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Roles of Oxygen in Photochemical Reaction of Naphthols in Aqueous Nitrite Solution and Mutagen Formation

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Naphthols were irradiated with ultraviolet light in aqueous nitrite solution under air, oxygen and nitrogen atmospheres. 2-Naphthol gave a mutagenic product in an amount proportional to the irradiation time under air. The mutagen formation was greatly accelerated under oxygen, whereas irradiation under nitrogen gave no mutagen. 1-Naphthol gave scarcely any mutagen under any conditions. The photoreactions of naphthols in the presence and absence of nitrite under the three conditions were analyzed by high performance liquid chromatography in terms of degradation of naphthols and production of nitrosonaphthols, nitronaphthols, quinones and isocoumarin. It was proved that the reactions of nitration and naphthoquinone production both require oxygen. Consequently, the oxygen requirement for mutagen formation was attributable to those for nitration and quinone production from 2-naphthol. Nitronaphthols were presumed to be produced directly by the reaction of photo-induced naphthoxy radical with NO_2 radical formed by oxidation of photo-induced NO radical. Both 1,2- and 1,4-naphthoquinones were found to be converted photochemically to photo-stable isocoumarin, which exhibited only ambiguous mutagenicity, at different rates. 1-Naphthol, compared with 2-naphthol, was hardly nitrated and was easily converted to isocoumarin, and such reactivity was presumed to be the main reason for the lack of mutagen formation.

Keywords——1-naphthol; 2-naphthol; aqueous nitrite solution; UV irradiation; oxygen; mutagen formation; nitronaphthol; nitrosonaphthol; naphthoquinone; isocoumarin

Introduction

We have been investigating photochemical mutagen formation from aromatic compounds in water containing nitrite or nitrate ion as a cause of mutagen formation in aquatic environments.[1-7] In earlier studies, we found that mutagens were formed from a wide variety of aromatic compounds such as benzene, phenol, chlorobenzene, benzoate and aromatic amino acids, as well as polycyclic aromatics, by ultraviolet (UV) irradiation in aqueous solution containing nitrite ion.[2,4] On the basis of mutagenic or nonmutagenic reaction products identified, the major photoreactions had been considered to be hydroxylation, nitration and nitrosation.[3,5,6]

In the previous paper, however, we reported the isolation of 1-nitro-2-naphthol, 1-nitroso-2-naphthol, isocoumarin, 5- or 8-nitro-2-naphthol, a monoquinonoid dimer of 2-naphthol, a dinitro-2-naphthol and 1,2-naphthoquinone as the photoreaction products of 2-naphthol in aqueous nitrite solution. Among these compounds, 1-nitro-2-naphthol, 5- or 8-nitro-2-naphthol, a dinitro-2-naphthol and isocoumarin exhibited only very weak mutagenicity toward *Salmonella typhimurium* TA 98 without S9 mix, and no major mutagen was isolated. However, it was confirmed that irradiations of a solution of non-mutagenic monoquinonoid dimer of 2-naphthol with nitrite and of a mixed solution of 1,2-naphthoquinone and 1-nitro-2-naphthol without nitrite resulted in the formation of further

mutagenic compounds, indicating that not only nitration but also oxidative quinone production is a key step in the photochemical mutagen formation.[7] These findings suggest that oxygen must be involved in the photoreaction for mutagen formation. Accordingly, elucidation of oxygen-dependent and nitrite-dependent reactions is expected to offer important information on the mutagen formation.

In this paper, we show that oxygen is required for the photochemical mutagen formation from 2-naphthol in aqueous nitrite solution, and we present the results of a quantitative analysis of the changes in the reaction products from naphthols upon irradiation under air, oxygen and nitrogen. Additionally, based on a comparison of the reactivity of 2-naphthol with that of 1-naphthol, we discuss the reason why 1-naphthol gives almost no mutagen upon UV irradiation under the same conditions.

Experimental

Chemicals——1-Naphthol and 2-nitro-1-naphthol were obtained from Kanto Kagaku Co. and Aldrich Chemical Co., respectively. 2-Nitroso-1-naphthol and 1,4-naphthoquinone were obtained from Nakarai Chemical Co. All other chemicals were as described in the previous paper.[7]

UV Irradiation——Aqueous solutions of 1- and 2-naphthols (50 mg/l) with or without nitrite ($NaNO_2$, 80 mg/l) were irradiated with the same apparatus as described previously[7] under the following three conditions. Irradiation was performed under an oxygen or a nitrogen stream, after sufficient bubbling of the gas through the solution before irradiation (reactions under an oxygen or a nitrogen atmosphere). For the reaction in air, the stopper of the reaction vessel was left open during irradiation without bubbling of any gas.

