

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: $R^1=p\text{-NC-C}_6\text{H}_4$ 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**^{•+} 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**^{•+} 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 BNAH⁸⁾ 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*-cyano-benzaldehyde 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 Chemisorb 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 N₂-saturated water-free methanolic solutions containing **2a**—**c** (1 mM) and NaClO₄ (0.1 M) as the supporting electrolyte using an Ag/AgNO₃ reference electrode, a dropping mercury working electrode, and a Yanagimoto P-1100 potentiostat.

Direct Photolysis. A 3 cm³-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 uranyl glass filter (>330 nm) under cooling with water. The progress of the photoreactions was followed by GLC and HPLC.

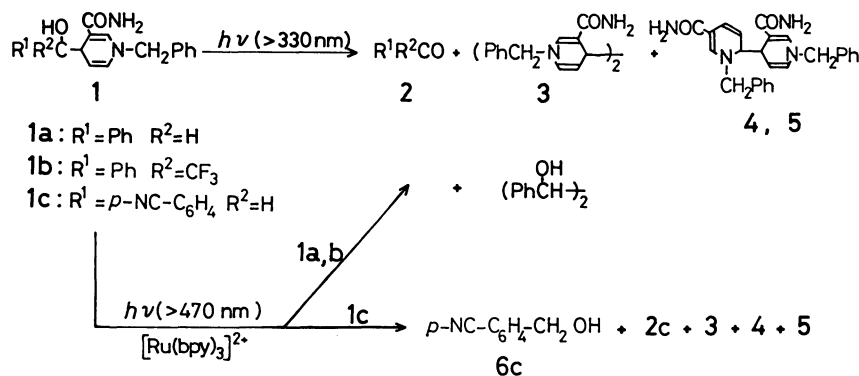
Photosensitized Reactions by $[Ru(bpy)_3]^{2+}$. A 3 cm³-methanolic solution containing **1a**—**c** (50 mM) and $[Ru(bpy)_3]^{2+}$ (1 mM) was bubbled with Ar for 15 min and then irradiated with a tungsten-halogen lamp using a solution filter of potassium chromate (20 g dm⁻³), sodium nitrate (200 g dm⁻³), 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

[†] 1 M=1 mol dm⁻³.



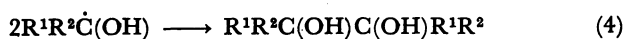
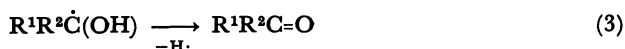
Scheme 1.

Table 1. Direct Photolysis of **1a—c**^{a)}

	1		Time h	Convsn. %	Yield/% ^{b)}			
	R ¹	R ²			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 ₆ H ₄	H	10	35	57	43	26	20

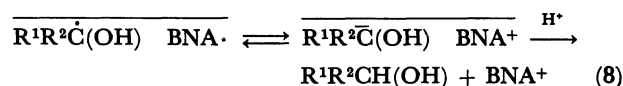
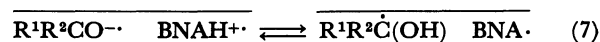
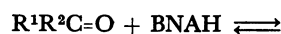
a) For 3-cm³ methanolic solutions containing **1a—c** (0.05 M) irradiated at >330 nm. b) Based on **1a—c** consumed. c) 1,2-Diphenyl-1,2-ethanediol was formed in a 12% yield.

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 R¹R²C(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 R¹R²C(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.



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 mechanism¹³⁾ 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 PhC(OH)CF₃ and p-NCC₆H₄CH(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 R¹R²C(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 R¹R²C(OH) to BNA·, the reverse pathway of Eq. 7, is very unlikely to occur.



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 R¹R²CH(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. $[\text{Ru}(\text{bpy})_3]^{2+}$ -Photosensitized Reactions^{a)}

	1		Time h	Convsn. %	Yield/% ^{b)}				
	R ¹	R ²			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	<i>p</i> -NCC ₆ H ₄	H	10	20	40	10	22	29	50

a) For 3-cm³ methanolic solutions containing **1a–c** (0.05 M) and $[\text{Ru}(\text{bpy})_3\text{Cl}_2] \cdot 6\text{H}_2\text{O}$ (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.

