20	12	Trace
c	*p*-NCC_6H_4	H	10	20	40	10	22	29	50

a) For 3-cm^3 methanolic solutions containing **1a**—**c** (0.05 M) and $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (1 mM) irradiated at >470 nm. b) Based on **1a**—**c** consumed. c) 1,2-Diphenyl-1,2-ethanediol and hydrogen were detected in 13 and 2% yields respectively.

Table 3. Rate Constants for Quenching of $[Ru(bpy)_3]^{2+}$ Luminescence[a)]

Quencher	$k_q\tau/M^{-1}$	k_q[b)]$/M^{-1}\ s^{-1}$
1a	57	7.1×10^7
1b	17	2.1×10^7
1c	15	1.9×10^7
BNAH	120	1.5×10^8
DMT[c)]	840	1.1×10^9
3	1700	2.1×10^9

a) Obtained from linear Stern-Volmer plots of the luminescence quenching for deaerated methanolic solutions. b) Calculated from the $k_q\tau$ values using $\tau=800$ ns at 20 °C in methanol.[2)] c) *N*,*N*-Dimethyl-*p*-toluidine.

to those of the other cases. The results are summarized in Table 2 and in Scheme 1.

The luminescence of $[Ru(bpy)_3]^{2+}$ was quenched by **1a**—**c** at rate constants, which are significantly smaller than the quenching rate constant of BNAH and which decrease with increasing inductive effects of R^1 and/or R^2 as shown in Table 3. It is therefore reasonable to assume that electron transfer from **1a**—**c** to $[Ru(bpy)_3]^{2+}$ in the metal-to-ligand charge-transfer excited state occurs to initiate the photosensitized reactions (Eq. 9). Electron-withdrawing inductive effects of the aromatic rings and the trifluoromethyl group should weaken the electron-donating power of the dihydronicotinamide moiety of **1a**—**c** compared with BNAH.

$$\textbf{1a—c} + [Ru(bpy)_3]^{2+} \overset{h\nu}{\rightleftharpoons} \textbf{1a—c}^{+\cdot} + [Ru(bpy)_3]^{+} \qquad (9)$$

The follow-up reaction of **1a**—**c**$^{+\cdot}$ has two choices; one is the bond cleavage to yield **2a**—**c**, H^+, and BNA$^\cdot$ (Eq. 10) and the other involves the formation of $R^1R^2\dot{C}(OH)$ and BNA^+ (Eq. 11). Although there is no unequivocal evidence supporting either or both of the two pathways, comparisons of reduction potentials between **2a**—**c** and BNA^+ in methanol might imply that Eq. 10 is thermodynamically more favorable than Eq. 11. The polarographic reduction waves of **2a** and **2c** in methanol appear at −1.86 and −1.52 V vs. Ag/Ag^+, respectively, which are more negative than the reduction wave of BNA^+ (−1.445 V).[1,15)] Reduction waves of aromatic carbonyl compounds in the presence of a proton donor usually occur as the consequences arising from the formation of $R^1R^2\dot{C}(OH)$ by sequential electron-proton transfer to R^1R^2CO.[16)] Therefore electron transfer from $R^1R^2\dot{C}(OH)$ to BNA^+ should be exothermic to yield **2a**—**c** and BNA· (Eq. 12).

$$\textbf{1a—c}^{+\cdot} \longrightarrow R^1R^2CO + H^+ + BNA\cdot \qquad (10)$$

$$\textbf{1a—c}^{+\cdot} \longrightarrow R^1R^2\dot{C}(OH) + BNA^+ \qquad (11)$$

$$R^1R^2\dot{C}(OH) + BNA^+ \xrightarrow[(\Delta G<0)]{} R^1R^2CO + H^+ + BNA\cdot \qquad (12)$$

However, the formation of 1,2-diphenyl-1,2-ethanediol implies the intervention of $Ph\dot{C}H(OH)$. This can be easily interpreted by assuming the occurrence of electron transfer from $[Ru(bpy)_3]^+$ to **2a** (Eq. 13), which has already been discussed previously.[3)] This might be a major origin for lower yields of **2a**,**b** compared with the BNA· dimers, provided that **2a**,**b**$^{-\cdot}$ and $R^1R^2\dot{C}(OH)$ afford unreclaimed products even in part.

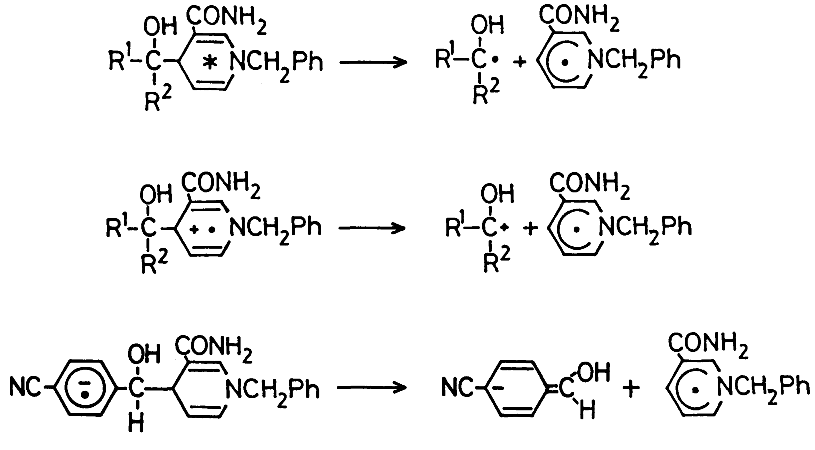
$$[Ru(bpy)_3]^{+} + \textbf{2a—c} \rightleftharpoons [Ru(bpy)_3]^{2+} + \textbf{2a—c}^{-\cdot} \qquad (13)$$