Mutation Assay——The mutagenicity of the reaction solution was assayed by Ames' method as described in the previous paper[7] using *S. typhimurium* TA98.

Identification of Reaction Products from 1-Naphthol——The reaction products of 1-naphthol have not been established, although those of 2-naphthol were identified as reported previously.[7] Therefore, the reaction products were analyzed by high performance liquid chromatography (HPLC). Figure 1 shows chromatograms of the reaction mixture of 1-naphthol irradiated in aqueous nitrite solution under air and oxygen (the HPLC conditions were as described below). The retention times (t_R) of the peaks a (t_R, 4.0 min), b (t_R, 5.7 min) and c (t_R, 17.3 min) in Fig. 1A coincided with those of authentic 2-nitroso-1-naphthol, 1-naphthol and 2-nitro-1-naphthol, respectively. The t_Rs of the peaks b (t_R, 8.7 min), d (t_R, 4.1 min) and e (t_R, 5.6 min) in Fig. 1B coincided with those of authentic 1-naphthol, isocoumarin and 1,4-naphthoquinone, respectively.

The ether extracts from the reaction mixtures irradiated for 30 min under oxygen and for 3 h under air were fractionated by means of the same silica gel column chromatography (Kiesel gel 60) as described previously.[7] The product corresponding to each peak in Fig. 1 was separated and purified by HPLC. Nuclear magnetic resonance (NMR) and mass spectra (MS) of the isolated substances were obtained with a JNM-FX 100 NMR spectrometer (in $CDCl_3$, internal standard tetramethylsilane) and a Hitachi RMU-7M double-focussing mass spectrometer operating at 70 eV, respectively. The isolated substances were identified from their NMR, MS and HPLC data as follows.

The compound corresponding to peak c (mp 128—130 °C) was determined to be 2-nitro-1-naphthol, because the following spectral data coincided with those of a commercial standard (mp 128 °C). NMR (in $CDCl_3$) δ: 7.31 (1H, d,

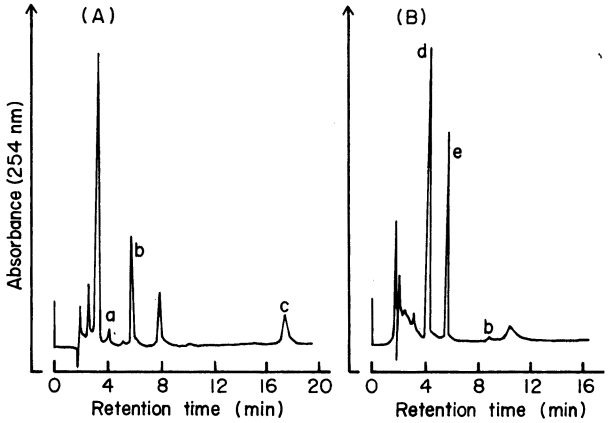

Fig. 1. HPLC Chromatograms of the Reaction Mixture of 1-Naphthol Irradiated in Aqueous Nitrite Solution

(A) Irradiation for 1 h under air. Solvent for HPLC, MeOH–water adjusted to pH 2 with phosphoric acid (65 : 35); the t_Rs of peaks a (4.0 min), b (5.7 min) and c (17.3 min) coincided with those of authentic 2-nitroso-1-naphthol, 1-naphthol and 2-nitro-1-naphthol, respectively. The strong peak at 3 min was due to isocoumarin and 1,4-naphthoquinone (not separated) and the peak at 7.8 min and other minor peaks were unidentified.

(B) Irradiation for 30 min under oxygen. Solvent for HPLC, MeOH–water (60 : 40); the t_Rs of peaks b (8.7 min), d (4.1 min) and e (5.6 min) coincided with those of authentic 1-naphthol, isocoumarin and 1,4-naphthoquinone, respectively. The peak at 10.4 min and other minor peaks were unidentified.

