form of acetals III–VI. Values for k_3 are calculated from the directly determined values of k_1 and K_a with the use of eq. 8 and 9. Comparison of k_3 to k_2 reveals that the former is considerably larger (Table II). The large magnitude of the k_3's reflects the very great electron-donating ability of the *o*- or *p*-phenolic oxyanions relative to other phenyl substituents (even –OH is much poorer). A quantitative estimate of this electron-donating ability is not possible here, for the data are too limited and the reaction too complex. Both the equilibrium protonation, which should correlate with σ, and the heterolysis, which would probably correlate with σ^+, are presumably significantly affected by the substituents in the aromatic ring.[16]

Deuterium oxide solvent isotope effects can serve as a useful test of the postulated mechanism. The value for $k(H_2O)/k(D_2O)$ in the hydrolysis of acetal at 15° in dilute HCl is 0.38.[17] We have found that the specific acid-catalyzed hydrolysis of the neutral acetals I–V has a similar isotope effect: $k_2(H_2O)/k_2(D_2O)$ = 0.32–0.42 (Table II).

Determination of the D_2O effect on k_1 (using eq. 5) indicates that the ratio $k(H_2O)/k(D_2O)$ is greater than unity. However, it is not proper to compare this isotope effect with that calculated for k_2 above. The proper comparison involves k_3 and k_2 since both these processes represent a pre-equilibrium followed by a slow ionization step (eq. 7). It would therefore be predicted that the D_2O effect on k_3 should be similar to that on k_2. Using eq. 6 and the pK_a of the phenols in D_2O it is found that $k_3(H_2O)/k_3(D_2O)$ = 0.31–0.38 (Table II). The deuterium oxide solvent isotope effects are therefore completely in accord with the interpretations placed upon the kinetic data.

The net effects of the *o*- and *p*-phenolate anions on the hydrolysis of the acetal linkage are the same. However, it does not follow that the effect of these substituents on the component steps must be the same. The closer proximity of the *o*-phenolate anion to the site of protonation on the acetal oxygen might, by electrostatic field effects, increase the basicity (K_3) of the *o*-phenolate acetals relative to their *p*-isomers. If k_3' were larger for the *p*-isomers, the over-all rate, as reflected in k_3, could still be the same for the isomeric pairs.[18] At present, there is no justification for differentiating between the roles of the *o*- and *p*-phenolate substituents in the present acetal hydrolyses. However, a *m*-phenolate substituent could not provide the direct resonance stabilization of the intermediate and would be expected to show a much smaller unimolecular reaction.

The unimolecular reaction we have observed is formally an intramolecular general acid-catalyzed reaction, having the same kinetic expression as eq. 1. Mechanistically, however, it represents the specific hydronium ion-catalyzed hydrolysis of the phenolate anion form of the acetal as shown in eq. 7. The rate of the phenolate anion reaction in eq. 7 is so great that the reaction of eq. 1 would have to be extremely facile if it were to be detected in the presence of the former reaction. However, it is conceivable that a reaction analogous to eq. 1 could occur and be detected with an acidic *o*-substituent whose anion could not engage in a direct resonance stabilization of the carbonium ion formed in the reaction.[19]

Mechanisms 1 and 7 differ essentially only in the position of the proton in the transition state. Mechanism 1 indicates that the proton is partially transferred in the transition state while mechanism 7 indicates that it is fully transferred. A number of other apparent intramolecular acidic catalyses appear to conform to the results found in this paper, namely, that the proton transfer is essentially complete in the transition state of the reaction.[20]

(16) Treatment of a more extensive set of data by the method of H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **78**, 815 (1959), might prove of interest.

(17) W. J. C. Orr and J. A. V. Butler, *J. Chem. Soc.*, 330 (1937).

(18) A crude test of the proposition regarding protonations was made by determining the ionization constants of analogs of the phenolic acetals, 2- and 4-hydroxy-5-nitrobenzylamines, which appear to exist as the zwitterions. The first pK_a's and the second pK_a's are essentially identical for the two isomers. In these aromatic systems, the effect of charge is relayed with equal effectiveness, whatever the means, to the *ortho* and *para* positions.

(19) NOTE ADDED IN PROOF.—This prediction is borne out in the recent demonstration (B. Capon, *Tetrahedron Letters*, **14**, 911(1963)) that in the hydrolysis of *o*-carboxyphenyl-β-D-glucoside, the *o*-carboxy group acts as an intramolecular general acid catalyst and increases the rate of hydrolysis substantantially as compared to the corresponding *p*-carboxy derivative.

(20) M. L. Bender and J. M. Lawlor, *J. Am. Chem. Soc.*, **85**, 3010 (1963).

