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Synthesis of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate and Its Solvolytic Properties with or without Bivalent Copper

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1,2-Naphthoquinone 1-oxime *O*-sulfate (**1**) was synthesized by sulfation of 1-nitroso-2-naphthol with chlorosulfonic acid and *N*,*N*-dimethylaniline. The sodium salt of **1** was decomposed to form inorganic sulfate and 1-nitroso-2-naphthol in neutral (pH 4.9, 80°) and acidic (0.1 N HCl, 40°) conditions, with their half-lives of 380 and 140 min, respectively. In an alkaline medium (0.1 N NaOH, 20°), the salt was instantaneously decomposed to give a quantitative amount of inorganic sulfate and a ring-cleaved product of 1,2-naphthoquinone 1-oxime moiety, and this product was identified as *o*-cyano-*cis*-cinnamic acid (**2**). The effect of Cu(II) on the hydrolysis of **1** was more accelerative in a neutral condition than in an acidic condition, resulting in the reduction of its half-life to 60 min. It was also observed that polar organic solvents such as pyridine, dioxan, and tetrahydrofuran markedly accelerated the hydrolysis of the triethylammonium salt of **1**, in both neutral and acidic conditions.

Reactivity of the triethylammonium and the pyridinium salts of **1** in trans-sulfation was examined in Me_2SO·pyridine (4: 1), with or without Cu(II). As estimated by the formation of sulfated products from riboflavin, **1** had a much smaller reactivity than 8-quinolyl sulfate reported previously, although the effect of Cu(II) was accelerative on the reaction.

Keywords——1,2-naphthoquinone-1-oxime *O*-sulfate; 1,2-naphthoquinone-1-oxime; 1-nitroso-2-naphthol; *o*-cyano-*cis*-cinnamic acid; Cu(II)-catalytic decomposition; solvent catalytic desulfation; alkali-induced ring-scission

One of us (K.N.) reported the metal-catalyzed reaction of 8-quinolyl sulfate and its application to the synthesis of biochemically related sulfate esters.[2] This paper describes the work on the synthesis of 1,2-naphthoquinone 1-oxime *O*-sulfate and its solvolytic properties with or without bivalent copper.

Experimental

Reagents and Solvents——Reagents, which were all special reagent grade, were used without further purification. Organic solvents were dried and redistilled by a conventional method.

Analytical Methods——Inorganic sulfate was determined by a modified method of Dodgson's turbidimetry.[3] A mixture of 1 ml of the sample solution and 3 ml of 3.8% CCl_3COOH was incubated for 15 min at 37°, followed by the addition of 1 ml of $BaCl_2$-gelatin reagent (prepared by dissolving 0.5 g of gelatin and 1.0 g of $BaCl_2$ in 100 ml of H_2O, and left to stand at 4° overnight). After standing at room temperature for 20 min, absorbancy (A) of the solution was measured at 500 nm. Solutions of K_2SO_4 (10, 20, 30, 40, and 50 γ of S/ml) were used for preparing the calibration curves. Because the solutions containing 1,2-naphthoquinone 1-oxime *O*-sulfate or 1-nitroso-2-naphthol colored yellow, the following correction was necessary. To a mixture of 1 ml of the sample solution and 3 ml of 3.8% CCl_3COOH, 1 ml of the gelatin solution (prepared by dissolving 0.5 g of gelatin in 100 ml of hot water, and left to stand at 4° overnight) was added. After shaking at room temperature for 20 min, absorbancy (A′) of this solution at 500 nm was measured. Difference in the absorbancies at 500 nm (A–A′) was used for the calculation of inorganic sulfate concentration.

Thin-layer chromatography on Kieselgel GF_{254} was developed with a solvent system of acetone–MeOH (4: 1). The spots were detected with UV irradiation. *Rf* values of 1-nitroso-2-naphthol, sodium 1,2-

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2) K. Nagasawa and H. Yoshidome, *J. Org. Chem.*, **39**, 1681 (1974).

