BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1553—1556 (1970)

Reaction of *p*-Nitrophenyl Sulfate with Thiophenol

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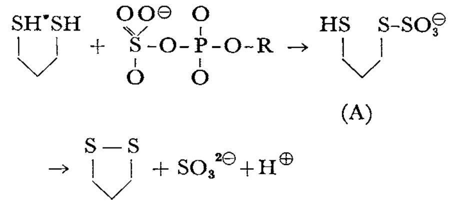
(Received November 19, 1969)

The reaction of *p*-nitrophenyl sulfate with *p*-substituted thiophenols were carried out in aqueous dimethylformamide under varying conditions. The rate was found to be independent of the concentration of thiophenolate, and to vary very little with the change of substituent. The Hammett correlation with σ value gives $\rho=0.12$. There was no rate-change in the pH range 6—12. Those observations seem to suggest the reaction to be of A-1 type.

Oxidation and reduction of organic sulfur compounds are important reactions in the metabolic pathway of living organisms.[1] However, the chemistry of these enzymatic processes, especially the reduction process, has not been investigated thoroughly.

An interesting model reaction for this enzymic reduction is that between organic sulfates and thiols. Hilz and Kittler[2] studied the reduction of sulfate ion to sulfite ion by lipoic acid, and suggested the following mechanism.



(A)

(1)

The reaction is actually a SN2 type displacement reaction at a sulfur atom as shown by (A). It has to compete with the hydrolysis of the sulfate in aqueous media, especially in a high pH region,

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[1] F. Challenger, "Aspects of the Organic Chemistry of Sulfur," Academic Press, New York (1959). N. Kharasch, "The Chemistry of Organic Sulfur Compounds," Vol. 2, Pergamon Press, London, New York (1966).

[2] H. Hilz. M. Kittler, *Biochem. Biophys. Res. Commun.*, **3**, 140 (1960).

since organic sulfates are considered to be hard acids[3] and hence would readily be attacked by hard bases, *i.e.*, $OH^{\ominus}$ ion in this case.

Thus, in order to understand the nature of oxidation and reduction on the sulfur atom of organic sulfur compounds, one should investigate the relative rates of alkaline hydrolysis and nucleophilic substitution of organic sulfates, as in the cases of aryl thiosulfonates,[4] aryl thiosulfate and aryl thiosulfonate.[5]

Hydrolysis of aryl sulfates has been studied considerably.[6] The mechanism suggested for the acid-catalyzed hydrolysis of alkyl sulfates involves the A-1 type cleavage of S–O bond.[7]

Kice and Anderson[8] studied the reaction in detail and concluded that the mechanism of the acid hydrolysis of sodium aryl sulfates is of A-1 type as shown by

$$ArOSO_3^{\ominus}+H^{\oplus} \underset{}{\overset{\text{fast}}{\rightleftarrows}} Ar\text{-}\underset{\substack{|\\H}}{\overset{\oplus}{O}}\text{-}SO_3^{\ominus}$$

$$\xrightarrow{\text{slow}} ArOH + \underset{\substack{\text{fast}\ \downarrow\ H_2O\\ H_2SO_4}}{SO_3} \qquad (2)$$

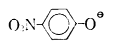
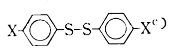
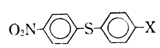
Benkovic[9] studied the pH-rate profile for the spontaneous hydrolysis of *p*-nitrophenyl sulfate and observed that the k_{obs} values are essentially independent of pH in the range 7—12, but change linearly with hydroxide ion concentration at higher pH values.

Thus, the spontaneous hydrolysis of *p*-nitrophenyl sulfate has been discussed in terms of a possible elimination of sulfur trioxide analogous to the monomeric metaphosphate formation in the hydrolysis of certain phosphate dianions. We have investigated the reaction of *p*-nitrophenyl sulfate with thiophenolate expecting it to result in the reduction of sulfate through nucleophilic substitution by thiol group.

Result and Discussion

An equimolar mixture of *p*-nitrophenyl sulfate and thiophenolate was heated in DMF in N_2 atmosphere in sealed tubes for 18 hr at 90°C. The products isolated were characterized by comparing the IR spectra, UV spectra and mps with those of the authentic samples. The products and yields are listed in Table 1.

