Photoreactions of Heteroaromatic Compounds. IV.[1] Solvent and Acidity Dependence of the Photoreactions of Nicotinic Acid and Its Derivatives

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Nicotinic acid and its derivatives show manifold photoreactivity depending on the solvent and the acidity of the solution. The cationic form of these compounds in general undergoes photo-hydroxylation in aqueous solutions, and photo-ethylation in ethanol solutions. The anionic form of nicotinic acid is resistant to UV-irradiation in strongly alkaline aqueous solution, but undergoes photo-decarboxylation in alkaline ethanol solution. Nicotinic acid yielded 2-(3-pyridyl)-5-pyridinecarboxylic acid in aqueous solutions at pH=4—6. Photo-substitution by 1-hydroxyethyl group occurs in the neutral forms of 3-cyanopyridine and ethyl nicotinate in ethanol solution. The photoreactivity of nicotinic acid is considered on the basis of CNDO/2 calculation.

Various types of photoreactions have been reported for heteroaromatic compounds. However, a few studies have been made on the photoreaction of nicotinic acid and its derivatives. Wang reported that 3-carbamoyl-1-methylpyridinium salt undergoes photo-hydroxylation in aqueous solution, but 3-carboxy-1-methylpyridinium salt does not undergo the same type of photoreaction in neutral aqueous solution. [2]Natsume and Wada observed the photochemical addition of methanol to 3-cyanopyridine and ethyl nicotinate in neutral methanol solutions.[3]

We have reported the photochemical decarboxylation of pyridinecarboxylic acids.[4] We studied the photoreactions of nicotinic acid and its derivatives systematically by varying the solvent and the acidity of the solution. We found that these compounds show a variety of photoreactions depending on the reaction conditions, namely, depending on the solvent and the chemical forms which absorb UV-light. The preliminary results were reported previously.[1b] The present paper deals with the detailed investigation on the photo-reactivities of nicotinic acid and its derivatives including nicotinamide, 3-cyanopyridine and ethyl nicotinate.

Experimental

Materials. Commercial nicotinic acid, ethyl nicotinate (G.R. grade of Tokyo Kasei Co.), nicotinamide and 3-cyanopyridine (G.R. grade of Wako junyaku Co.) were used without further purification.

Preparation of Sample Solution. 5×10^{-4} mol/l solutions of each compound in water or 99% ethanol were used for the spectroscopic trace of the photoreaction. For isolation and identification of photo-products, 10^{-2} mol/l solutions were generally employed. The acidity of the solution was adjusted with hydrochloric acid or sodium hydroxide. For the detailed study of pH dependence of the photoreaction of nicotinic acid and 3-cyanopyridine in aqueous solutions, the acidity was adjusted with acetate or phosphate buffer, which did not absorb 254 nm light under our experimental condition. The solutions were deaerated by bubbling nitrogen for an hour prior to irradiation, if necessary.

UV-Irradiation. 40 ml of sample solution was irradiated in a quartz tube by a low pressure mercury lamp. The solution was cooled with running water and was stirred with a magnetic stirrer.

In special cases in which the spectral trace must be carried out without exposure to the air, a quartz cell for the measurement of UV-spectrum (10×10 mm) with a stopcock at the top was used. With this vessel, the UV-spectra could be recorded without taking out the solution.

Measurement of the Change in UV-Spectra upon the Irradiation. An aliquot of the solution was taken out from the irradiated solution at regular time-interval, and was submitted to the measurement of UV-spectra after appropriate dilution. UV-spectra were recorded with a Carl Zeiss spectrophotometer Model RPQ-20 or a Hitachi spectrophotometer Model 124.

Isolation of the Photo-products. After irradiation the solution was neutralized, and the solvent was removed under reduced pressure. The photo-products from nicotinic acid were separated by anion exchange chromatography (column, Dowex-1 formate; eluent, formic acid). The photo-product from nicotinamide, 3-cyanopyridine and ethyl nicotinate were separated with silica gel chromatography using Wakogel C-200.

For the measurement of IR- and NMR-spectra, an IR-spectrometer Shimadzu Model IR-27C and an NMR-spectrometer Nihon-Denshi Model JNM-60 HL were employed, respectively.

