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The Primary Photochemical Process of Isoquinoline *N*-Oxide in Hydroxylic Solvents

Isao Ono and Norisuke Hata

Department of Chemistry, Faculty of Science and Engineering, Aoyama Gakuin University, Chitosedai, Setagaya-ku, Tokyo 157

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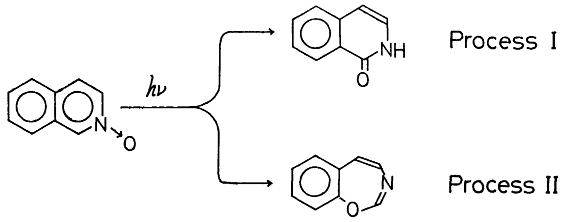
In order to deduce the nature of the reactive state of the photochemical isomerization of isoquinoline *N*-oxide in methanol or water, investigations by means of steady-light irradiation and flash spectroscopy were carried out under various conditions. Transient absorptions were observed in the spectral region between 360 nm and 600 nm; they were identified as being due to a T–T transition of isoquinoline *N*-oxide. Experiments on both the measurements of the quantum yields and the decay kinetics of the transient species under different conditions revealed that the excited singlet state of isoquinoline *N*-oxide was responsible for the isomerization. The photochemical behavior in aqueous solutions at various pH values was also examined; consequently, the photochemical isomerization was found to be independent of the hydrogen ions, although it did not occur in a strongly acidic solution (pH$<$3.0) because of the formation of the protonated *N*-oxide. The biacetyl-photosensitization for isoquinoline *N*-oxide led to the dissociation of the N–O bond instead of to isomerization.

It is well known that the azanaphthalene *N*-oxides undergo interesting but complex photochemical reactions in solution.[1] For example, the ultraviolet irradiation of quinoline *N*-oxide or isoquinoline *N*-oxide results in the formation of lactams and/or oxazepines, depending on the nature of the reaction medium or the substituent group. Hereafter, the photochemical change leading to the formation of a lactam will be referred to as Process I, while the photochemical conversion to an oxazepine will be termed Process II.



In hydroxylic solvents, such as methanol and water, the quinoline- or isoquinoline-*N*-oxide is predominantly transformed into its lactam (carbostyril or isocarbostyril) as a result of the ultraviolet irradiation, whereas in non-hydroxylic solvents, such as acetone and carbon tetrachloride, Process II generally becomes much more important than Process I. Mechanistic studies, including the identification of the reactive excited state, of the photochemical isomerizations of heterocyclic *N*-oxides have been extensively performed in recent years.[1–3] In order to account for such photochemical isomerizations, the oxaziridine has been customarily postulated to be a photochemical intermediate common to both Processes I and II. Very recently, however, Lohse has suggested that it is not valid to assume an oxaziridine as a photochemical intermediate common to both Processes.[2b] As an aid in the mechanistic elucidation of the photochemical reactions of azanaphthalene *N*-oxides, therefore, the present authors carried out studies by means of both steady-light and flash illumination for the isoquinoline *N*-oxide in methanol or water (Process I).

Experimental

Materials. The isoquinoline *N*-oxide used in this experiment was synthesized by Ochiai's method,[4] and the product was purified by vacuum distillation, followed by silica gel chromatography (using diethyl ether-ethanol as the eluant). In the irradiation experiments, reagent-grade methanol of Wako Pure Chemical Industries was used without further purification; a 1 M sodium hydroxide solution, 20% hydrochloric acid, and a standard buffer solution (pH 6.86) were also used. The 1,3-cyclohexadiene, piperylene, isoprene (Tokyo Kasei Kogyo Co.), and biacetyl (Wako Pure Chemical Ind.) used as triplet quenchers or sensitizers were purified by distillation.

Steady-light Experiment. Small-scale photolyses for the determination of the quantum yield were performed in a quartz cylindrical cell 5 cm in diameter and 1 cm in length. The UV light source was a 250 W high-pressure mercury lamp (Ushio-250). For the 313-nm irradiation, a filter combination of a nickel sulfate solution with UV-29 and UVD-25 Toshiba filters was used. The light intensity was determined by means of a potassium ferrioxalate actinometer. The disappearance of isoquinoline *N*-oxide was followed quantitatively at 298 nm with a Hitachi recording spectrophotometer, EPS-3T. The amounts of isocarbostyril produced were measured by means of a chromatographic separation (silica gel, chloroform–ethanol) combined with a spectrophotometric determination; for this purpose, a UV spectrometer, UVICON-540 (Tokyo Kagaku Sangyo Co.), and a recorder, EPR-2TP (Toa Dempa Kogyo Co.), were used. Large-scale photolyses were performed at concentrations of approximately 5.0×10^{-3} M (70 ml) in a Pyrex vessel using a 100 W high-pressure immersion mercury lamp (Riko Kagaku Sangyo Co.) under the bubbling in of nitrogen; the photoproducts were then separated by silica gel chromatography. In the case of the biacetyl-sensitization experiment, a methanol solution containing 6.0×10^{-3} M of isoquinoline *N*-oxide and 3.0×10^{-2} M of biacetyl in a quartz cylindrical reaction vessel (5 cm in diameter and 1 cm in