3) K.S. Dodgson, *Biochem. J.*, **78**, 312 (1961).

naphthoquinone 1-oxime *O*-sulfate (**1**), and *o*-cyano-*cis*-cinnamic acid (**2**) were 0.60, 0.74, and 0.32, respectively.

Paper electrophoreses were carried out on Toyo Roshi No. 50 filter paper at 20 V/cm for 40 min, using pyridinium acetate, pH 5.8 (pyridine: CH_3COOH: BuOH: H_2O=5: 1: 5: 250, v/v). Samples were applied on a line positioned at 4.5 cm from the center of the filter paper (25×9 cm). Quantitative analyses of sulfated products of riboflavin separated on the filter paper were made by the method described by Nagasawa and Yoshidome.[4]

Synthesis of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate (1)——Sodium Salt: A solution of $CHCl_3$ (25 ml) and *N*,*N*-dimethylaniline (6.4 ml, 0.05 mol) was mixed with a $CHCl_3$ solution (5 ml) of chlorosulfonic acid (1.4 ml, 0.02 mol) below −10° under stirring. A solution of 1-nitroso-2-naphthol (2.6 g, 0.015 mol) in $CHCl_3$ (25 ml) was added to this mixture and the whole was stirred for 2 hr at −10°. After neutralization with 1M Na_2CO_3 (*ca.* 25 ml) below −5°, the yellow precipitate formed was collected and washed successively with $CHCl_3$ and acetone. The dried powder was recrystallized from water to yellow needles, mp 85.5—86.5° (decomp.). Yield, 1.38 g (30.4%). *Anal.* Calcd. for $C_{10}H_6O_5NSNa\cdot 3/2H_2O$: C, 39.74; H, 3.00; N, 4.63; S, 10.61. Found: C, 40.03; H, 2.91; N, 4.65; S, 10.33. UV $\lambda_{max}^{H_2O}$ nm (ε): 259 (23500), 355 (4250). IR ν_{max}^{KBr} cm^{-1}: 1658 (C=O), 1530 (C=N), 1060 (N-O), 1080 (S=O), 1280 (SO_2).

Triethylammonium Salt: A solution of the sodium salt of **1** (150 mg) in 20 ml of water was passed through a column of Dowex 50W (×2, triethylammonium form, 50—100 mesh). The effluent and washings were combined, filtered, and freeze-dried to give a yellow powder, mp 109—112° (decomp.), yield, 180 mg (99.8%). *Anal.* Calcd. for $C_{16}H_{22}O_5N_2S\cdot 1/2H_2O$: C, 52.88; H, 6.33; N, 7.71; S, 8.84. Found: C, 52.61; H, 6.21; N, 7.52; S, 8.62. After drying *in vacuo* for 6 hr at 50°, the elemental composition of triethylammonium salt of **1** remained unchanged.

Pyridinium Salt: A solution of the sodium salt of **1** (100 mg) in 15 ml of H_2O was passed through a column of Dowex 50W (×2, pyridinium form, 50—100 mesh). The effluent and washings were combined, filtered, and freeze-dried to a yellow powder, mp 102—104° (decomp.). Yield, 105 mg (93%). *Anal.* Calcd. for $C_{15}H_{12}O_5N_2S\cdot 1/2H_2O$: C, 52.77; H, 3.81; N, 8.21. Found: C, 52.84; H, 3.58; N, 8.23.

Decomposition of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in Aqueous Media with or without Cu(II)——In neutral medium (pH 4.9) at 80°: The sodium salt of 1 was weighed (*ca.* 15 mg) into a volumetric flask (50 ml volume) and the content was diluted to 50 ml with water. The stoppered flask was immersed in an oil bath kept at 80°. Aliquots (5 ml each) were removed periodically from the flask and cooled in ice-water. Turbidimetric analysis of inorganic sulfate was carried out on 1 ml of the aliquot obtained as above.

In 0.1 N HCl at 40°: The sodium salt of **1** was weighed (*ca.* 30 mg) and diluted with 10 ml of 0.1 N HCl. The solution was kept at 40°, and 1 ml aliquots were removed periodically and diluted with water to 10 ml. After cooling in ice-water for 5 min, turbidimetry was carried out on 1 ml of the solution obtained as above.