$J_{4,3}=9$ Hz, 4-H), 7.46—7.82 (3H, m, 5-, 6-, 7-H), 7.98 (1H, d, $J_{3,4}=9$ Hz, 3-H), 8.48 (1H, dd, $J_{8,7}=8$ Hz, $J_{8,6}=2$ Hz, 8-H), 12.24 (1H, s, 1-OH). MS *m/z* (%): 189 (100, M^+), 172 (17, M^+-OH), 159 (11, M^+-NO), 143 (13, M^+-NO_2), 131 (24, $M^+-NO-CO$), 115 (52, M^+-NO_2-CO), 114 (70, M^+-NO_2-CHO), 103 (12), 89 (23), 77 (17), 63 (27).

The compound corresponding to peak d (mp 45.5—46.5 °C) was determined to be isocoumarin (mp 46—47 °C),[8] because the NMR and MS data coincided with those of the isocoumarin identified in the previous paper.[7]

The compound corresponding to peak e (mp 123—124 °C) was determined to be 1,4-naphthoquinone, because the following spectral data coincided with those of a commercial standard (mp 126 °C). NMR (in $CDCl_3$) δ: 7.04 (2H, s, 2-, 3-H), 7.75—7.85 (2H, m, 6-, 7-H), 8.05—8.18 (2H, m, 5-, 8-H). MS *m/z* (%): 158 (100, M^+), 130 (44, M^+-CO), 104 (57, $M^+-CO-CHCH$), 102 (52, M^+-2CO), 76 (54, $M^+-2CO-CHCH$), 50 (35), 28 (32).

The compound corresponding to peak a, which was presumed to be 2-nitroso-1-naphthol from the retention time, was obtained in such a small amount and was so unstable that isolation was impossible.

None of the identified compounds exhibited apparent mutagenicity toward *S. typhimurium* TA98 with or without S9 mix. Isocoumarin also exhibited only ambiguous mutagenicity, although it has been reported that it exhibited weak mutagenicity.[7] This discrepancy seems to be due to a trace amount of a mutagenic impurity in the isocoumarin isolated from the reaction mixture of 2-naphthol in the previous paper.

Quantitative Analysis of Reaction Products——Naphthols, 1,2-and 1,4-naphthoquinones and isocoumarin in the irradiated solution were analyzed by means of HPLC under the following conditions, after addition of the internal standard solution as described below (1 ml) to the reaction solution (5 ml): column, SSC-ODS-262 (6 mm i.d. × 100 mm); solvent, MeOH–H_2O (60 : 40); flow rate, 1 ml/min; wavelength for detection, 254 nm; internal standard, *o*-chloronitrobenzene for the reaction solution of 1-naphthol and *m*-dinitrobenzene for that of 2-naphthol. The HPLC conditions for analysis of nitronaphthols and nitrosonaphthols were as follows: solvent, MeOH–water adjusted to pH 2 with phosphoric acid (65 : 35); internal standard, 2-nitronaphthalene; the other conditions were as mentioned above.

Results

The Effect of Oxygen on the Mutagen Formation from Naphthols

Figure 2 shows the time courses of mutagen formation from 1- and 2-naphthols by UV irradiation in aqueous nitrite solution under air, oxygen and nitrogen atmospheres. 2-Naphthol produced an amount of mutagen proportional to the irradiation time in the usual photoreaction under air. In the irradiation under nitrogen, no mutagen was produced. On the other hand, the photochemical mutagen formation was greatly accelerated under oxygen. The decrease in the number of revertant colonies after prolonged irradiation seems to be due to

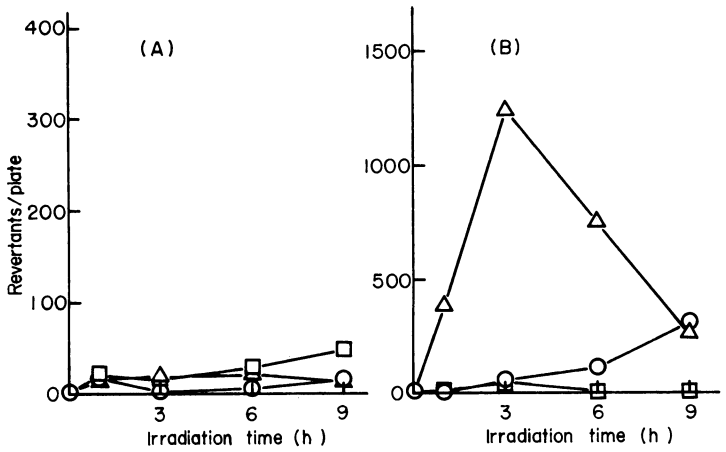

Fig. 2. Time Courses of Mutagen Formation from 1- and 2-Naphthols by UV Irradiation in Nitrite Aqueous Solution