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[1] G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

[2] (a) G. Favaro, *Mol. Photochem.*, **2**, 323 (1970). (b) C. Lohse, *J. Chem. Soc. Perkin II*, **1972**, 229. (c) F. Bellamy, L. G. R. Barragan, and J. Streith, *Chem. Commun.*, **1971**, 456. (d) A. Alkaitis and M. Calvin, *ibid.*, **1968**, 292.

[3] (a) C. Kaneko, *Yuki Gosei Kagaku Kyokai Shi.*, **26**, 758 (1968). (b) C. Kaneko, Sa. Yamada, I. Yokoe, and T. Kubota, *Tetrahedron Lett.*, **1970**, 2333.

[4] E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam (1967), Chapter 3.

length) was irradiated with a 250 W high-pressure mercury lamp (Ushio-250) equipped with a Toshiba V-Y 43 filter for 10 hrs under a nitrogen atmosphere. The phosphorescence spectra were taken with a Hitachi fluorescence spectrophotometer MPF-2A, with a phosphorescence accessory attached.

Flash Spectroscopic Experiment. The flash-photolysis apparatus used in this experiment was the same as that described elsewhere.[5] An energy of 120J was dissipated by discharging a bank of condenders of 2 μF charged to 11 kV; the duration of the flash was about 10 μs.

Results and Discussion

The isoquinoline *N*-oxide in methanol or ethanol isomerizes upon irradiation by ultraviolet light to give isocarbostyril in *ca.* 70% yield.[6] This photochemical isomerization (Process I) also proceeded in an aqueous solution to give a good yield (*ca.* 75%), irrespective of the atmosphere, nitrogen or oxygen. Figure 1 shows the progressive spectral change in isoquinoline *N*-oxide on 313-nm irradiation in methanol; it was observed that the absorption of isoquinoline *N*-oxide decreased in intensity, and a new absorption band due to isocarbostyril appeared with isosbestic points, as the irradiation time increased.

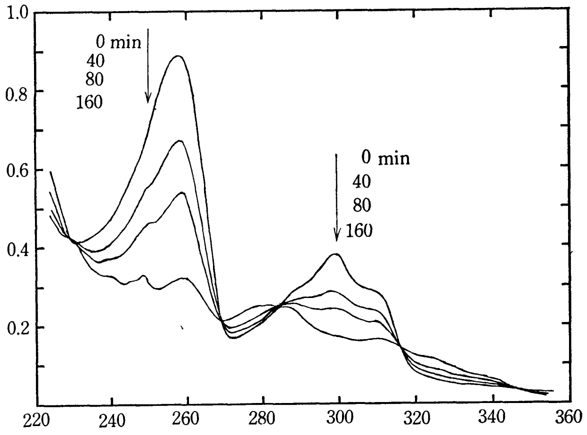

Fig. 1. The progressive spectral change of isoquinoline *N*-oxide (3.5×10^{-5} M) on 313 nm irradiation in methanol. Numbers refer to the irradiation time.

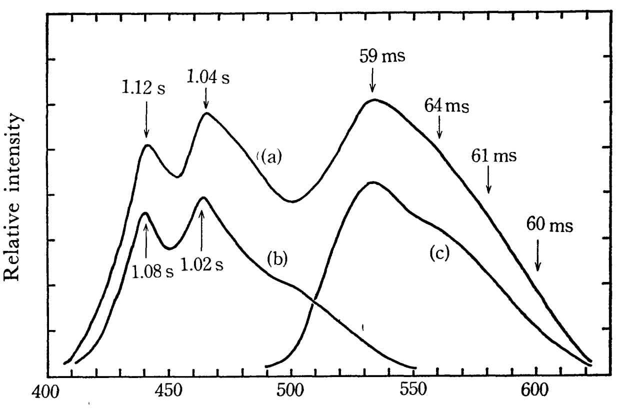

Fig. 2. Phosphorescence spectra of (a) isoquinoline *N*-oxide (5.0×10^{-5} M), (b) isocarbostyril (1.0×10^{-4} M), and (c) highly fresh solution of isoquinoline *N*-oxide (5.0×10^{-5} M) in EPA glass at 77 K.