For determination of the yields of the photo-products from 3-cyanopyridine and ethyl nicotinate, gas chromatography was employed using a gas chromatograph Yanagimoto Model G.C.G. 550F equipped with a glass column of Carbowax 20M.

Identification of Photo-products. *Photo-products from the UV-irradiation in Acidic Aqueous Solutions*: 2-Hydroxynicotinic acid from the photoreaction of nicotinic acid in acidic aqueous solution was identified by comparing the spectral properties with an authentic specimen prepared by the method of Taylor and Crovetti.[5]

2-Hydroxynicotinamide (mp 263—266 °C; lit,[6] sinter at 265 °C, mp 270—272 °C) and 2-hydroxy-3-cyanopyridine (mp 231—233 °C, lit,[7] 225—229 °C) were identified by comparing spectral properties with those of 2-hydroxynicotinic acid.

2-Hydroxy-3-cyanopyridine. Found: C, 59.40; H, 3.35;

Table 1. NMR-spectra of ethylnicotinic acid and its derivatives
(Expressed in δ-value)

	4-Ethylnicotinic acid	Ethyl 6-ethyl-nicotinate	6-Ethyl-3-cyano-pyridine
H at 2-position	8.95 (d)	8.97 (d)	8.85 (d)
H at 4-position	—	8.05 (dd)	7.88 (dd)
H at 5-position	6.93 (d)	7.12 (d)	7.30 (d)
H at 6-position	8.60 (dd)	—	—
CH_2	3.07 (q)	2.83 (q)	2.95 (q)
CH_3	1.33 (t)	1.28 (t)	1.35 (t)

N, 23.03%.

2-Hydroxynicotinamide. Found: C, 50.14; H, 4.56; N, 19.43%.

Photo-products from the UV-irradiation in Acidic Ethanol Solutions: Ethylated nicotinic acid and its derivatives were identified mainly on the basis of NMR-spectra (Table 1). 4-Ethylnicotinic acid (mp 137—138 °C), λ_{max} 268 nm. Found: C, 61.85; H, 5.82; N, 9.15%.

Photo-ethylation product from 3-cyanopyridine was a mixture consisted of 6-ethyl- and 4,6-diethyl-3-cyanopyridines. These compounds could not be separated by column chromatography. Identification was made only on the basis of NMR-spectra.

Photo-products from the UV-irradiation of Nicotinic Acid in Aqueous Solutions: UV-irradiation of nicotinic acid in aqueous solution (without adding acid or alkali) brought about the increase in absorption at 284 nm. The photo-product (mp 229—230 °C, decomp.) was identified as 2-(3-pyridyl)pyridine-5-carboxylic acid from the following ground. Equivalent as an acid (by titration with sodium hydroxide), 188; Calcd, 200. The NMR-spectrum was assigned as shown in Fig. 1. The assignment was confirmed by double resonance technique.

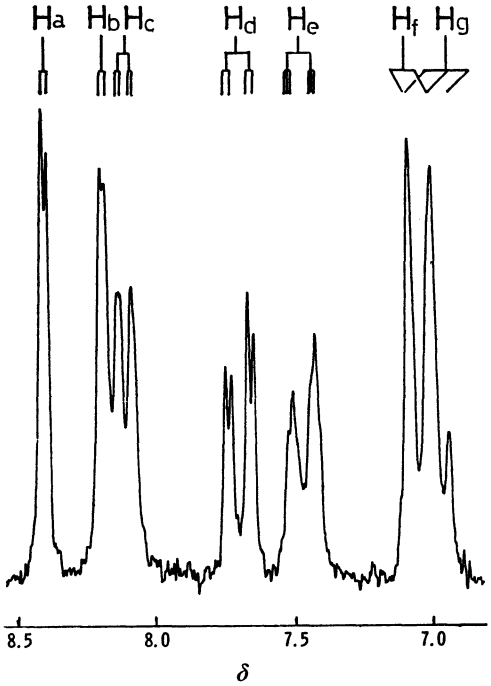
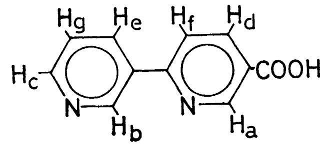


Fig. 1. NMR spectrum of 2-(3-pyridyl)pyridine-5-carboxylic acid



Found: C, 65.32; H, 3.87; N, 13.96%. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99%.