(A) 1-Naphthol. (B) 2-Naphthol.
Irradiation under air (○), oxygen (△) and nitrogen (□). Mutagenicity is that toward *S. typhimurium* TA98 without S9 mix at a dose per plate of ether extract corresponding to 2 μg of original naphthol.

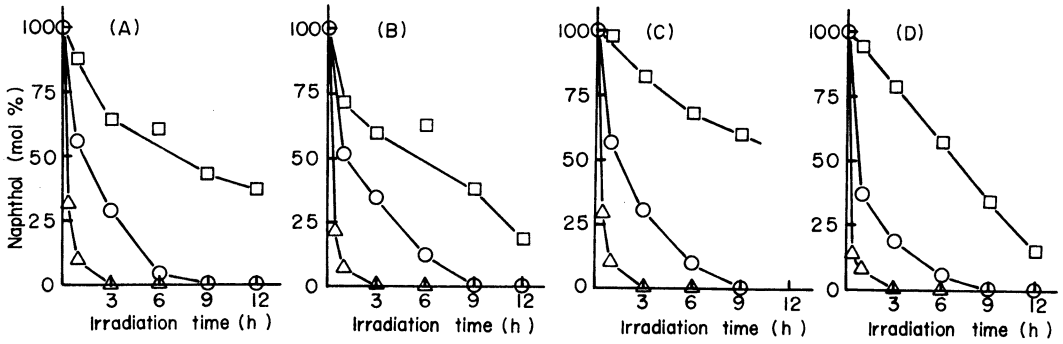

Fig. 3. Degradation of Naphthols by UV Irradiation in Aqueous Solution in the Absence and Presence of Nitrite

Irradiation of 1-naphthol with nitrite (A), 2-naphthol with nitrite (B), 1-naphthol without nitrite (C) and 2-naphthol without nitrite (D) under air (○), oxygen (△) and nitrogen (□).

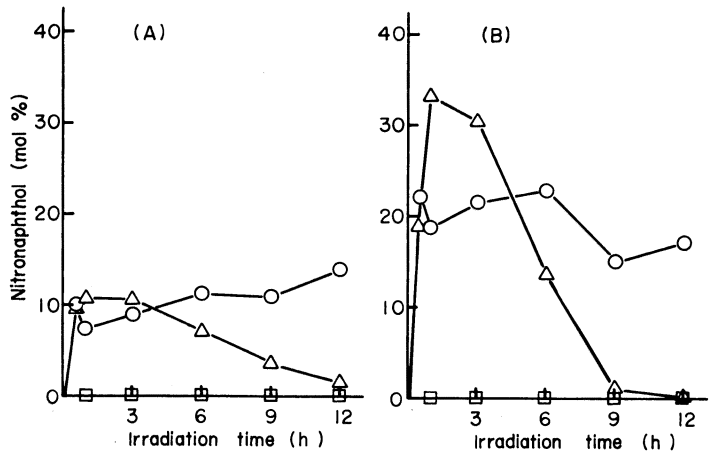

Fig. 4. Production of Nitronaphthols from Naphthols by UV Irradiation in Aqueous Nitrite Solution

Productions of 2-nitro-1-naphthol from 1-naphthol (A) and of 1-nitro-2-naphthol from 2-naphthol (B) by irradiation under air (○), oxygen (△) and nitrogen (□).

degradation of the mutagen (no clear change in the state of background lawn on the test plate was observed). These results indicate that the photochemical mutagen formation requires oxygen.

On the other hand, the reaction solution of 1-naphthol exhibited only very weak mutagenicity under all conditions, indicating that 1-naphthol gave scarcely any mutagen upon photochemical reaction in aqueous nitrite solution.

Quantitative Analysis of Photochemical Reaction of Naphthols

The effects of oxygen and nitrite ion on the photoreaction of naphthols in water were analyzed quantitatively by means of HPLC. The results are described below.