Phosphorescence Spectra. Curve (a) in Fig. 2 shows the phosphorescence spectrum from EPA glass containing 5.0×10^{-5} M of isoquinoline *N*-oxide at 77 K. As is shown in the figure, the phosphorescence lifetime was quite dependent on the emission wavelength; that is, it was *ca.* 1.0 s at the shorter wavelengths (400—500 nm), while it was *ca.* 60 ms at the longer wavelengths (500—600 nm). Ziolkowsky and Dörr[7] have obtained the same results; they have assigned the shorter wavelength band to the phosphorescence of isoquinoline *N*-oxide. However, the experimental results to be presented below definitely show that the longer wavelength band can better be ascribed to the phosphorescence of isoquinoline *N*-oxide, whereas the shorter wavelength one should be ascribed to the phosphorescence of the isocarbostyril resulting photochemically from isoquinoline *N*-oxide.

(i) The shorter wavelength band was quite similar to the phosphorescence spectrum of isocarbostyril (Curve (b) in Fig. 2); the decay time (1.08 s) was also in good agreement with the phosphorescence lifetime of isocarbostyril (1.05 s). (ii) The very fresh solution (5.0×10^{-5} M), immediately after preparation, gave only the longer-wavelength emission (Curve (c) in Fig. 2). When the solution was allowed to stand for a while in the light, however, the shorter-wavelength emission appeared also. (iii) The longer-wavelength emission band was in a mirror-image relation with the S–T absorption band of isoquinoline *N*-oxide determined by Kubota et al.[8] (Fig. 3).

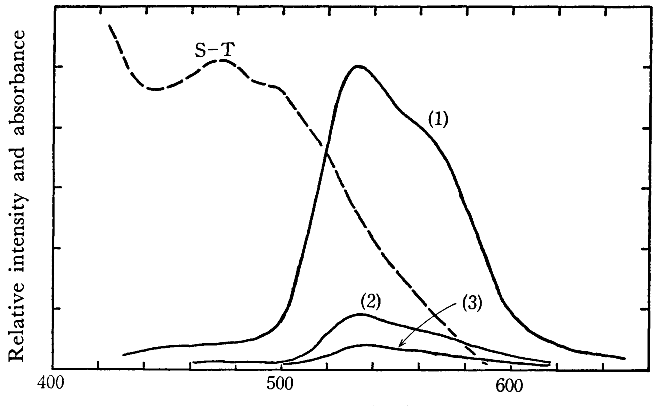

Fig. 3. Phosphorescence and S-T absorption spectra of isoquinoline *N*-oxide. —— : Phosphorescence spectrum in EPA glass at 77 K. ---- : S-T absorption spectrum in chloroform at room temperature.[8]
(1) [1,3-cyclohexadiene]: 0 M
(2) [1,3-cyclohexadiene]: 2×10^{-1} M
(3) [1,3-cyclohexadiene]: 5×10^{-1} M

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[5] N. Hata, I. Ono, and T. Tsuchiya, This Bulletin, **45**, 2386 (1972).

[6] M. Ishikawa, Sa. Yamada, H. Hotta, and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **14**, 1102 (1966).

[7] B. Ziolokowsky and F. Dörr, *Ber. Bunsenges. Phys. Chem.*, **69**, 448 (1965).

[8] T. Kubota, M. Yamakawa, and Y. Mizuno, This Bulletin, **45**, 3282 (1972).

From the maximum of the phosphorescence spectrum of isoquinoline *N*-oxide (532 nm), the excitation energy of the lowest triplet state was estimated to be about 53.7 kcal·mol^{-1}. Consequently, the addition of 1,3-cyclohexadiene (E_T=52.5 kcal·mol^{-1}) to a methanol solution of isoquinoline *N*-oxide in amounts much greater than the molar equivalence led to the complete disappearance of the phosphorescence (Fig. 3). On the other hand, the addition of piperylene (E_T=56.9 kcal·mol^{-1}) or isoprene (E_T=60.1 kcal·mol^{-1}) did not quench the phosphorescence of isoquinoline *N*-oxide, but it did quench the phosphorescence of isocarbostyril. Interestingly, in a concentrated solution (4.0×10^{-4} M) of isoquinoline *N*-oxide, only its phosphorescence spectrum was observed. This is probably because the phosphorescence of isocarbostyril can be quenched by an unexcited *N*-oxide, since the T–T energy transfer between them is energetically possible.

