[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY]

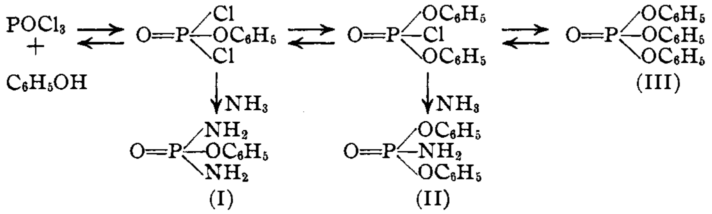
The Aquo Ammono Phosphoric Acids. I. Preparation of Phenyl Esters of Amido- and Diamidophosphoric Acids

BY L. F. AUDRIETH AND A. D. F. TOY

In connection with a study of the reactions and properties of amido- and diamidophosphoric acids, it became necessary to prepare in considerable quantity the corresponding esters of these aquo ammono phosphoric acids, in particular the phenyl derivatives. These had been made previously in poor yields by Stokes[1] by treatment of the respective chlorophosphates with aqueous or alcoholic ammonia. However, various investigators[2] have obtained alkyl phosphoric acids by hydrolysis of the product resulting from the action of phosphorus oxychloride on the alcohol in presence of pyridine. More recently, King and Nicholson[3] have described the synthesis of phenylphosphoric acids and of substituted phenylphosphoric acids by the hydrolysis of the product obtained when molar proportions of phenol, or substituted phenols, dissolved in pyridine, are allowed to react with phosphorus oxychloride. The latter reaction takes place quickly without the necessity of prolonged heating. Preliminary experiments following the suggested procedure, indicated that this same product could be ammonolyzed. However, mixtures of the phenyl esters of mono- and diamidophosphoric acid always formed whereas King and Nicholson obtained only phenylphosphoric acid by hydrolysis.

A more extended study of the King and Nicholson procedure was therefore undertaken in order to adapt it to the preparation of phenyl diamidophosphate (I) and diphenyl amidophosphate (II). Since these two products are readily separated from each other, conditions for preparation of the C_5H_5N–$POCl_3$–C_6H_5OH reaction product were varied in order to gain a clearer insight into the mechanism of the primary reaction.

Our experimental results indicate that a complex equilibrium is established when phosphorus oxychloride and phenol react in the presence of pyridine



Pyridine not only effects removal of hydrogen chloride, but also the stabilization of the intermediate chlorophosphates presumably by formation of pyridine complexes. Rise in temperature, increase in the molar ratios both of pyridine and of phenol to phosphorus oxychloride, favor a shift in the equilibrium to the right.

Experimental

The addition of phenol dissolved in pyridine directly to phosphorus oxychloride is accompanied by a considerable evolution of heat. Chloroform was therefore used as a solvent and diluent (a) since it permitted more careful temperature control and (b) because the reaction product was found to be completely soluble in it.

Ammonolysis of the resulting product can be effected by aqueous or gaseous ammonia. However, liquid ammonia was found not only to be most convenient, but also to give higher yields of the phenyl esters of amido- and diamidophosphoric acids.

A. Effect of the C_5H_5N–$POCl_3$ Ratio ($POCl_3$–C_6H_5OH = 1–1).—In order to determine the effect of pyridine upon the course of the reaction, a series of experiments was carried out using equimolar quantities of phosphorus oxychloride and phenol, but varying the molar ratios of pyridine to phosphorus oxychloride from 6:1 (as recommended by King and Nicholson) to 1:1. A typical procedure follows.

Seventeen and one-tenth grams (0.111 mole) of phosphorus oxychloride was dissolved in 75 cc. of chloroform and the mixture cooled in an ice-salt-bath. The solution containing the requisite quantity of pyridine and 10.5 g. (0.111 mole) of phenol was then added dropwise to the chloroform solution, the rate of addition being controlled in order to maintain the temperature at $-2 \pm 2°$. The reaction product was then stirred for fifteen minutes, transferred to a dropping funnel and added slowly to an excess of liquid ammonia. Upon evaporation of the excess ammonia, the residual solution was filtered, the precipitate washed with water to remove all soluble constituents (largely ammonium chloride), while the filtrate was evaporated to dryness to effect removal of chloroform and pyridine.

---

(1) Stokes, *Am. Chem. J.*, **15**, 198 (1893); **16**, 123 (1894).

(2) Abderhalden and Eichwald, *Ber.*, **51**, 1308 (1918); Fischer, *ibid.*, **47**, 3193 (1914); Boyd and Ladhams, *J. Chem. Soc.*, 215 (1928); Houssa and Phillips, *ibid.*, 108 (1932).

(3) King and Nicholson, *Biochem. J.*, **33**, 1182 (1939).

The water insoluble portion was recrystallized by dissolving in hot 95% alcohol and subsequently cooling to give phenyl diamidophosphate, m. p. 183–185° (uncor.). The residue obtained by evaporation of the chloroform–pyridine solution was combined with the product remaining after removal of the alcohol from the alcoholic mother liquor. This mixture was extracted with hot chloroform which dissolves readily the diphenyl amidophosphate (m. p. 145–146°), while the diamidophosphate is only slightly soluble.

