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The Syntheses and Hydrolyses of *p*-Substituted Phenyl Phosphosulfates[1]

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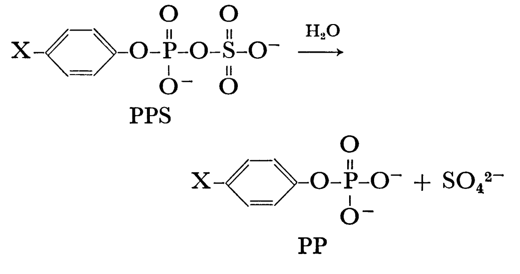
Very recently, Benkovic and Hevey have reported a study on the mechanism of nonenzymatic hydrolysis of phenyl phosphosulfate.[2] Independently, we have also been investigating the mechanism of the hydrolysis of the same compound. Since little is known about the chemistry of phosphosulfate linkage and in view of its importance for biochemistry,[3] it seems to be significant to report our own results. In this paper, we will describe the syntheses and hydrolyses of *p*-substituted phenyl phosphosulfates (PPS, I).



I. $X=CH_3O, CH_3, H, Cl$ (diammonium salts)

Results and Discussion

Syntheses of PPS (I). Pyridine-SO_3 complex has been used for the preparation of PPS.[2] However much better yield of PPS (usually 60—70%) was obtained when the reaction was conducted using the diammonium salts of PP and dimethylformamide (DMF)-SO_3 complex in DMF.

Hydrolyses of PPS. The products were found to be exclusively phenyl phosphate (PP) and inorganic sulfate under both alkaline and acidic conditions.

1. The rate of alkaline hydrolysis was first order with respect to the hydroxide ion concentration in a range of [NaOH]=0.01—1.0 M. The substituent effect was larger than that for the acidic hydrolysis (Fig. 1). The value of entropy of activation (Table 1) was in the range expected for a bimolecular reaction.[4]

In an alkaline solution, the major ionic form of PPS is undoubtedly the dianion. This dianion would undergo a nucleophilic attack by hydroxide ion on either sulfur or phosphorus to give PP and inorganic sulfate in the rate determining step. An alternative mechanism is a rate determining unimolecular fission of S-O bond of

TABLE 1. KINETICS OF HYDROLYSES OF UNSUBSTITUTED PHENYL PHOSPHOSULFATE

Reagent	Temp., °C	$k_{obs}\times 10^4 sec^{-1}$	
1. Alkaline hydrolysis			
0.5N NaOH	70	1.31	
0.5N NaOH	85	3.43	$E_a=15.9$ kcal/mol
0.5N NaOH	98	7.65	$\Delta S^{\ne}=-32.5$ e.u. (98°C)
2. Acidic hydrolysis			
0.5N HCl	17.8	8.55	
0.5N HCl	30	33.8	$E_a=20.3$ kcal/mol
0.5N HCl	39.5	99.5	$\Delta S^{\ne}=-4.9$ e.u. (30°C)
0.5N DCl[a]	30	98.5	$k^{D_2O}/k^{H_2O}=2.91$ (30°C

a) In D_2O

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[1] A part of this study has been reported at the 23rd Annual Meeting of the Chemical Society of Japan, April 4, 1970, Tokyo.

[2] S. J. Benkovic and R. C. Hevey, *J. Amer. Chem. Soc.*, **92**, 4971 (1970).

[3] a) P. W. Robbins and F. Lipmann, *ibid.*, **78**, 2652, 6409 (1956); b) P. W. Robbins and F. Lipmann. *J. Biol. Chem.*, **229**, 837 (1957); c) P. W. Robbins and F. Lipmann, *ibid.*, **233**, 686 (1958); d) F. Lipmann, *Science*, **128** 575 (1958).

[4] F. A. Long, J. G. Pritchard, and F. E. Stafford, *ibid.*, **79**, 2363 (1957).

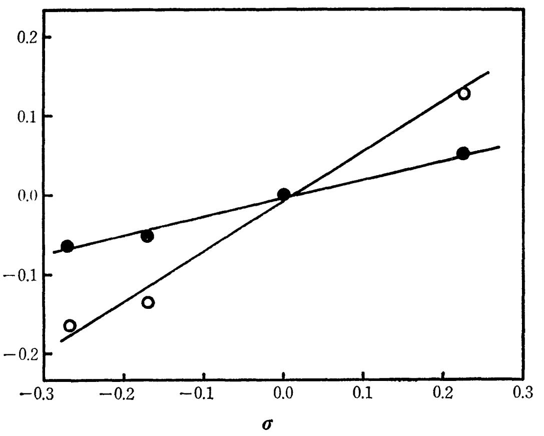

Fig. 1. Hammett substituent effect for the hydrolyses of *p*-substituted phenyl phosphosulfates.
●: 0.8N HCl, 30°C, $\rho=0.22$
○: 0.01N NaOH, 98°C, $\rho=0.67$

PPS to give PP and sulfur trioxide. The above results seem to support the first bimolecular mechanism.