Steady-light Irradiation. The quantum yields of both the disappearance of isoquinoline *N*-oxide (Φ_d) and the formation of isocarbostyril (Φ_f) were examined in a deaerated methanol at room temperature. Figure 4(a) shows the effect of the irradiation time on the quantum yield in a 1.0×10^{-4} M solution; the results indicate that the quantum yield was independent of the irradiation time. The quantum yields were also determined as a function of the initial concentration of isoquinoline *N*-oxide. As is shown in Fig. 4 (b), a long-lived excited species susceptible to a collisional deactivation by an unexcited *N*-oxide is not involved in the photochemical reaction. In order to clarify whether or not the triplet species are responsible for this isomerization, therefore, the triplet quenching or sensitization experiments for the photochemical reaction of isoquinoline *N*-oxide were undertaken by using a 1,3-cyclohexadiene (triplet quencher) or a biacetyl (triplet sensitizer) in a deaerated methanol. As can be seen from Fig. 4(c), the quantum yield of the *N*-oxide disappearance was unaffected by the addition of 1,3-cyclohexadiene. Furthermore, the biacetyl-sensitization for the isoquinoline *N*-oxide in deaerated methanol did not lead to the isomerization of *N*-oxide, but instead resulted in the dissociation of the N–O bond, thus giving rise to the isoquinoline in a 30% yield. Similar results were also obtained in the case of a deaerated chloroform or benzene solution. These results suggest that the lowest triplet state of isoquinoline *N*-oxide is responsible for the deoxygenation, but not for the isomerization.

Flash Spectroscopy. In order to get information on the photochemical intermediate which may be formed during the reaction, the flash-spectroscopic examinations were carried out in EPA glass at 77 K or in a deaerated methanol at room temperature. As is shown by Curve (a) in Fig. 5, the transient absorption was observed around 400 nm (strong) and 480 nm (weak) in EPA glass at 77 K. Figure 6 shows the results when the first-order rate law was applied to the decay of transients at 77 K at various wavelengths. The decay time was evaluated from the slope of the straight-line to be 57 ms, a value which agreed closely with the phosphorescence lifetime (60 ms). When the deaerated methanol solution of isoquinoline *N*-oxide was flash-illuminated at room temperature, a distinct maximum was observed only around 400 nm, since the absorption

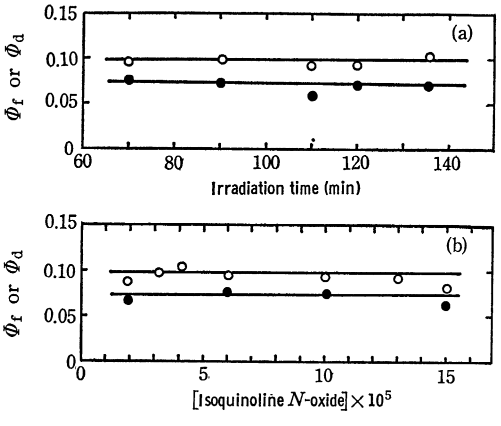


Fig. 4. Quantum yields of the photochemical isomerization of isoquinoline *N*-oxide in deaerated methanol at room temperature.

-●- : quantum yield of the formation of isocarbostyril, Φ_f, -○- : Quantum yield of the isoquinoline *N*-oxide disappearance, Φ_d. (a) Effect of the irradiation time (concentration of isoquinoline *N*-oxide: 1.0×10^{-4} M). (b) Effect of the initial concentration of isoquinoline *N*-oxide. (c) Effect of the addition of 1,3-cycrohexadiene (concentration of isoquinoline *N*-oxide: 6.0×10^{-5} M).

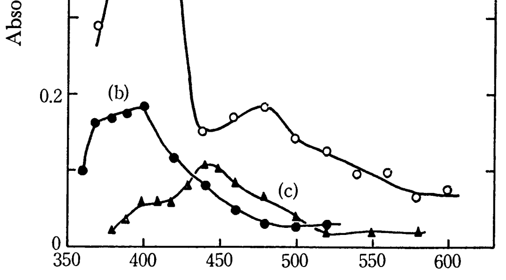


Fig. 5. Transient absorption spectra of isoquinoline *N*-oxide and isocarbostyril.