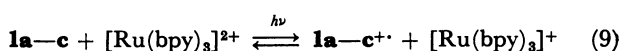
Table 3. Rate Constants for Quenching of $[\text{Ru}(\text{bpy})_3]^{2+}$ Luminescence^{a)}

Quencher	$k_q\tau/\text{M}^{-1}$	$k_q^b/\text{M}^{-1}\text{s}^{-1}$
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.

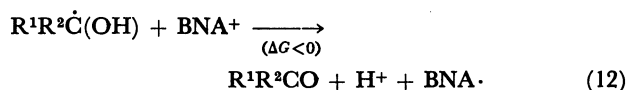
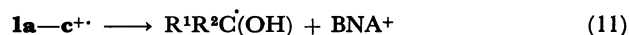
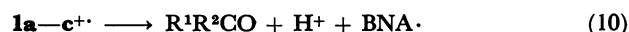
to those of the other cases. The results are summarized in Table 2 and in Scheme 1.

The luminescence of $[\text{Ru}(\text{bpy})_3]^{2+}$ 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 R¹ and/or R² as shown in Table 3. It is therefore reasonable to assume that electron transfer from **1a–c** to $[\text{Ru}(\text{bpy})_3]^{2+}$ 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.

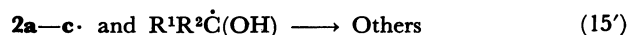
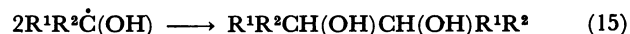
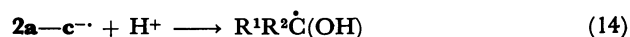
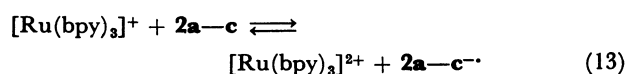


The follow-up reaction of $\mathbf{1a-c}^{+ \cdot}$ has two choices; one is the bond cleavage to yield **2a–c**, H⁺, and BNA[·] (Eq. 10) and the other involves the formation of R¹R²Ċ(OH) and BNA⁺ (Eq. 11). Although there is no unequivocal evidence supporting either or both of the two pathways, comparisons 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

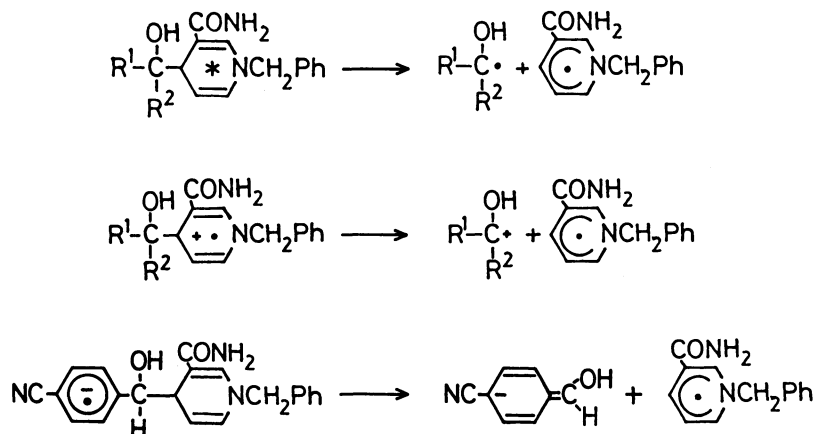
presence of a proton donor usually occur as the consequences arising from the formation of R¹R²Ċ(OH) by sequential electron-proton transfer to R¹R²CO.¹⁶⁾ Therefore electron transfer from R¹R²Ċ(OH) to BNA⁺ should be exothermic to yield **2a–c** and BNA[·] (Eq. 12).