As can be seen from Fig. 3, the photodegradation rate of naphthols was the highest under oxygen and the lowest under nitrogen, indicating that the photochemical reaction was accelerated by oxygen. Figure 3 also shows that there was little difference in the photodegradation rate between 1-naphthol and 2-naphthol, and that the degradation rates were scarcely affected by nitrite ion.

Figure 4 shows nitronaphthol production from 1- and 2-naphthols under various

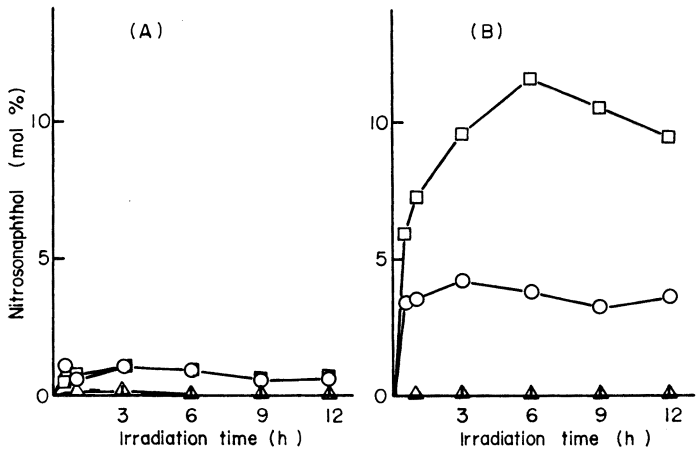

Fig. 5. Production of Nitrosonaphthols from Naphthols by UV Irradiation in Aqueous Nitrite Solution

Productions of 2-nitroso-1-naphthol from 1-naphthol (A) and of 1-nitroso-2-naphthol from 2-naphthol (B) by irradiation under air (○), oxygen (△) and nitrogen (□).

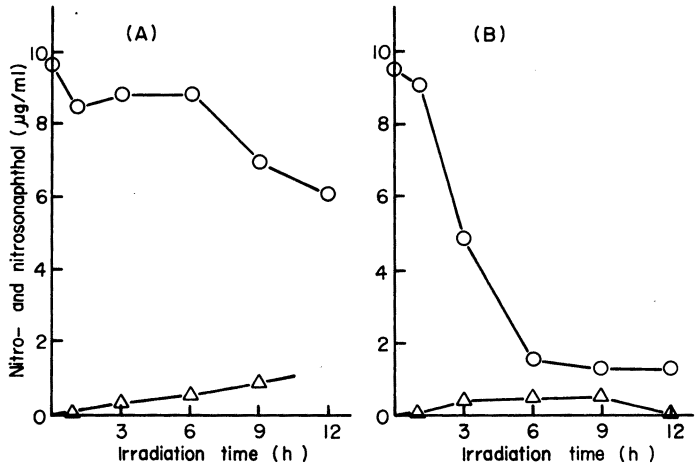

Fig. 6. Conversion of 1-Nitroso-2-naphthol to 1-Nitro-2-naphthol (10 mg/l) by UV Irradiation in Aqueous Solution

Degradation of 1-nitroso-2-naphthol (○) and production of 1-nitro-2-naphthol (△) under oxygen (A) and nitrogen (B).

reaction conditions. In the case of photoreaction of 2-naphthol under air, about 20 mol (%) of the original naphthol was converted to 1-nitro-2-naphthol by UV irradiation for 30 min and this remained approximately constant during further irradiation. In the case of photoreaction under an oxygen atmosphere, the amount of 1-nitro-2-naphthol produced reached 35 mol (%) of the original naphthol after irradiation for 1 h. However, it gradually decreased on further irradiation, indicating that nitronaphthol was converted rapidly to another compound in the presence of abundant oxygen. Under nitrogen, on the contrary, nitronaphthol was not detected, indicating that oxygen is required for the photochemical nitration. Needless to say, irradiation in nitrite-free aqueous solution resulted in no production of nitronaphthol. On the other hand, the amount of nitronaphthol produced from 1-naphthol was one-half to one-third that from 2-naphthol, although the 2-nitro-1-naphthol production was similarly affected by oxygen. These results indicate that photochemical nitration proceeds more readily in the case