Photo-products from the UV-irradiation in Ethanol Solutions: 3-Cyano-6-(1-hydroxyethyl)pyridine (liquid) and ethyl 6-(1-hydroxyethyl)nicotinate (liquid) were identified on the basis of UV, IR, and NMR spectra.

3-Cyano-6-(1-hydroxyethyl)pyridine: UV; λ_{max}, 268 nm; IR, 3400 (OH), 2980 (aliph. CH), 1480, 1380 (CH_3) and 2240 cm^{-1} (CN). The assignment of NMR-spectra is shown in Table 2.

Ethyl 6-(1-hydroxyethyl)nicotinate: UV; λ_{max}, 266 nm; IR, 3340 (OH), 1720 (C=O), 2960, 1470 and 1370 cm^{-1} (aliph. CH); NMR, Table 2.

Table 2. NMR-spectra of (1-hydroxyethyl)-nicotinic acid derivatives
(Expressed in δ-value)

	Ethyl 6-(1-hydroxy-ethyl)nicotinate	3-Cyano-6-(1-hydroxy-ethyl)pyridine
H at 2-position	9.00 (d)	8.86 (d)
H at 4-position	8.19 (dd)	8.10 (dd)
H at 5-position	7.42 (d)	7.66 (d)
$-\overset{\mathrm{OH}}{\underline{\mathrm{CH}}}-\mathrm{CH_3}$	4.84 (q)	5.00 (q)
$-\overset{\mathrm{OH}}{\mathrm{CH}}-\underline{\mathrm{CH_3}}$	1.43 (d)	1.55 (d)
OH	~4.3	~4.1

Photo-products from the UV-irradiation in Alkaline Ethanol Solution: The photo-product in the irradiation of nicotinic acid in alkaline ethanol solution was not trapped by anion exchange resin. The UV spectra (λ_{max}, 266 and 251 nm) and the effects of acid and alkali on UV spectra agreed with those of pyridine. They were different from those of ethylpyridine, another candidate of the photo-product.

Results and Discussion

Photoreactions in Acidic Solutions. Nicotinic acid and its derivatives show a similar UV spectral change on irradiation with 254 nm light in acidic aqueous solutions. An example of nicotinic acid is shown in Fig. 2. The absorption at ~320 nm brought about by UV irradiation corresponds to the introduction of hydroxyl group at the 2-position of pyridine nucleus. This type of UV spectral change was also observed in the irradiation of 3-cyanopyridine and nicotinamide in acidic aqueous solutions. The results of the product

TABLE 3. PHOTOREACTIONS OF NICOTINIC ACID AND 3-CYANOPYRIDINE IN ACIDIC AQUEOUS SOLUTIONS (pH: 0—1)

Compound	Reaction condition	Product	
Nicotinic acid	5×10^{-4} mol/l LP[a]-17 W 120 min	2-Hydroxynicotinic acid Recovered	40% 0%
3-Cyanopyridine	5×10^{-4} mol/l LP-17 W 25 min	2-Hydroxy-3-cyano-pyridine Recovered	60% 0%