$$\textbf{2a—c}^{-\cdot} + H^+ \longrightarrow R^1R^2\dot{C}(OH) \qquad (14)$$

$$2R^1R^2\dot{C}(OH) \longrightarrow R^1R^2CH(OH)CH(OH)R^1R^2 \qquad (15)$$

$$\textbf{2a—c}\cdot \text{ and } R^1R^2\dot{C}(OH) \longrightarrow \text{Others} \qquad (15')$$

The formation of **6c** is of particular interest with regard to the electron-transfer mechanism. In order to obtain further mechanistic insights, we carried out the $[Ru(bpy)_3]^{2+}$-photosensitized reactions of **1a**—**c** in the presence of BNAH or *N*,*N*-dimethyl-*p*-toluidine (DMT) in an equimolar amount, a concentration at which excited $[Ru(bpy)_3]^{2+}$ is exclusively quenched by BNAH or DMT (Table 3) via electron transfer (Eq. 16). Interestingly, the photosensitized reaction of **1c** in the presence of either BNAH or DMT selectively gave **6c** at a rate 3.7 or 2 times each more efficient than that in its absence, while **2c** was not formed at all. Furthermore, we could not detect BNAH in the photoreaction with DMT but **3**, **4**, and **5** though yields were not determined. In contrast, the photosensitized



Scheme 2.

reactions of **1a,b** in the presence of BNAH or DMT did not give the corresponding alcohols at all.

$$[\mathrm{Ru(bpy)_3}]^{2+} + \mathrm{D} \overset{h\nu}{\rightleftarrows} [\mathrm{Ru(bpy)_3}]^{+} + \mathrm{D}^{+\cdot} \quad (\mathrm{D{=}BNAH\ or\ DMT}) \tag{16}$$

$$[\mathrm{Ru(bpy)_3}]^{+} + \mathbf{1c} \longrightarrow [\mathrm{Ru(bpy)_3}]^{2+} + \mathbf{1c}^{-\cdot} \tag{17}$$

$$[\mathrm{Ru(bpy)_3}]^{+} + \mathbf{1a,b} \;\text{—//→}\; [\mathrm{Ru(bpy)_3}]^{2+} + \mathbf{1a,b}^{-\cdot} \tag{18}$$

$$\mathbf{1c}^{-\cdot} + \mathrm{H}^+ \left\{ \begin{array}{ll} \longrightarrow p\text{-}\mathrm{NC\text{-}C_6H_4\text{-}CH_2OH} + \mathrm{BNA}\cdot & (19) \\ \text{—//→}\; p\text{-}\mathrm{NC\text{-}C_6H_4\text{-}\dot{C}H(OH)} + \mathrm{BNAH} & (20) \end{array} \right.$$

On the basis of these observations, the formation of **6c** can be interpreted in terms of Eqs. 16, 17, and 19. A key pathway is the electron transfer from $[\mathrm{Ru(bpy)_3}]^+$ to **1c**, in which the cyanophenyl group should be essential because of the electron-accepting nature. Since **3** is a much more efficient quencher of excited $[\mathrm{Ru(bpy)_3}]^{2+}$ than either **1c** or BNAH (Table 3), it is expected that the BNA· dimers formed can also act as D in Eq. 16, being thus consumed during the photosensitized reaction of **1c**. This would be a reason for the lower yield of the BNA· dimers compared with the combined yield of **2c** and **6c** as shown in Table 2. On the other hand, $[\mathrm{Ru(bpy)_3}]^+$ appears to be incapable of donating an electron to **1a,b** since the phenyl group has no extra electron-withdrawing substituent. The anion radical (**1c**$^{-\cdot}$) thus formed undergoes a bond cleavage to give **6c** and BNA$^\cdot$ in the presence of a proton donor. On the other hand, little participation of Eq. 20 can be expected, since both **2c** and BNAH were not formed in the photoreaction in the presence of DMT.

Summary

The present investigation exemplifies chemical bahaviors of photoexcited **1a**—**c**, the cation radicals, and the anion radical of **1c** as shown in Scheme 2. In the direct photolysis, the photoexcitation should be localized on the BNA moiety since it absorbs the incident light at >330 nm. This leads to the homolysis between the $\mathrm{R^1R^2\dot{C}(OH)}$ and BNA moieties, while intramolecular electron transfer from the excited BNA chromophore to the $\mathrm{R^1}$ group does perhaps not occur. Likewise, the positive charge of **1a**—**c**$^{+\cdot}$ should be localized on the BNA chromophore, being apparently the driving force for the bond cleavage between $\mathrm{R^1R^2C(OH)}$ and BNA. This is reminescent of the very acidic nature of $\mathrm{BNAH}^{+\cdot}$.[17] On the other hand, the negative charge of **1c**$^{-\cdot}$ should be localized on the *p*-cyanophenyl group, thus leading to the formation of *p*-cyanobenzyl alcohol. In any case, BNA· is commonly formed.

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