In 0.1 N NaOH at 20°: The sodium salt of **1** was weighed (*ca.* 30 mg) and diluted with 10 ml of 0.1 N NaOH. The solution was kept at 20°, and 1 ml aliquots were removed periodically and diluted to 10 ml with 0.01 N HCl. After cooling in ice–water for 5 min, turbidimetry was carried out on 1 ml of the solution obtained as above.

Decomposition of **1** in the presence of Cu(II) was carried out on the acidic or neutral solution containing the sodium salt of **1** (15.00 mg) and $CuCl_2$ (6.68 mg, 1 molar eq.) at an indicated temperature. When the precipitate of 1-nitroso-2-naphthol·Cu(II) complex was formed, it was filtered off, and turbidimetry of the inorganic sulfate liberated in the filtrate was performed as described above.

Isolation and Characterization of *o*-Cyano-*cis*-cinnamic Acid Formed by Degradation of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in Alkaline Medium——A solution of the sodium salt of **1** (91.1 mg) in H_2O (10 ml) and 2 N NaOH (2 ml) was kept for 30 min at room temperature. After acidification with 2 N HCl, the solution was extracted with $CHCl_3$, and the $CHCl_3$ layer was dried over anhyd. Na_2SO_4. The solvent was evaporated and the residue was recrystallized from H_2O to colorless needles, mp 137—138° (reported,[5] 137—138°), with an yield of 43.8 mg (84%). *Anal.* Calcd. for $C_{10}H_7O_2N$: C, 69.39; H, 4.07; N, 8.09. Found: C, 68.84; H, 4.09; N, 8.00. IR ν_{max}^{KBr} cm^{-1}: 1635 (C=C), 1685 (C=O), 2240 (C≡N). UV $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 258 (8640), 298 (shoulder). NMR ($CDCl_3$) δ ppm: 8.6 (1H, broad, COOH), 7.6 (4H, broad, aromatic ring protons), 7.3 (1H, doublet, *cis*-ethylenic β-proton), 6.2 (1H, doublet, *cis*-ethylenic α-proton). Mass Spectrum *m/e*: 173 (M^+).

A solution of the compound (692 mg) obtained as above in EtOH (30 ml) was hydrogenated over 5% Pd-C (70 mg) in a H_2 atmosphere (1 atm) at room temperature. After absorption of H_2 ceased, the catalyst and EtOH were removed from the reaction mixture. The crystalline residue was recrystallized from H_2O to *o*-cyanophenylpropionic acid, as colorless needles, mp 124.5—126.5° (reported,[6] 127°). Yield, 614 mg (88%).

Decomposition of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in Organic Solvents Containing Water——

4) K. Nagasawa and H. Yoshidome, *Chem. Pharm. Bull.* (Tokyo), **18**, 2023 (1970); K. Nagasawa and H. Yoshidome, *ibid.*, **19**, 906 (1971).
5) W. Davies and H.G. Poole, *J. Chem. Soc.*, **1927**, 2661.
6) G.A. Edwards, *J. Chem. Soc.*, **1926**, 813.

Triethylammonium salt of **1** was weighed (*ca.* 4 mg) and diluted with 10 ml of the indicated solvent. The solution was kept at 20°, and 2.5 ml aliquots were removed periodically. After cooling in ice-water for 5 min, turbidimetric analysis of inorganic sulfate was carried out on 1 ml of the aliquots. A corresponding amount of the solvent used must be added to the standard solutions and the blank solutions necessary for the turbidimetry.