a) LP: Low pressure mercury lamp

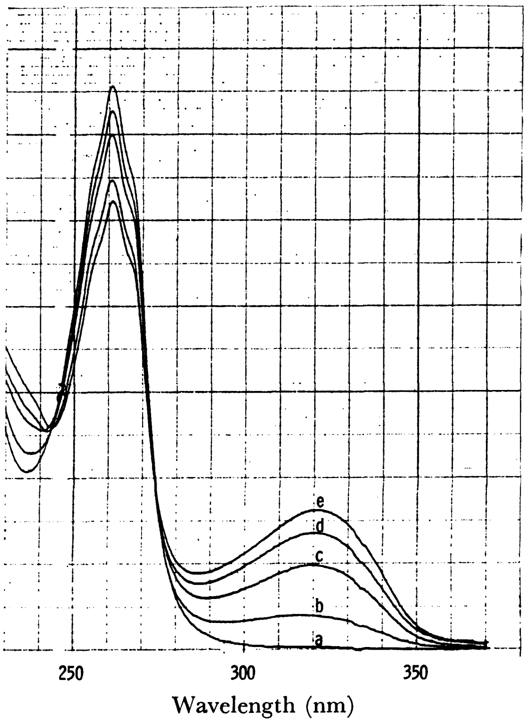


Fig. 2. Change of UV-spectra during the irradiation of nicotinic acid in acidic aqueous solution.
(5×10^{-4} mol/l solution saturated with nitrogen)
a: before irradiation, b: 30 min, c: 60 min, d: 90 min, e: 120 min.

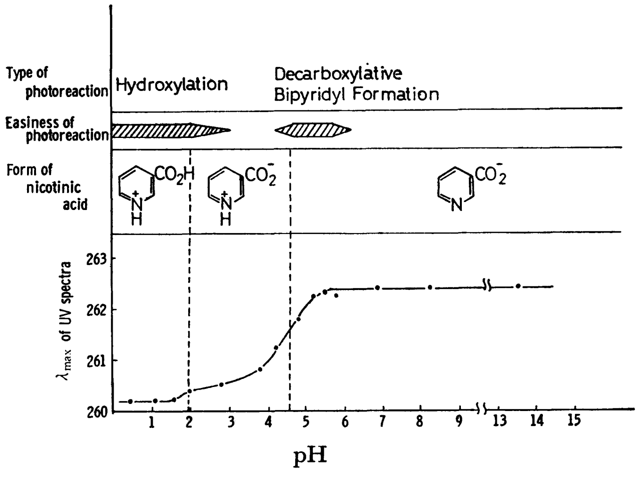


Fig. 3. pH dependence of the photoreaction and λ_{max} of nicotinic acid in aqueous solutions

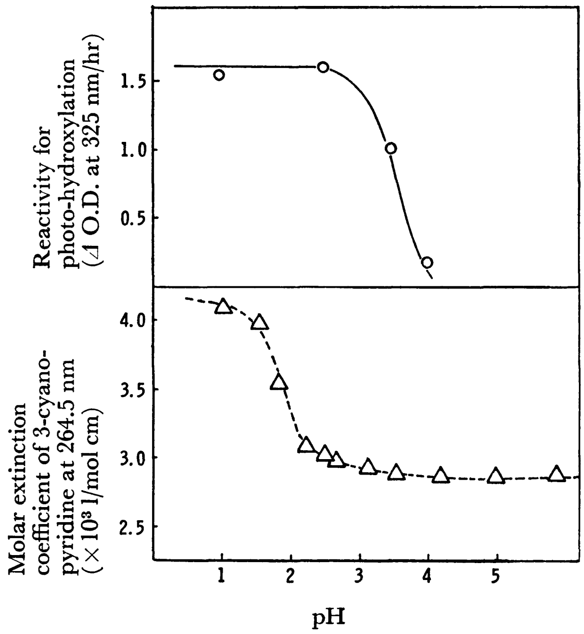
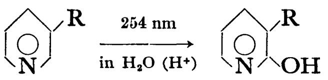


Fig. 4. pH dependence of the reactivity for photo-hydroxylation and the molar extinction coefficient (at 264.5 nm) of 3-cyanopyridine
UV-Irradiation: 5×10^{-4} mol/l under nitrogen
Measurement of UV-absorption: 10 fold dilution

analysis are shown in Table 3. 2-Hydroxynicotinamide was identified in the photo-product from nicotinamide, but the rate of its formation was much smaller compared with 2-hydroxy-3-cyanopyridine and 2-hydroxynicotinic acid.



R = COOH, CN, $CONH_2$

The photo-hydroxylation of nicotinic acid was quenched by oxygen. Oxygen not only inhibited the formation of 2-hydroxynicotinic acid, but also diminished remarkably the transformation of nicotinic acid. This indicates that the photoreaction is ascribed to the triplet state.