However, the formation of 1,2-diphenyl-1,2-ethanediol implies the intervention of PhĊH(OH). This can be easily interpreted by assuming the occurrence of electron transfer from $[\text{Ru}(\text{bpy})_3]^+$ 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**[·] and R¹R²Ċ(OH) afford unreclaimed products even in part.

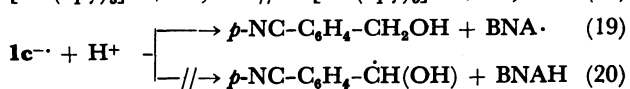
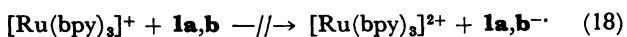
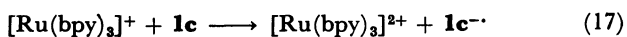
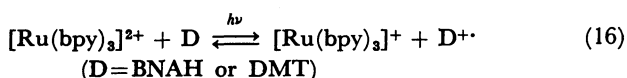


The formation of **6c** is of particular interest with regard to the electron-transfer mechanism. In order to obtain further mechanistic insights, we carried out the $[\text{Ru}(\text{bpy})_3]^{2+}$ -photosensitized reactions of **1a–c** in the presence of BNAH or *N,N*-dimethyl-*p*-toluidine (DMT) in an equimolar amount, a concentration at which excited $[\text{Ru}(\text{bpy})_3]^{2+}$ 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.



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 $[\text{Ru}(\text{bpy})_3]^+$ 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 $[\text{Ru}(\text{bpy})_3]^{2+}$ than either **1c** or BNAH (Table 3), it is expected that the BNA $\cdot$ 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 $\cdot$ dimers compared with the combined yield of **2c** and **6c** as shown in Table 2. On the other hand, $[\text{Ru}(\text{bpy})_3]^+$ appears to be incapable of donating an electron to **1a,b** since the phenyl group has no extra electron-withdrawing substituent. The anion radical ($\mathbf{1c}^{\bullet-}$) 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 behaviors 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 $\text{R}^1\text{R}^2\dot{\text{C}}(\text{OH})$ and BNA moieties, while intramolecular electron transfer from the excited BNA chromophore to the R^1 group does perhaps not occur. Likewise, the positive charge of **1a—c** $^{\bullet+}$ should be localized on the BNA chromophore, being apparently the driving force for the bond cleavage between $\text{R}^1\text{R}^2\text{C}(\text{OH})$ and BNA. This is reminiscent of the very acidic nature of $\text{BNAH}^{\bullet+}$.¹⁷ On the other hand, the negative charge of $\mathbf{1c}^{\bullet-}$ should be localized on the *p*-cyanophenyl group, thus leading to the formation of *p*-cyanobenzyl alcohol. In any case, BNA $\cdot$ is commonly formed.

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- 11) The diols, $[p\text{-NC-C}_6\text{H}_4\text{CH(OH)}]_2$ and $[\text{PhC(OH)(CF}_3)_2]$, which had been independently prepared, revealed no peak on GLC, whereas HPLC peaks of the diols were inseparably overlapped with many other peaks.

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- 14) In a previous paper,³⁾ we reported that the $\text{Ru}(\text{bpy})_3^{2+}$ -photosensitized reactions of BNAH with **2b** and **2c** give the corresponding alcohols (**6c** and **6d**) as minor products. Although these observations would indicate the occurrence of electron transfer from BNAH to $\text{R}_1\text{R}_2\dot{\text{C}}\text{OH}$, close analyses of the reactions¹⁾ demonstrate that **6c** is not a primary product but a secondary one, perhaps from the $\text{Ru}(\text{bpy})_3^{2+}$ -photosensitized reduction of **1c** by BNAH as described in the present paper; see Eqs 16, 17, and 19. Furthermore, it was confirmed that the formation of **6b** is not photochemical but thermally arises from the reduction of **2b** by BNAH in the dark.
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