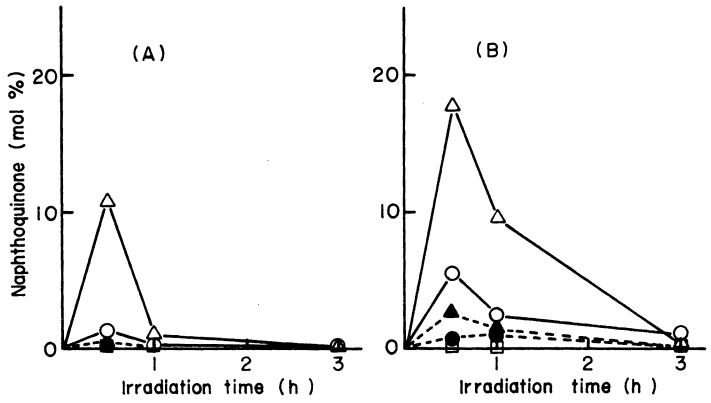

Fig. 7. Production of Naphthoquinones from Naphthols by UV Irradiation in Aqueous Solution in the Absence or Presence of Nitrite

Productions of 1,4-naphthoquinone from 1-naphthol (A) and of 1,2-naphthoquinone from 2-naphthol (B) by irradiation under air (○), oxygen (△) and nitrogen (□) in the presence (solid line, open symbols) or absence (broken line, closed symbols) of nitrite.

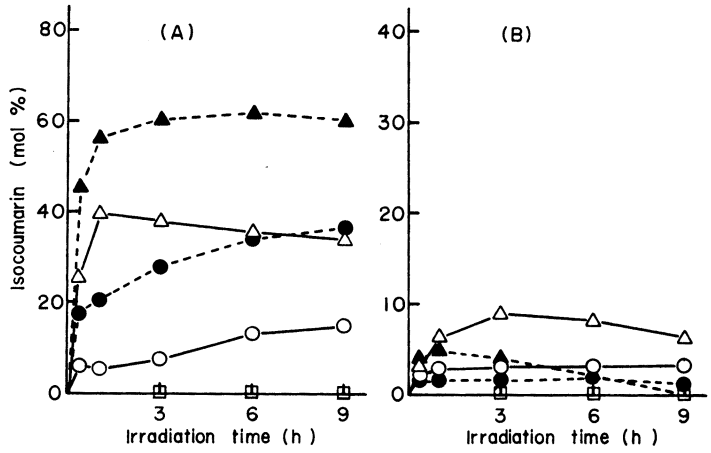

Fig. 8. Production of Isocoumarin from Naphthols by UV Irradiation in Aqueous Solution in the Absence and Presence of Nitrite

Irradiations of 1-naphthol (A) and 2-naphthol (B) under air (○, ●), oxygen (△, ▲) and nitrogen (□) in the presence (solid line, open symbols) and absence (broken line, closed symbols) of nitrite.

of 2-naphthol than 1-naphthol.

Figure 5 shows the production of nitrosonaphthols by photochemical reaction of naphthols. The photochemical nitrosation proceeded more readily in the case of 2-naphthol than 1-naphthol, as with the above-mentioned nitration. However, contrary to the nitration, nitrosation was accelerated by nitrogen and not observed under oxygen. This result raised the possibility that the nitronaphthols produced under air and oxygen may be formed by oxidation of the nitroso compound. Therefore, we irradiated an aqueous solution of 1-nitroso-2-naphthol (10 mg/l) under oxygen and nitrogen atmospheres. As shown in Fig. 6, only a small amount of 1-nitro-2-naphthol was produced in both cases. In addition, 1-nitroso-2-naphthol was more stable under oxygen than under nitrogen. These results demonstrated that most nitronaphthol was formed from naphthols by irradiation in aqueous nitrite solution under an atmosphere containing oxygen was due to direct nitration caused by photoreaction

with nitrite ion but not due to oxidation of nitrosonaphthol.

Figure 7 shows the productions of 1,4- and 1,2-naphthoquinones from 1- and 2-naphthols, respectively. The productions of both quinones were accelerated by oxygen, but did not occur under nitrogen. The naphthoquinones were produced even in nitrite-free aqueous solution, although the amounts were smaller than in the presence of nitrite. The amount of quinone detected in the photoreaction of 2-naphthol was larger than that of 1-naphthol, 18 and 11 mol (%) of the original naphthol, respectively, on irradiation for 30 min under oxygen. Both naphthoquinones, however, decreased rapidly on further irradiation, indicating that naphthoquinone was an initial intermediate in the photoreaction.