TABLE 1. PRODUCT ANALYSIS OF THE REACTION OF *p*-NITROPHENYL SULFATE WITH THIOPHENOLATE[a)]

Product		Yields[b)] (%)
	(I)	94
	(II)	90
	(III)	5

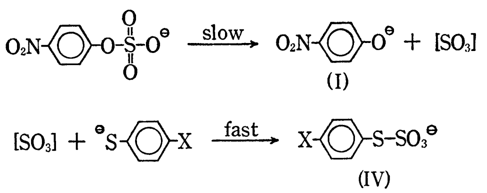
a) In DMF 90°C, 18 hr in sealed tubes under nitrogen atmosphere.
b) Based on the ester used.
c) X=H

Two conceivable mechanisms for the reaction obtained from analysis of products are shown below. According to the mechanism of A-1 type, Eq. (3), the initial step of the reaction is S–O bond fission. Sulfur trioxide thus formed reacts immediately with thiophenolate to yield a Bunte salt (IV). In this case, the rate-determining step appears to be the elimination of sulfur trioxide. This seems to be analogous to the mechanism suggested for the solvolysis of phosphate esters which proceeds by way of monomeric metaphosphate intermediate.[7,10]

Sulfur trioxide thus formed incipiently can function as the sulfate donor in the synthesis of various biologically important organic sulfates.[11] Another possible path, shown as A-2 type, is essentially a SN2-type reaction involving the nucleophilic replacement of *p*-nitrophenyl sulfate by thiophenolate. Reaction (a) is a simple synchronous SN2-type displacement reaction on sulfur atom, while reaction (b) proceeds *via* the initial addition of nucleophile to the benzene ring (bond making), followed by the leaving of sulfate group (bond breaking) to give *p*-nitrophenyl aryl sulfide.

The kinetics of the reaction of *p*-nitrophenyl sulfate with thiophenolate was studied spectrophotometrically by following the rate of formation of *p*-nitrophenolate (I).

A-1 type



(3)

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[3] J. O. Edwards and R. G. Pearson, *J. Amer. Chem., Soc.*, **84**, 16 (1962); R. G. Pearson, *ibid.*, **85**, 3533 (1963). R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

[4] S. Oae, W. Tagaki and T. Kurusu, This Bulletin, **42**, 2894 (1969).

[5] S. Oae, W. Tagaki, R. Nomura and Y. Yoshikawa, *ibid.*, **42**, 2903 (1969).

[6] G. N. Burkhardt, W. G. K. Ford and E. Singleton, *J. Chem. Soc.*, **1936**, 17.

[7] E. T. Kaiser, M. Panar and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 602 (1963); S. Burstein and S. Liberman, *ibid.*, **80**, 5235 (1958).

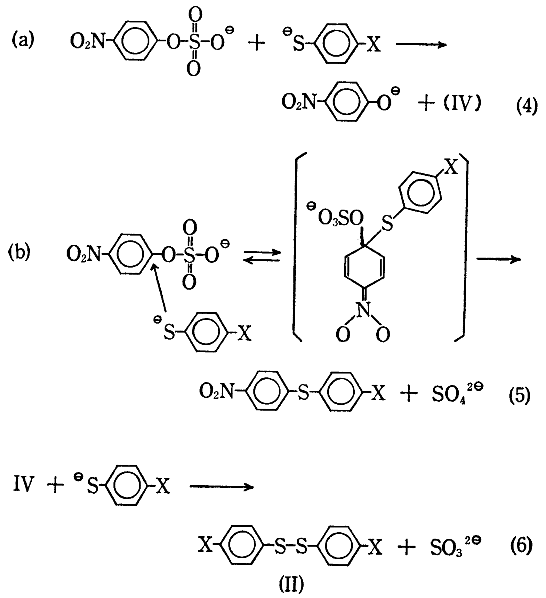
[8] J. L. Kice and J. M. Anderson, *ibid.*, **88**, 5242 (1966).

[9] S. J. Benkovic and P. A. Benkovic, *ibid.*, **88**, 5504 (1966).

[10] G. Di. Sabato and W. P. Jencks, *ibid.*, **83**, 4393, 4400 (1961).

[11] P. W. Robbins and F. Lipmann, *J. Biol. Chem.*, **229**, 837 (1957).

A-2 type



$X=Br, CH_3, CH_3O, H$

In order to avoid any complication due to possible side reactions, such as shown in Eq. (6), only the initial rate was used for calculation of the rate constants.

The pseudo-first-order constants of the reaction with substituted thiophenolate, k_{obs}, are listed in Table 2.

TABLE 2. PSEUDO-FIRST-ORDER RATE CONSTANTS OF THE REACTION OF *p*-NITROPHENYL SULFATE WITH *p*-SUBSTITUTED THIOPHENOLS
(in DMF at 90°C)

X-	$k_{obs} \times 10^6$ (sec^{-1})
p-Br	5.82
H	5.90
p-CH_3	6.14
p-CH_3O	6.40

It is apparent that the presence of electron-donor substituents in aromatic ring leads to only a very slight increase in the rate. From a good correlation with σ values, one can calculate the Hammett ρ value as $+0.12$. This means that the participation of nucleophilic attack by thiophenolate is very small at the transition state of the rate-determining step of this reaction. Therefore, the observed substituent effect seems to provide significant support for possible occurrence of an A-1 type pathway in (3).

The pH-rate profile for the reaction of *p*-nitrophenyl sulfate with thiophenol is shown in Fig. 1.