The results of these experiments are depicted graphically in Fig. 1, indicating that maximum yields of (I) are obtained with a C_5H_5N-$POCl_3$ ratio of 2 to 3–1. Increase in the pyridine ratio favors formation of the diphenyl amidophosphate (II), while the yield of (I) decreases. While the triphenyl phosphate was not isolated quantitatively in these experiments, its presence at higher pyridine ratios was definitely verified. With ratios of C_5H_5N-$POCl_3$ of less than 2–1, a marked decrease in total yield was observed. Enough pyridine, apparently at least two moles per mole of phosphorus oxychloride, must be present to remove not only hydrogen chloride, but to complex the resulting phenyl chlorophosphates.

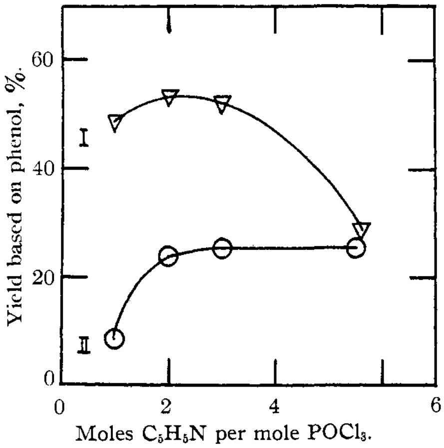


Fig. 1.—Effect of varying the C_5H_5N-$POCl_3$ ratio (where $POCl_3$-C_6H_5OH = 1:1) upon the yields of phenyl diamidophosphate (I) and diphenyl amidophosphate (II).

B. Variation of $POCl_3$-C_6H_5OH Ratio (when $POCl_3$-C_5H_5N = 1–3).—All previous experiments had indicated that the reaction between phenol in pyridine with phosphorus oxychloride was not clean cut, for the reaction product upon ammonolysis always gave both the amido—as well as the diamido—compound. It seemed advisable to determine the effect upon the yields of the different products by varying the $POCl_3$-C_6H_5OH ratio while keeping the $POCl_3$-C_5H_5N = 1–3.

In these experiments 46 g. (0.3 mole) of phosphorus oxychloride in 225 cc. of chloroform and 71 g. (0.9 mole) of pyridine were used, while the quantity of phenol was varied. In other respects experimental conditions were the same as those described above. In those cases where triphenyl phosphate was present in small quantities, it was recovered from the residue remaining upon evaporation of the chloroform–pyridine solution by extraction with cold carbon tetrachloride solution. The carbon tetrachloride extract was evaporated to dryness and the residue first washed with 5% potassium carbonate solution to remove unreacted phenol and then recrystallized from high boiling petroleum ether. When triphenyl phosphate was obtained in large quantities, it was isolated in fairly pure state from the carbon tetrachloride extract by means of vacuum distillation (b. p. 245° (11 mm.); m. p. 48–50°).

The experimental results are depicted graphically in Fig. 2, in which the yields are based on the percentage of phosphorus oxychloride converted to each of the possible products, namely, phenyl diamidophosphate (I), diphenyl amidophosphate (II), and triphenyl phosphate (III). It should be pointed out, however, that the conversion of phosphorus oxychloride at mole ratios of $C_6H_5OH/POCl_3$ less than one would necessarily be low, since the simplest product would require a 1–1 ratio. Maximum yields of (II) and (III) can likewise not be expected until the ratios of phenol to phosphorus oxychloride are 2–1 and 3–1, respectively.

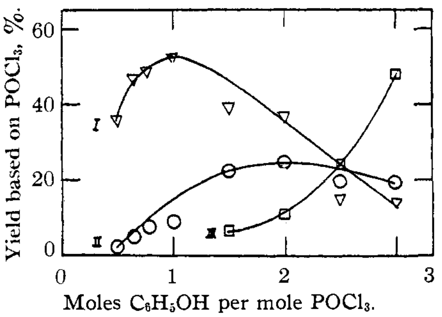


Fig. 2.—Effect of varying the C_6H_5OH-$POCl_3$ ratio upon yields of phenyl diamidophosphate (I), diphenyl amidophosphate (II) and triphenyl phosphate (III).

The experimental results indicate that the interaction of phenol with phosphorus oxychloride in the presence of pyridine yields a product whose composition depends upon the mole ratio of phenol to phosphorus oxychloride. In any case a product is obtained which consists of a mixture of all possible components from unchanged phosphorus oxychloride and phenol to triphenyl phosphate. The relative amounts of the various constituents depend upon the C_6H_5OH-$POCl_3$ ratios, larger quantities of phenol causing a shift in composition of the mixture to the more highly arylated products.