Determination of Riboflavin Sulfates Formed by *trans*-Sulfation of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate with or without Cu(II)——A mixture of riboflavin (0.02 mmol), triethylammonium or pyridinium salt of **1** (0.1 mmol), and $CuCl_2$ (0.06 mmol) in 2 ml of Me_2SO–pyridine (4: 1) was reacted at the indicated temperature with stirring. After the reaction period, the mixture was added with 2 ml of water, and the 1-nitroso-2-naphthol·Cu(II) complex formed was removed by centrifugation. To decompose excess of **1**, the supernatant was mixed with 0.5 ml of 1 N NaOH and left to stand for 10 min at room temperature. The solution thus obtained was neutralized with a small amount of Dowex 50 W (×2, H^+ form, 50—100 mesh), and the supernatant was applied to paper electrophoresis. Each paper zone corresponding to riboflavin and sulfated riboflavins was cut off and aqueous extract of each of the paper zones was analyzed by the method described in previous papers.[4]

Results and Discussion

It has been known that 1-nitroso-2-naphthol is one of the known ligands in metal-chelation, and its predominant form present in both solid state and solutions is 1,2-naphthoquinone 1-oxime.[7] A sulfated derivative of 1-nitroso-2-naphthol was obtained by its sulfation with chlorosulfonic acid in the presence of *N*,*N*-dimethylaniline in 30.4% yield. It was found later that the poor yield of the sulfated product was due to its ring-opening degradation during neutralization of the reaction mixture with alkali. Both elemental and instrumental analyses proved that the sulfated product was the sodium salt of 1,2-naphthoquinone 1-oxime *O*-sulfate(**1**).

1 was fairly stable in H_2O or 0.01 N HCl for at least 24 hr at 4° (degree of decomposition after 24 hr, $<1\%$). As shown in Fig. 1, decomposition of **1** in water was relatively rapid at an elevated temperature (80°), and its half-life was 380 min. Addition of an equimolar amount of Cu(II) to the solution accelerated the decomposition of **1** resulting in the reduction of its half-life to 60 min, and the precipitation of 1-nitroso-2-naphthol·Cu(II) complex progressed during the reaction. Thus, this acceleration was considered to be due to the chelate forming interaction between **1** and Cu(II) as reported on the compounds substituted with 8-hydroxyquinolyl groups.[2,8] In the medium of 0.1 N HCl, **1** rapidly decomposed at 40°, and its half-life was 140 min. Addition of Cu(II) to this medium accelerated the decomposition of **1** only to a limited extent, suggesting a poor contribution of the chelate forming interaction of **1** with Cu(II) in 0.1 N HCl.

An equimolar amount of inorganic sulfate and 1-nitroso-2-naphthol was always formed on the decomposition of **1** in H_2O or dilute HCl, indicating that hydrolysis of **1** occurred under the conditions used. In 0.1 N NaOH at 20°, the whole of **1** was instantaneously decomposed to inorganic sulfate and an unknown substance which was different from 1-nitroso-2-naphthol in its TLC and spectrometric properties. A preparative reaction in 0.1 N NaOH at 20° was carried out to isolate the unknown compound which was identified as *o*-cyano-*cis*-cinnamic acid (**2**) by elemental and instrumental analyses. *o*-Cyano-*cis*-cinnamic acid is known to be formed from 1-nitroso-2-naphthol in aqueous alkali by treatment with toluene-*p*-sulfonyl chloride.[5] Elvidge and Jones[9] presumed that this reaction proceeds by way of the *N*-*p*-toluenesulfonyloxy derivative, by the attack of a hydroxide ion at the carbonyl group, resulting in ring opening, with elimination of *p*-toluenesulfonic anion, and

7) D. Dryssen and E. Johansson, *Acta Chem. Scand.*, **9**, 763 (1955).
8) R.H. Barca and H. Freiser, *J. Am. Chem. Soc.*, **88**, 3744 (1966); R.W. Hay and J.A.G. Edmonds, *Chem. Commun.*, **1967** (19), 969; Y. Murakami and J. Sunamoto, *Bull. Chem. Soc. Japan.*, **44**, 1827 (1971); K. Nagasawa and H. Yoshidome, *Chem. Pharm. Bull.* (Tokyo), **21**, 2438 (1973).
9) J.A. Elvidge and D.E.H. Jones, *J. Chem. Soc.* (*C*), **1967**, 2059.