2. The rate of acidic hydrolysis was first order with respect to the hydronium ion concentration in a range of $-\log[H^+]=0-2$. The ρ value for the substitution effect was small (Fig. 1). Such small ρ values have also been observed in the hydrolyses of sulfates[5] and phosphates[6] of substituted phenols, and the values have been interpreted as to support A-1 type mechanisms. The value of entropy of activation (Table 1) was appreciably larger than that for the alkaline hydrolysis and is consistent with that expected for an A-1 type solvolysis. The solvent isotope effect (Table 1) was also in the range expected for an A-1 type mechanism.[7]

Experimental

DMF-SO_3 solution was prepared by distilling SO_3 into anhydrous DMF, and the concentration of SO_3 was estimated by an alkaline titration and by the yield of *p*-nitrophenyl sulfate (obtained by the reaction wih sodium *p*-nitrophenoxide). *DCl-D_2O solution* (5N) for the determination of the isotope effect was prepared by dissolving dry DCl gas in D_2O (99.8%, Showa Denko).

p-*Substituted Phenyl Phosphorodichloridates* were prepared by the reaction of phenols and $POCl_3$ at 110°C and the desired fractions were collected by distilling the reaction mixture under reduced pressure.[8]

p-*Substituted Phenyl Phosphates (PP)* were prepared by the hydrolyses of the above dichloridates in water at room temperature:[8] *p*-substituent, mp (°C); CH_3O, 90—100; CH_3, 113—114; H, 99—100; Cl, 123—124.

Diammonium salts of p-*Substituted Phenyl Phosphosulfates (PPS, 1).* The diammonium salt of unsubstituted PP (2.0g, 9.6 mmol) was dissolved in DMF solution (16*ml*) of DMF-SO_3 complex (14.4 mmol), and this reaction mixture was left at room temperature for one hour. The reaction mixture was then cooled down to about −50°C and neutralized with a saturated ethanol solution of ammonia to give somewhat pasty mass. This mixture was allowed to warm up to room temperature and ether was added to effect further precipitation. The solid was collected by filtration, and then dissolved in ethanol and filtered again to remove some insoluble solid. The filtrate was concentrated to give colorless needles. This was recrystallized twice from ethanol ether mixture to give pure diammonium salt of PPS, yield 1.7 g. A small amount of the starting PP was recovered from the mother liquor.

The other substituted PPS were prepared similarly. The R_f values of paper chromatography and elementary analyses of thus obtained diammonium salts of PPS are shown in Tables 2 and 3.

TABLE 2. THE R_f VALUES IN PAPER CHROMATOGRAPHY[a)]

Substituent	Phenyl phosphosulfate[b)]	Phenyl phosphate
CH_3O	0.67	0.50
CH_3	0.72	0.54
H	0.65	0.48
Cl	0.77	0.60
	SO_4^{2-}[b)]	HPO_4^{2-}[b)]
	0.33	0.0

a) Conditions: paper, Toyo Filter Paper No. 50; solvent, n-PrOH: NH_3: $H_2O=6:3:1$ v/v
b) Diammonium salts

TABLE 3. THE ELEMENTARY ANALYSES OF THE DIAMMONIUM SALTS OF *p*-SUBSTITUTED PHENYL PHOSPHOSULFATES (PPS)

Substituent	Found (Calcd)			
	C%	H%	N%	P%[a)]
CH_3O	26.75	4.89	7.65	9.78
	(26.42	4.75	8.81	9.74)
CH_3	27.50	5.03	8.25	10.09
	(27.82	5.00	9.25	10.25)
H	24.64	4.43	9.88	10.98
	(25.02	4.51	9.72	10.77)
Cl	23.33	4.45	9.02	
	(22.33	3.74	8.68)	

a) Determined by the method of Fleury and Leclere (P. Fleury and M. Leclere, *Bull. Soc. Chim. Biol.*, **25**, 201 (1943)).

The following UV absorption maxima were observed for the substituted PPS and PP in alkaline solutions. a) For PPS, *p*-substituent and λ_{max} in mμ (ε_{max}) were: CH_3O, 276 (1420); CH_3, 267 (720); H, 260 (440); Cl, 269 (530). b) For PP: CH_3O, 280(1830); CH_3, 274(1100); H, 267(740); Cl, 274(840).

Kinetics. *a) Alkaline hydrolysis.* An alkaline solution of PPS (1.0×10^{-3}M) was sealed in 10 ampoules and kept in a constant temperature bath. At suitable time intervals, an ampoule was withdrawn and chilled in an ice-water bath, and the optical density of the content was recorded at the absorption maximum of PP which increased smoothly as the reaction proceeded. From this optical density change, good first order rate costants (deviation, within ±3%) were calculated by using an equation, $k_{obs}=1/t\ \ln\ (OD_\infty\text{-}OD_0)/(OD_\infty\text{-}OD_t)$.

At high temperature (98°C) and with a high hydroxide ion concentration (>0.5 N NaOH), further hydrolysis was observed giving an absorption at 290 mμ due to the formation of phenoxide ion. However, the amount of phenol produced at the end

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[5] E. J. Fendler and J. H. Fendler, *J. Org. Chem.*, **33**, 3852 (1968).
[6] G. Disabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4400 (1961).
[7] C. A. Bunton and V. J. Shiner, *ibid.*, **83**, 3207 (1961).
[8] H. F. Freeman and C. W. Colver, *ibid.*, **60**, 750 (1938).

of reaction was estimated to be less than 1%, and therefore the correction of optical density for the phenol formation was neglected. Plots of log k_{obs} against log[OH^-] gave a straight line with a slope=1.0. Other data are shown in Table 1 and Fig. 1.

b) Acidic hydrolysis. Aqueous solutions of PPS and HCl were temperature equilibrated and mixed to make a reaction mixture containing PPS, 1.0×10^{-2}M, and the acid of desired concentration. A part of this reaction mixture was quenched at suitable time intervals by diluting with an alkaline solution (to 1.0×10^{-3}M of PPS) and the optical density change was recorded as described above. The formation of phenol was not detected. Plots of log k_{obs} against log[H^+] gave a straight line with a slope=1 as observed by Benkovic and Hevey.[2] Other data are shown in Table 1 and Fig. 1.

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