In order to obtain further information on the photo-hydroxylation, the pH dependence of the reaction was investigated on nicotinic acid and 3-cyanopyridine (Figs. 3 and 4). In addition, is shown the pH dependence of either λ_{max} of UV-absorption (for nicotinic acid) or the molecular extinction coefficient (for 3-cyanopyridine) of the starting materials. They inform of the form of the substances in solutions. In both

Table 4. Photoreactions of nicotinic acid and its derivatives in acidic ethanol solutions
(Concentration of HCl, 0.1 mol/l)

Compound	Reaction Condition	Product	Yield
Nicotinic acid	5×10^{-4} mol/l LP[a]-17 W 10 min	4-Ethylnicotinic acid Recovered starting material	85% 0%
3-Cyanopyridine	10^{-2} mol/l LP-100 W 15 hr	6-Ethyl-3-cyanopyridine 4,6-Diethyl-3-cyanopyridine Ethyl nicotinate Recovered starting material	10% 6% 5% 13%
Ethyl nicotinate	10^{-2} mol/l LP-170 W 3 hr	Ethyl 6-ethylnicotinate Recovered starting material	30% 34%

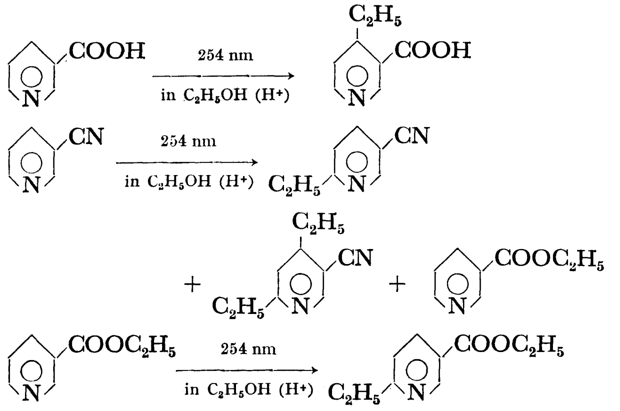
a) LP: Low pressure mercury lamp

cases, the change of chemical form correlates well to that of photoreactivity. Since pK_a value of the protonated nicotinic acid is 2.07, photo-hydroxylation is considered to occur in pyridinium form.

It has been reported that in several pyridine derivatives such as quinoline and acridine, the basicity of the lowest singlet excited state differes by 10^5 from that of the ground state, whereas the basicity of the lowest triplet state is similar to that of the ground state.[8,9] If the photo-hydroxylation derives from the excited singlet state and the lifetime of the excited state is long enough to permit the proton transfer before reaction, the pH range for the photo-hydroxylation should be much wider than our results indicate. This fact also supports that the triplet state is responsible for the photo-hydroxylation. The photo-hydroxylation is thus characteristic for the triplet state of the cationic form of nicotinic acid and its derivatives.

For photo-hydroxylation, the electron attracting group at the pyridine nucleus is essential. Pyridine and the zwitterion form of 3-carboxy-1-methylpyridinium do not undergo photo-hydroxylation.[2] 2-Pyridinecarboxylic acid also shows similar photoreactivity.[1a]

The photoreaction of nicotinic acid and its derivatives in acidic ethanol solutions are summarized in Table 4. The dominant photoreaction of the cationic form of nicotinic acid and its derivatives is the substitution on the pyridine nucleus introducing an ethyl group.



The position of substitution is dependent on the functional group attached to the pyridine nucleus. Nicotinic acid gives 4-ethylnicotinic acid, while ethyl nicotinate is ethylated at 6-position. The UV-irradiation of 3-cyanopyridine yields 6-ethyl- and 4,6-diethyl-3-cyanopyridines. In the photo-ethylation of 3-cyanopyridine, ethylation at 6-position is the initial photoreaction, because at lower conversion, 6-ethyl-3-cyanopyridine was the dominant ethylation product. In the prolonged UV-irradiation of nicotinic acid in acidic methanol, 4-methyl- and 4,6-dimethylnicotinic acids were obtained.

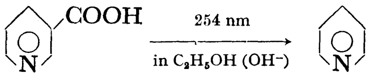
Photo-ethanolysis of nitrile was observed in 3-cyanopyridine. In our reaction condition, ethyl nicotinate was not formed without UV-irradiation.