(a) -○- : Isoquinoline *N*-oxide, in EPA glass at 77 K.

(b) -●- : Isoquinoline *N*-oxide, in methanol at room temperature.

(c) -▲- : Isocarbostyril, in methanol at room temperature.

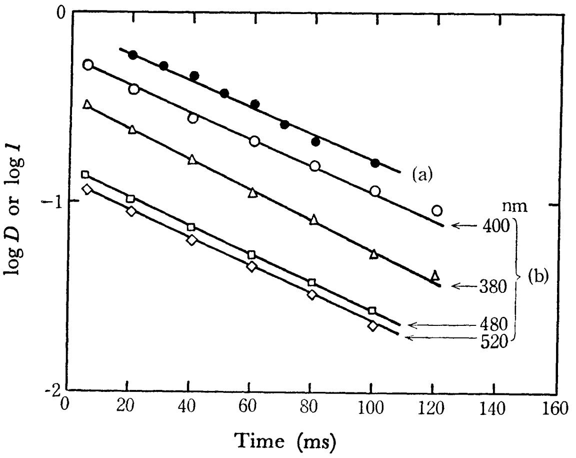


Fig. 6. Decay analysis for the phosphorescence (a) and for the transient species (b) in EPA glass at 77 K (concentration of isoquinoline N-oxide: 5.0×10^{-5} M).

intensity was lowered considerably at room temperature compared to that at 77 K (Fig. 5). The decay time estimated from the first-order rate plot was *ca.* 30 μs.

Next, the effect of the triplet quencher on the transient absorption was investigated in a deaerated methanol at room temperature. As can be seen from Fig. 7, the decay rate of the transient increased linearly with an increase in the concentration of 1,3-cyclohexadiene, although the piperylene or isoprene had no effect on the decay rate. The quenching rate constant evaluated from the slope of the straight-line was $8.1\times10^{8}\ \mathrm{l\cdot mol^{-1}\cdot s^{-1}}$. The possibility that the transient absorption could be due to a T–T transition of the photoproduct (isocarbostyril) was definitely excluded by the flash-spectroscopic examinations for isocarbostyril itself. That is, as is shown in Figs. 5 and 7, the T–T absorption of isocarbostyril in a deaerated methanol at room temperature was completely different from that of isoquinoline N-oxide in maximum wavelength and in decay rate. In addition, the decay rate was observed to increase linearly with an increase in the concentration of the piperylene or isoprene (Fig. 7). Therefore, the transient absorption (Curve (a) in Fig. 5) was definitely identified as being due to a T–T transition of isoquinoline N-oxide. Although the triplet species was effectively quenched by 1,3-cyclohexadiene, the quantum yield of the photochemical isomerization was unaffected, as has been described before (Fig. 4). This also supports the idea that the lowest triplet state of isoquinoline N-oxide is not involved in the photoisomerization, but that the isocarbostyril results from an excited singlet state.

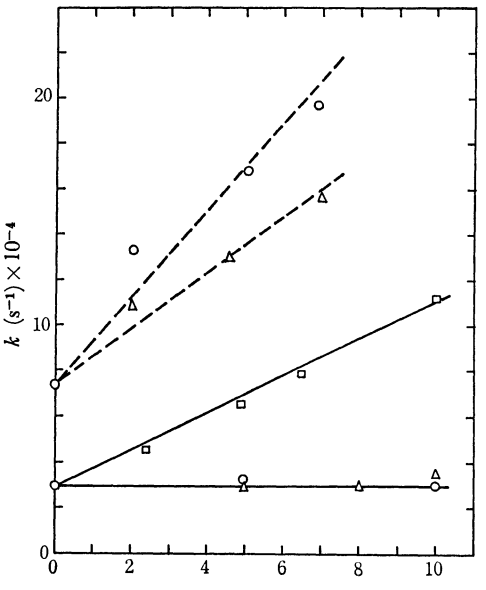
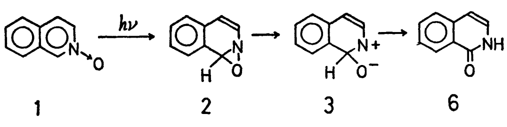
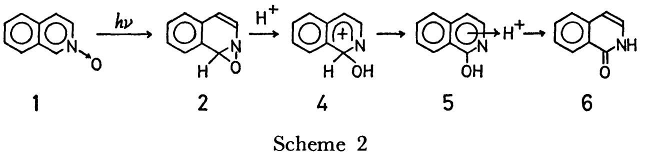


Fig. 7. Effect of the triplet quencher (-○- : isoprene, -△- : piperylene, -□- : 1,3-cyclohexadiene) on the transient species of isoquinoline N-oxide and isocarbostyril in deaerated methanol at room temperature. —— : for isoquinoline N-oxide (5.0×10^{-5} M), ---- ; for isocarbostyril (1.0×10^{-4} M).