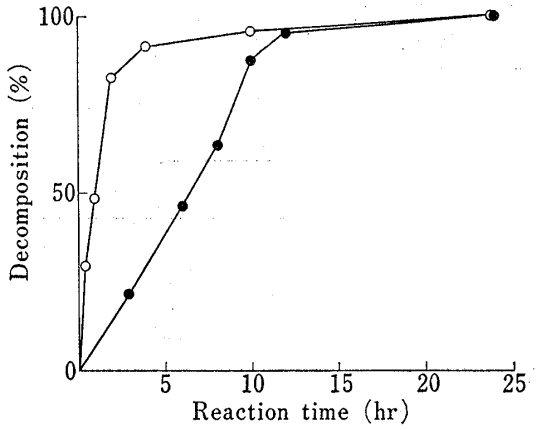

Fig. 1. Decomposition of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in Water at 80° with or without Cu (II)

—○—: with Cu (II); —●—: without Cu (II)

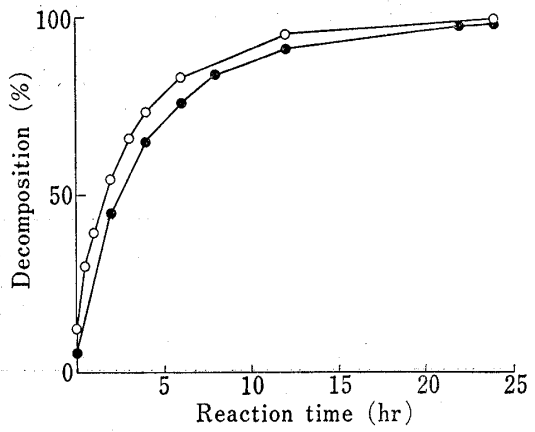

Fig. 2. Decomposition of 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in 0.1 N HCl at 40° with or without Cu (II)

—○—: with Cu (II); —●—: without Cu (II)

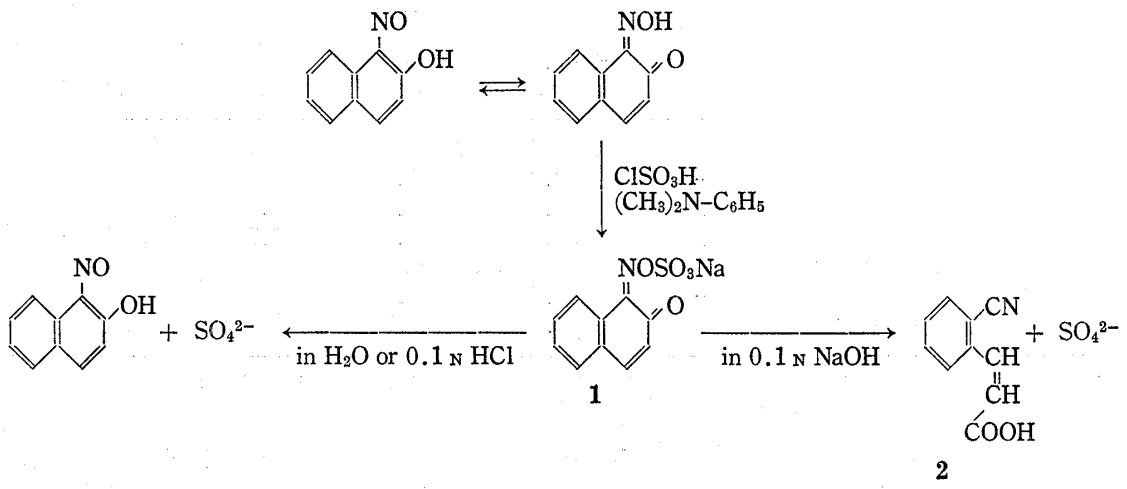

Chart 1

formation of *o*-cyano-*cis*-cinnamic acid. According to this reaction mechanism, 1,2-naphthoquinone 1-oxime *O*-sulfate in the present work corresponds to the sulfated analog of the intermediate in the ring-scission reaction induced by *p*-toluenesulfonyl chloride in aqueous alkali.