Photo-alkylation has been reported for several *N*-heteroaromatic compounds such as pyridine,[10] quinoline,[11,12] phenanthridine,[13] and pyrimidine.[14] Similarly to other *N*-heteroaromatic compounds, photo-ethylation of nicotinic acid and its derivatives would be initiated by the hydrogen abstraction from ethanol by N atom of the π-π^* excited state of nicotinic acid, followed by the combination of monohydrogenated nicotinic acid and 1-hydroxyethyl radicals and finally dehydration by acid.

In neutral ethanol solution, 3-cyanopyridine and ethyl nicotinate gave 6-(1-hydroxyethyl) derivative in UV-irradiation, but in lower yield, in comparison with in photo-ethylation in acidic solution. Natsume *et al.* obtained only addition product in UV-irradiation in methanol.[3] We identified the aromatized product. This behavior is similar to that of quinoline reported by Stermitz *et al.*[12]

Photoreactions in Alkaline Solutions. The high photo-stability of nicotinic acid and its derivatives in strongly alkaline aqueous solutions is remarkable. Nicotinic acid and nicotinamide were satisfactorily recovered after comparatively long irradiation (Table 6). 3-Cyanopyridine is also resistant to UV-irradiation, but a part of it is hydrolyzed thermally to nicotinamide.

In contrast to the behavior in aqueous solutions, nicitinic acid undergoes photo-decarboxylation in basic ethanol solution.



The corresponding photoreaction in aqueous solution would be the decarboxylative bipyridyl formation accompanying the formation of a trace of pyridine in

Table 5. Photoreactions of nicotinic acid derivatives in ethanol solutions

Compound	Reaction condition	Product	Yield
3-Cyanopyridine	10^{-2} mol/l LP-a) 17 W 15 hr	6-(1-Hydroxyethyl)-3-cyanopyridine Recovered starting material	16% 10%
Ethyl nicotinate	7×10^{-3} mol/l LP-17 W 2 hr	Ethyl 6-(1-hydroxyethyl)-nicotinate Recovered starting material	8% 53%

a) LP: Low pressure mercury lamp

Table 6. Photoreactions of nicotinic acid and its derivatives in alkaline aqueous solutions (pH: 13—14)

Compound	Reaction condition	Recovery
Nicotinic acid	5×10^{-4} mol/l LPa)-17 W 200 min	82%
3-Cyanopyridine	5×10^{-4} mol/l LP-17 W 120 min	77%
Nicotinamide	5×10^{-4} mol/l LP-17 W 120 min	90%