C. Effect of Heating upon the Composition of the $POCl_3$-C_6H_5OH-C_5H_5N Reaction Product.—A chloroform solution of $POCl_3$-C_6H_5OH-C_5H_5N in the molecular ratio of 1–2–3 was prepared at 0° identical in quantities with that described in (B) and then refluxed for fifteen minutes before treatment with liquid ammonia. From the ammonolyzed product, there were recovered 5.3 g. (10.3%) of (I), 32.5 g. (43.5%) of (II), and 21.6 g. (22.2%) of (III). The percentage yields are based upon the quantities of phosphorus oxychloride converted to each of the products. Comparison of these yields with those obtained in B (see Fig. 2), indicates that larger quantities of both diphenyl amidophosphate and of triphenyl phosphate were obtained, largely at the expense of the phenyl diamidophosphate. Subsequent heating of the $POCl_3$-C_6H_5OH-C_5H_5N reaction product causes more complete arylation of phosphorus oxychloride with a consequent shift to the right of the equilibrium proposed in the introductory portion of this paper.

Summary

The composition of the product obtained when phenol is allowed to react with phosphorus oxychloride in the presence of pyridine is influenced by the mole ratios of the constituents and by the subsequent temperature treatment. Increases in mole ratios of pyridine to phosphorus oxychloride and of phenol to phosphorus oxychloride bring about more complete arylation. A complex equilibrium is established with the result that ammonolysis gives mixtures of phenyl diamidophosphate, diphenyl amidophosphate and triphenyl phosphate. In view of the fact that the phenyl esters of amido- and diamidophosphoric acids are readily separable, this procedure is recommended for their preparation.

UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
RECEIVED APRIL 18, 1941

[CONTRIBUTION NO. 431 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Heat Capacities and Entropies of Three Disaccharides

BY ADOLPH G. ANDERSON[1] AND GEBHARD STEGEMAN

During recent years a program has been carried out in this Laboratory to secure thermal data on biologically important compounds. As part of this project, the heat capacities of three disaccharides have been measured from 60 to 298°K.

Method and Apparatus.—The method and apparatus were similar to those used by Gibson and Giauque.[2] This particular assembly has been described by Haas and Stegeman,[3] and only changes in design will be mentioned here.

Calorimeter.—The calorimeter used in this investigation was made from a thin copper cylinder of about 130-ml. capacity, closed at the ends by thin copper plates. Eight radial copper vanes were soldered into position between the inside surface of the cylinder and a small central brass tube. Into this central tube a heating element could be placed with a snug fit. This heating element consists of a thin brass tube on which was wound a constantan wire of 140 ohms resistance. The very small change of resistance with the temperature during a measurement makes the estimation of the energy input a less tedious task than before. Three measurements of the heating current were usually made to guard against a potential change in the operating battery. The resistance of the heater was always measured before and after a determination and the constancy of the heating current appeared to indicate that no contact potentials of any consequence were developed during the operation. The heat capacity of the calorimeter was about 13 cal. at 298°K.

The temperature change of the calorimeter was determined by measuring the resistance of a gold wire containing about 0.1% of silver. This double silk-covered wire of no. 36 B. and S. gage was wound on the outside of the calorimeter and baked on with Bakelite lacquer. It had a resistance of about 400 ohms at room temperature. The ends of the calorimeter were plated with gold and the wire was covered with gold leaf. The whole arrangement gave a very satisfactory performance.

The Dewar flask holding the cooling liquid was enclosed in a brass cylinder closed at both ends. By the use of a Cenco Hypervac pump, liquid nitrogen could be evaporated sufficiently rapidly to reach a temperature between 55 and 60°K.

All electrical measurements were made on a White double potentiometer of 100,000 microvolts range, using a Leeds and Northrup type H. S. galvanometer. The galvanometer sensitivity varied between the following limits: 0.0016 ohm, or 0.0010°K., per mm. scale deflection at 60°K.; 0.0124 ohm, or 0.0087°K., per mm. scale deflection at 298°K. The scale was read to 0.1 mm. A Weston unsaturated standard cell, certified by the Bureau of Standards, was used as a reference.

Calibration of the Calorimeter.—The temperature scale from 60 to 90°K. was established by the use of a copper–constantan thermocouple,[4] previously compared with a thermocouple standardized against a hydrogen gas thermometer by Giauque, Buffington and Schulze.[5] The temperature scale from 90 to 298°K. had been established previously by the use of a copper–constantan thermocouple standardized by the Bureau of Standards. A comparison of the two thermocouples showed them to be in agreement at 90°K. and also at higher temperatures. It was estimated by the Bureau of Standards that the thermocouple was correct to ±2.0 microvolts which corresponds to ±0.1°K. at 90°K. and to ±0.05°K. at 298°K.

As a check on the standardization of the calorimeter, the heat capacity of naphthalene was measured at intervals from 70 to 298°K. Typical results taken from curves are compared with published data[6] in the table below.

---

[1] From a thesis submitted by A. G. Anderson in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Gibson and Giauque, THIS JOURNAL, **45**, 93 (1923).

[3] Haas and Stegeman, *ibid.*, **58**, 879 (1936).

[4] This thermocouple was made available through the kindness of Dr. C. Travis Anderson, United States Bureau of Mines.

[5] Giauque, Buffington and Schulze, THIS JOURNAL, **49**, 2343 (1927).

[6] Huffman, Parks and Daniels, *ibid.*, **52**, 1547 (1930); Southard and Brickwedde, *ibid.*, **55**, 4378 (1933).