Solvolysis of **1** in polar organic solvents such as pyridine, dioxan, and tetrahydrofuran was examined. Triethylammonium salt of **1** which is soluble in these solvents was reacted in a solvent containing 1% of H_2O, and the amount of inorganic sulfate liberated was determined as detailed in the experimental section. As can be seen in Table I, decomposition of **1** occurred extensively at 0 time of the reaction in all the solvents tested. This marked decomposition seems to be due to acidification of the reaction mixture in the determination procedure of inorganic sulfate, as suggested from the reported acceleration of the hydrolysis of various types of sulfate esters with polar organic solvents.[10] Progress of the solvolysis at 20° is estimated from the decomposition percentage less those obtained at 0 time. The data in Table I indicate that the hydrolysis of **1** was markedly accelerated by these organic solvents, in both neutral and acidic conditions.

10) S. Lieberman, L.B. Hariton, and D.K. Fukushima, *J. Am. Chem. Soc.*, **70**, 1427 (1948); S. Burstein and S. Lieberman, *ibid.*, **80**, 5235 (1958); B.D. Batts, *J. Chem. Soc.* (*B*), **1966**, 547.

Table I. Rate of Decomposition of Triethylammonium 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in Some Organic Solvents Containing 1% (v/v) of Water at 20°

Reaction medium	Rate of decomposition (%)			
	0 hr	24 hr	72 hr	168 hr
H_2O (Na salt, pH 4.9)	3.1	3.3	3.3	—
Pyridine	11.6	41.9	67.0	84.6
Tetrahydrofuran	41.2	65.8	—	—
Dioxan	33.3	85.3	—	—

Table II. Yield and Composition of Riboflavin Sulfates Formed by Sulfation of Riboflavin with 1,2-Naphthoquinone 1-Oxime *O*-Sulfate in Dimethyl Sulfoxide·Pyridine (4: 1)

Reaction condition			Yield and composition of riboflavin sulfates (%)			
Temp. (°C)	Time (hr)	Cu(II)	Unreacted riboflavin	Riboflavin sulfate		
				Mono–	Di–	Tri–
Triethylammonium salt of 1,2-naphthoquinone 1-oxime *O*-sulfate						
40	24	–	92.9	7.1	0	0
40	5	+	82.4	15.4	0.3	0
40	24	+	64.2	30.2	5.7	0
Pyridinium salt of 1,2-naphthoquinone 1-oxime *O*-sulfate						
80	24	–	65.7	31.5	2.8	0
80	24	+	54.3	38.7	4.8	2.2

Molar ratio of reactants: 1,2-naphthoquinone 1-oxime *O*-sulfate·riboflavin·$CuCl_2$ (5: 1: 3)

To examine the trans-sulfating activity of **1**, sulfation of riboflavin with triethylammonium or pyridinium salt of **1** was carried out in a homogeneous solution of Me_2SO and pyridine (4: 1), with or without Cu(II). After several steps of operation, electrophoretic separation and colorimetric determination of riboflavin and its sulfated products were performed on the reaction mixture. As shown in Table II, riboflavin was hardly sulfated with triethylammonium salt of **1** in the absence of Cu(II). When Cu(II) was present, the sulfation progressed but its reactivity was much smaller than that of 8-quinolyl sulfate reported previously.[2] It was notable that pyridinium salt of **1** had a relatively high reactivity. Difference in the reactivities between the triethylammonium salt and pyridinium salt is considered to be due to their ionic properties. Most of the pyridinium salt would exist in its non-dissociated form which is liable to change into a reactive species (a dipolar ion) in polar solvents,[10] contrary to the triethylammonium salt, most of which would be present in its stable anionic form. Although data are not shown here, the effect of Co(II) was evidently less than that of Cu(II).

A comparison of the results described above with those of 8-quinolyl sulfate suggests that the solvent effect and chelate forming interaction in **1** are much smaller than those in 8-quinolyl sulfate.[2]

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