a) LP: Low pressure mercury lamp

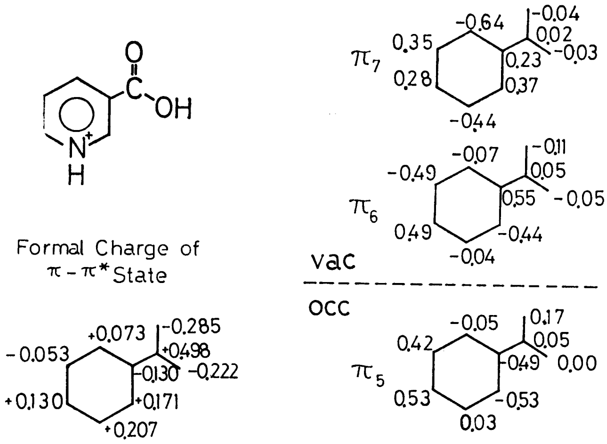


Fig. 5. Electronic states of nicotinic acid in pyridinium form

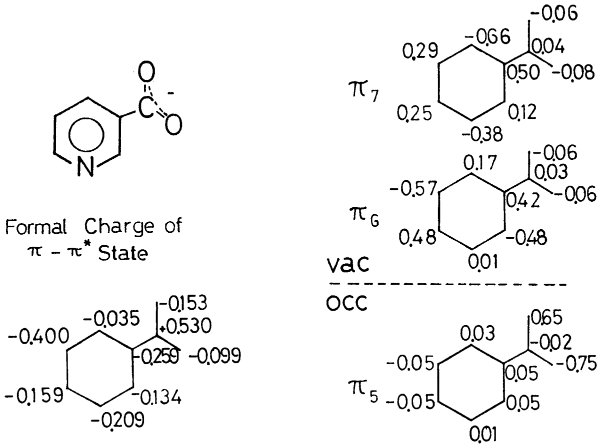
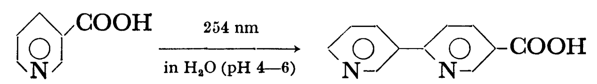
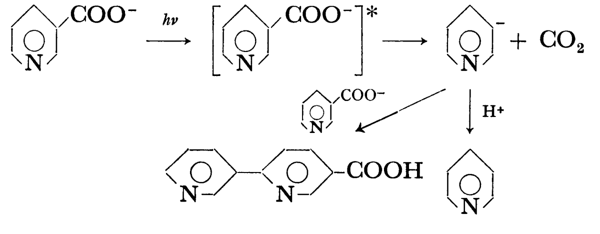


Fig. 6. Electronic states of nicotinic acid in anionic form

the comparatively small pH range from 4 to 6 (Fig. 3).



The pH dependence of the photochemical bipyridyl formation indicates that the reaction is initiated by the excitation of the anionic form of nicotinic acid (pK_a value of nicotinic acid is 4.81 at 25 °C). This photoreaction involves probably the attack of pyridyl carbanions formed by the decarboxylation of nicotinate ions to the positively charged 6-position of the ground state nicotinate ions.

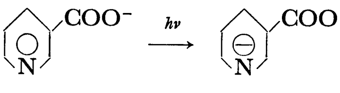


CNDO/2 Considerations of the Photoreactivity. Some of the photoreactivities of nicotinic acid can be reasoned on the basis of CNDO/2 consideration.

Electronic State of the Cationic Form of Nicotinic Acid. The electronic configurations of π-orbitals near highest occupied and lowest vacant levels as well as the total electron density of π-π^* state of the cationic form of nicotinic acid are shown in Fig. 5. Photo-hydroxylation occurs at 2-position with the greatest positive charge in π-π^* state. This suggests that the photosubstitution proceeds *via* nucleophilic attack of water toward the positively charged 2-position of excited nicotinic acid, although the mechanism of photohydroxylation has not yet been elucidated.

Photo-ethylation is considered to be initiated by the hydrogen abstraction by the N atom of excited nicotinic acid. This behavior can not be reasoned by the CNDO/2 calculation, because the free valence of nicotinic acid cation at N atom is not large.[15]

Electronic State of Anionic Form of Nicotinic Acid. The electronic configurations of π-orbitals (π_5, π_6, and π_7) are shown in Fig. 6. In this case, it is remarkable that one electron localized at carboxylate group in highest occupied level is promoted to π_7, where the electron is localized only in the pyridine ring. This electronic promotion could be schematically expressed in the following way;



In analogy with benzoyloxy radicals, the excited nicotinate anion would be easily decarboxylated.

The photo-decarboxylation of nicotinic acid in alkaline ethanol solution and the decarboxylative bipyridyl formation can be interpreted well in terms of CNDO/2 calculation.

Concerning the photoreactivity of the excited nicotinate anion, the following problems remain unsolved:

i) Why does the excited nicotinate anion become photo-resistant in strongly alkaline aqueous solution?

ii) Why does the excited nicotinate anion give bipyridyl derivative instead of pyridine in aqueous solution, in which the protonation of pyridyl carbanion is more favorable than in ethanol solution?

The authors wish to thank Mr. Humitaka Miyazawa and Miss Harumi Nakazawa for their experimental assistance. They are grateful to Prof. Shigeo Nishimura and Mrs. Michiko Tsuchimoto for the measurement of NMR spectra and to Nihon Denshi Co. for the careful measurement of double resonance spectra.

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15) The contribution of π_7 state to the character of excited nicotinic acid (in pyridinium form) can explain the photoreactivity of nicotinic acid both in aqueous and in ethanol solutions. In π_7 state, the electron density at 2-position is low and the partial free valence at N is large.