Effect of pH *on the Photochemical Isomerization.* In order to account for Processes I and II of the azanaphthalene N-oxides, Buchardt and Kaneko have independently proposed the idea that an oxaziridine may be initially formed as a photochemical intermediate common to both Processes.[1,3] On the basis of this assumption, Process I has been explained as follows. According to Buchardt,[1] the zwitter ion, **3**, resulting from a heterolytic cleavage of the oxaziridine **2** may be supposed to rearrange by a 1,2 shift (Scheme 1). Since a protonation of the $-\mathrm{O}^{-}$ group may take place during the rearrangement, the photochemical isomerization in an aqueous solution is inferred to be affected by a variation in the pH values. Kaneko[3] has assumed a heterolytic cleavage of the oxaziridine **2**, followed by the formation of a carbonium ion, **4**, which can then rearrange to the lactam (Scheme 2); thus, the photoisomerization is considered to be facilitated by the presence of hydrogen ions. In either case, the photochemical isomerization in an aqueous solution is expected to be influenced to some extent by a lowering of the pH values.



Scheme 1



Scheme 2

Therefore, in order to clarify the effect of hydrogen ions on the isomerization process, photochemical examinations of isoquinoline N-oxide were performed on aqueous solutions at different pH values. Curve (a) in Fig. 8 shows the quantum yields of the disappearance of isoquinoline N-oxide plotted against the pH; that is, the independence of the quantum yield (*ca.* 0.07) of the pH in the 13.0—3.0 range was observed,[9] al-

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[9] The similar result has been also obtained in the case of quinoline N-oxide by Favaro.[2a]

though there was a steep increase at lower pH values (<3.0). In addition, the chemical yield of the isocarbostyril produced (Curve (b) in Fig. 8) was also found to be independent of the pH values except for the case of a strongly acidic solution ($\mathrm{pH}<3.0$). These facts probably mean that Process I does not proceed ionically through the oxaziridine intermediate, as is shown in Schemes 1 and 2. For this reason, it seems to be difficult to assume that Procesess I and II involve a common intermediate such as an oxaziridine. This view seems to support the conclusion of Lohse.[1b)]

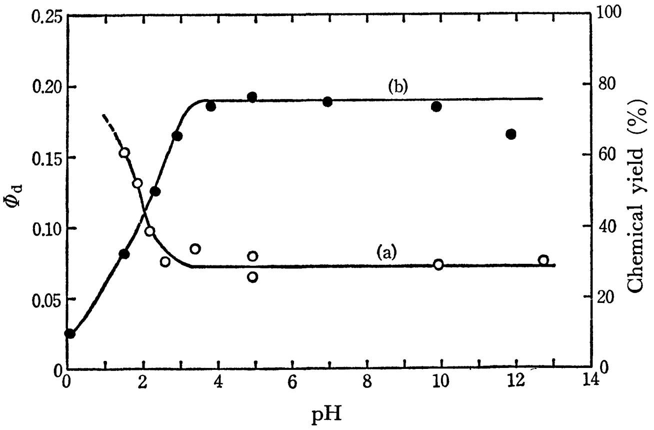

Fig. 8. Effect of pH on the quantum yield of isoquinoline *N*-oxide disappearance (-○-) and the chemical yield(%) of isocarbostyril (-●-) in aqueous solutions at room temperature.

Meanwhile, the p*K*a values of isoquinoline *N*-oxide in the ground and lowest-excited singlet states have been reported by Kubota[10a)] to be 1.05 (or 1.01[10b)]) and 0.81 respectively. Therefore, the remarkable change in both the quantum and chemical yields in strongly acidic solutions could be interpreted in terms of an acid-base equilibrium in the ground or lowest excited singlet state; that is, the photochemical isomerization of isoquinoline *N*-oxide proceeds from the excited non-protonated *N*-oxide, while the excited protonated molecule undergoes decomposition instead of isomerization.

The authors wish to thank Professor Shiro Matsumoto of this university for his permission to use the flash-photolysis apparatus.

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10) (a) T. Kubota, *J. Spectrosc. Soc. Jap.*, **10**, 83 (1962). (b) H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.*, **77**, 4441 (1955).