The k_{obs} values are independent of pH change in the range 6—12. Evidence supporting the A-1 type mechanism may be found in the pH-rate profile of the reaction, since the rate of A-2 type process varies with thiophilicity of thiophenol which in turn changes with pH of the reaction mixture. However, as Fig. 1 indicates, the difference in the rate is hardly discernible in the pH range 6—12. The mechanism of this reaction must be identical in this pH range and is very likely the A-1 type. Only at higher pH values or in the alkaline hydrolysis of *p*-nitrophenyl sulfate, the mechanism of A-1 type which depends on the first-power of hydroxide ion concentration may prevail. Thus, all these observations strongly suggest that the reaction of *p*-nitrophenyl sulfate with thiophenol proceeds by way of the A-1 type process.

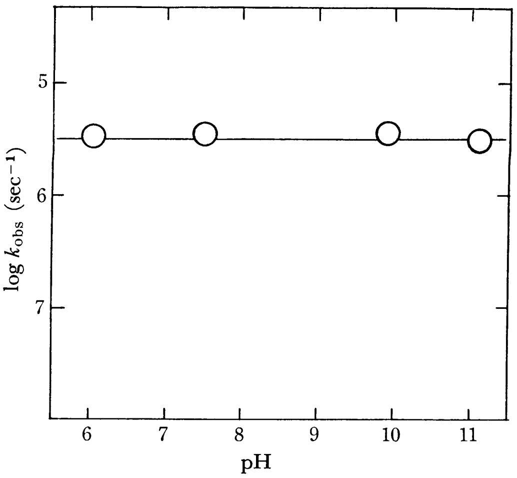


Fig. 1. The pH-rate profile for the reaction of *p*-nitrophenyl sulfate with thiophenyl (at 90°C, in 40% DMF-H_2O)

Experimental

Reagents. *Potassium p-Nitrophenyl Sulfate.* This was prepared by a modification of procedure of Burkhardt and Lapworth.[12]

Chlorosulfonic acid (12 g) was slowly added pyridine (16 g) with stirring and cooling with ice-salt mixture. Benzene (100 cc) was then added, and the mixture was heated to 70°C. *p*-Nitrophenol (12 g) was then added, and the mixture was boiled for 4 hr, during which the pyridinium *p*-nitrophenyl sulfate crystallized out. The salt was then collected and poured into a slight excess of aqueous potassium hydroxide. After unchanged nitrophenol was extracted with ether, then water and pyridine were evaporated off *in vacuo*, potassium *p*-nitrophenol sulfate was obtained. It was purified by repeated recrystallization by dissolution in water and subsequent trituration with ethanol. The salt was dried under reduced pressure over calcium chloride, mp 203°C.

Found: C, 28.00; H, 1.60%. Calcd for $C_6H_4NO_6SK$: C, 28.01; H. 1.57%.

Solvent. *Buffer Solution.* 40% DMF-H_2O solvent was used in all pH solutions. At pH 6-8, KH_2PO_4–Na_2HPO_4 buffer was employed. pH~10 Na_2CO_3–$Na_2B_4O_7$ $10H_2O$, pH 11, NaOH (N/10)-Na_2HPO_4(M/

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[12] G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, **1926**, 684.

10). The pH of the reaction mixtures were measured at 25°C by pH-meter (Horiba, Model-p, No. 17317).

Procedure for Kinetic Runs. Each kinetic run was carried out by monitoring the UV absorbance of *p*-nitrophenolate liberated during the reaction at 400 mμ. At first the solution of *p*-nitrophenyl sulfate (0.01 M 10 m*l*) in DMF was placed in a reaction vessel and immersed in a constant temperature bath which was kept at 90±0.05°C. 10 m*l* of thiophenoxide solution was then added to the ester solution. The reaction was followed by taking out 1 m*l* aliquots at suitable time intervals, diluting these aliquots with 25 m*l* of 0.01 N KOH–ethanol solution, and finally subjecting the solution for measurement of the optical density of the resulting solution at 400 mμ ($\varepsilon = 18000$). The calculation of the rate constants was described in detail in earlier studies on the reaction of *p*-nitrophenyl benzenesulfonate with thiophenol.[3]

The Reaction of *p*-Nitrophenyl Sulfate with Thiophenolate. *p*-Nitrophenyl sulfate (4.8 g) and thiophenolate (2.6 g) were dissolved in DMF (20 cc) in an ampoule. The ampoule was sealed under N_2 atmosphere and then kept at 90°C for 18 hr. The solvent of the reaction mixture was evaporated off *in vacuo* and the residue was poured into water and extracted with ether. Work up of the ether layer gave (6.9 g) a mixture of *p*-nitrophenol, diphenyl disulfide and *p*-nitrophenyl phenyl sulfide. They were isolated by chromatography on alumina. The yield of *p*-nitrophenol could also be obtained spectrophotometrically in alkaline solution. The products and yields are listed in Table 1.