Both 1-naphthol and 2-naphthol were found to produce isocoumarin by UV irradiation as described in the experimental part and the previous paper.[7] The time courses of isocoumarin production under various conditions are shown in Fig. 8. As can be seen from this figure, the amount of isocoumarin produced from 1-naphthol was significantly larger than that from 2-naphthol. The production of isocoumarin from both naphthols was highly accelerated by oxygen, whereas it was not observed under nitrogen. The amount of isocoumarin produced from 1-naphthol in nitrite-free aqueous solution was significantly larger than that in aqueous nitrite solution and reached 60 mol (%) of the original naphthol after irradiation for 1 h under oxygen. In addition, the amount of isocoumarin produced was approximately constant during prolonged irradiation, indicating that isocoumarin was stable to irradiation. On the other hand, nitrite ion inhibited the production of isocoumarin from 2-naphthol.

In the course of analyzing the reaction solution irradiated for a short time, we noticed that naphthoquinone decreased on standing, while isocoumarin increased, suggesting that isocoumarin is formed through naphthoquinone. Therefore, isocoumarin production from naphthoquinones by irradiation was followed with HPLC. 1,4-Naphthoquinone was found to give isocoumarin in a 90% yield on irradiation for 15 min under air. Under nitrogen, the yield was about 10%. On the other hand, the yield of isocoumarin from 1,2-naphthoquinone was only a few percent even after irradiation under air.

Discussion

The results reported here demonstrate that the photochemical mutagen formation from 2-naphthol requires oxygen and nitrite ion and that nitration of naphthol and naphthoquinone production also require oxygen. As reported in the previous paper,[7] irradiations of a solution of a monoquinonoid dimer of 2-naphthol in the presence of nitrite and of a mixed solution of 1,2-naphthoquinone and 1-nitro-2-naphthol in the absence of nitrite have been found to result in the formation of a potent mutagen, indicating that both nitration and quinone production are required for mutagen formation. Accordingly, the oxygen dependence of mutagen formation is attributable to that of nitration and quinone production. Of the two reactions, quinone production was found to proceed even in the absence of nitrite ion, although nitration, of course, did not occur without nitrite.

1-Naphthol in aqueous solution showed UV absorption maxima at 235, 294, 307 and 321 nm, whereas 2-naphthol showed maxima at 231, 262, 272, 283, 317 and 328 nm. Naphthols are excited upon UV absorption to give naphthoxy radicals.[9] Under these experimental conditions, 1-naphthol and 2-naphthol are presumed to give a naphthoxy radical upon absorptions at 307 and 321 nm and 317 and 328 nm, respectively, because light with wavelengths less than 300 nm was excluded with a Pyrex glass filter. Accordingly, naphthoquinones are presumed to be produced by reaction of the naphthoxy radicals with oxygen.

Interestingly, both naphthoquinones were found to be converted rapidly into iso-

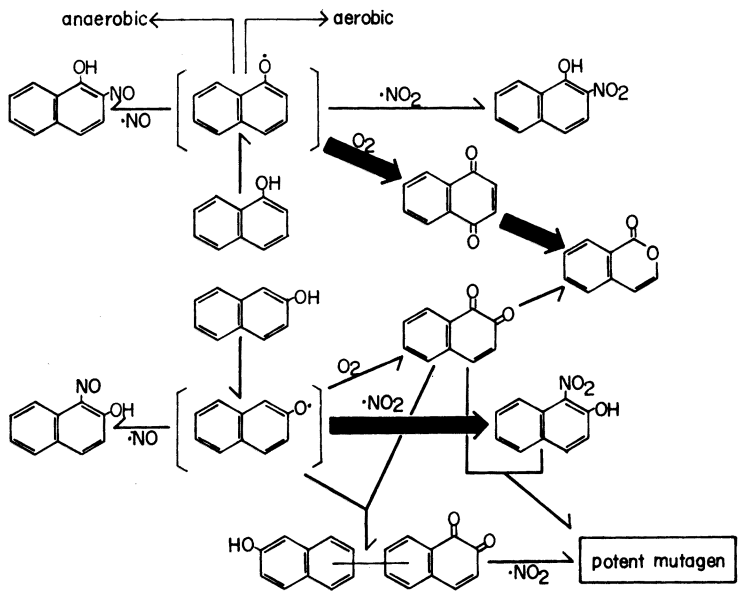

Fig. 9. Scheme of the Main Photochemical Reaction of 1- and 2-Naphthols in Aqueous Nitrite Solution under Aerobic and Anaerobic Conditions and the Route of Formation of a Potent Mutagen from 2-Naphthol

coumarin by photochemical reaction in aqueous solution under aerobic conditions. However, they differed from one another in the conversion rate (90 mol (%) in the case of 1,4-naphthoquinone and a few mol (%) for 1,2-naphthoquinone). Since isocoumarin is a very weak mutagen or non-mutagen[7] and is photochemically stable, the large difference in the conversion rate to isocoumarin between the two naphthoquinones must greatly affect the whole photochemical reaction and mutagen formation. The ease of conversion of 1,4-naphthoquinone to isocoumarin seems to make it difficult to produce a monoquinonoid dimer which is presumed to be a precursor of a potent mutagen[7] and to be formed by the reaction of naphthoquinone with a naphthoxy radical.

On the other hand, it is clear that nitrosonaphthols and nitronaphthols resulted from the photoreaction of naphthols with nitrite ion. In the previous paper, we reported that the photochemical nitrosation of phenol in aqueous nitrite solution was caused by both radicals, ·NO and ·OH, which are produced by the photolysis of nitrite ion.[3] In that case, nitrosation was considered to be caused by NO radical after hydrogen abstraction by OH radical. This mechanism was supported by the fact that the degradation rate of phenol was greatly stimulated by nitrite ions.[3] In the present case of naphthols, however, the nitrosation is presumed to be mainly caused by reaction of NO radical with naphthoxy radical produced by photoexcitation of naphthol itself, because the degradation rate of naphthol was scarcely affected by nitrite ion.

The production of nitronaphthols is usually considered to be due to oxidation of nitrosonaphthols. However, this seems not to be the case, since UV irradiation of aqueous nitrosonaphthol solution under oxygen only resulted in the production of a small amont of nitronaphthol. This means that nitronaphthols were directly produced by the photoreaction of naphthols with nitrite ion. In addition, the nitration was confirmed to proceed only in the presence of oxygen as mentioned above. Accordingly, it is presumed that the NO radical produced by photolysis of nitrite ion is oxidized with oxygen to give NO_2 radical ($2 \cdot NO + O_2 \rightarrow 2 \cdot NO_2$), and this nitrates naphthoxy radical to give nitronaphthol. The

oxidation of NO to NO_2 radical with oxygen has also been proposed by Usui and Shimizu.[10] On the basis of this mechanism, the lack of nitrosonaphthol formation in the photoreaction under oxygen is explicable in terms of the absence of NO radical, since most NO radical must be converted to NO_2 radical by abundant oxygen.

On the basis of the above-mentioned results and discussion, the main photochemical reactions of 1- and 2-naphthols in aqueous nitrite solution under aerobic and anaerobic conditions and the route of formation of potent mutagen may be summarized as in Fig. 9. The nitration of naphthoxy radical with NO_2 radical should compete with the oxidation of it to naphthoquinone with oxygen. On irradiation for 1 h in aqueous nitrite solution under oxygen, 1-naphthol gave 11 mol (%) of 2-nitro-1-naphthol and 41 mol (%) in total of 1,4-naphthoquinone and isocoumarin, whereas 2-naphthol gave 33 mol (%) of 1-nitro-2-naphthol and 16 mol (%) in total of 1,2-naphthoquinone and isocoumarin. Since isocoumarin originates from the naphthoquinones, these results indicate that 1-naphthoxy radical is predominantly oxidized to quinone and that 2-naphthoxy radical, on the contrary, is predominantly nitrated. The difference in the conversion rate of the naphthoquinones to isocoumarin as mentioned above may be responsible for the difference in the competing reaction of oxidation and nitration between the two naphthols. In any event, the ease of isocoumarin production and/or the difficulty of nitronaphthol production seems to be a main cause of the lack of potent mutagen formation from 1-naphthol.

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