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Isotopic and Kinetic Studies of the Mechanism of Hydrolysis of Salicyl Phosphate. Intramolecular General Acid Catalysis[1]

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Several experiments indicate that no salicyloyl phosphate intermediate is formed in the hydrolysis of salicyl phosphate: (1) no hydroxamic acid is formed when salicyl phosphate hydrolyzes in the presence of hydroxylamine; (2) when salicyl phosphate is hydrolyzed in $H_2{}^{18}O$, no oxygen-18 is introduced into the salicylic acid produced, unlike the corresponding experiment in aspirin hydrolysis. Salicyloyl cyclic phosphate hydrolyzes *via* salicyl phosphate as an intermediate; thus the former compound cannot be an intermediate in the hydrolysis of the latter. The shape of the pH–rate profile of salicyl phosphate hydrolysis in deuterium oxide is identical with that in water, although the curve is shifted to higher pH. The deuterium oxide solvent isotope effect for the hydrolysis of salicyl phosphate dianion has been determined: $k^{H_2O}/k^{D_2O} = 0.96$. The dianion of 8-hydroxy-1-naphthyl dihydrogen phosphate hydrolyzes 10 times faster than the dianion of the 8-methoxy ester. The experimental data given above are not consistent with mechanisms of salicyl phosphate hydrolysis involving intramolecular nucleophilic attack by either *o*-carboxylate ion or by phosphate dianion. The data are, however, consistent with a mechanism for the facile hydrolysis of salicyl phosphate in which the *o*-carboxylic acid group donates a proton to the leaving oxygen atom in the hydrolysis.

Introduction

The facile hydrolyses of *o*-carboxyaryl phosphates have been extensively studied.[4–7] The hydrolyses of these compounds are kinetically first order with respect to the ester, the dianion hydrolyzes faster than the

(1) This research was supported by the National Science Foundation and the U. S. Atomic Energy Commission.

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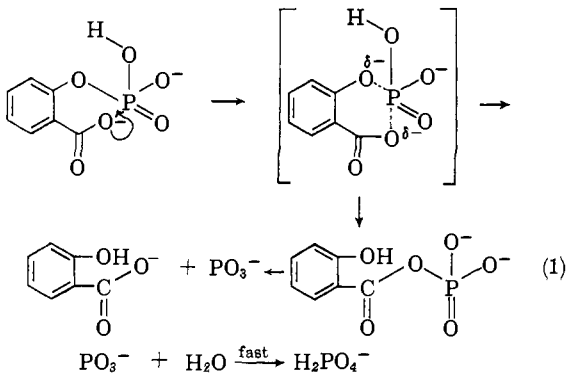
(4) J. Arai, *J. Biochem.* (Tokyo), **20**, 465 (1934).

(5) (a) J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, **74**, 4347 (1952); (b) J. D. Chanley and E. M. Gindler, *ibid.*, **75**, 4035 (1953); (c) J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955).

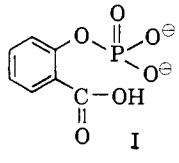
other ionic species, and the hydrolysis of the dianion is very much faster than the hydrolysis of the monoanion of phenyl phosphate. Of particular interest is the work of Chanley and his associates, who have shown that the ease of hydrolysis of *o*-carboxyaryl phosphates is not due to inductive or resonance effects, but is rather due to some direct interaction of the *o*-substituent with the reaction center since analogous *m*- and *p*-substituents do not exhibit the same enhanced reactivity.[5] The mechanism that Chanley proposed for these reactions envisages the nucleophilic attack of the *o*-carboxylate ion upon the phosphorus atom, as shown in eq. 1 (with the additional postulate of a metaphosphate ion intermediate).



(1)

$$PO_3^- + H_2O \xrightarrow{\text{fast}} H_2PO_4^-$$

However, there is an ambiguity with respect to the function of the *o*-carboxyl group in the hydrolysis of salicyl phosphate. Investigations of the mechanism of the hydrolysis of the monoanions of phosphate monoesters[8-10] and of the hydrolysis of the monoanions of acyl phosphate[11] have indicated that the acidic hydroxyl group of the molecule transfers a proton intramolecularly to assist the reaction. In some instances the unstable monomeric metaphosphate anion is postulated as the initial reaction product[8,11]; in others an external nucleophile is postulated to participate in the reaction to give the product directly. In either case, however, the conclusion is reached that an internal proton transfer from an acidic group to the leaving group is essential for the reaction. Therefore a compound containing an ionized phosphate group would be predicted to undergo facile hydrolysis when the compound contains an acidic hydrogen atom attached to the ester group in a position favorable for transfer of that hydrogen atom to the ester oxygen atom. Such a molecule is the dianion of an *o*-carboxylaryl phosphate (I) (which, of course, is kinetically equivalent to the species shown in eq. 1).



I

Experimental

Materials. Salicyl phosphate was prepared and purified according to the method of Chanley.[5a] The yield after the first recrystallization was 50%. The purified product, fine needles, had a m.p. of 160–160.5°, lit.[5a] m.p. 162.5–163°.

Salol phosphate was prepared by a modification of the method of Michaelis and Kerkhof.[12] Salol (100 g., 0.47 mole) and phosphorus pentachloride (130 g., 0.62 mole) were mixed in a flask fitted with a calcium chloride tube. The mixture was heated on a steam bath for 1 hr.; hydrogen chloride was evolved copiously. The resulting melt was allowed to cool, and the solid mass of products was extracted with boiling hexane. The boiling extract was filtered and the granular crystals deposited by the cold filtrate were recrystallized twice from hexane; yield 140 g., 36%. The hydrolysis of this material was slow; when crystals were placed in water they rapidly produced a viscous oil which took several hours to dissolve at room temperature. The compound was almost certainly not of the $RO-PCl_4$ type. The salol derivative (9.9 g., 0.025 mole) was dissolved in benzene (50 ml.) contained in a dish which was placed over potassium hydroxide pellets inside a desiccator. Water (1.8 g., 0.1 mole) was added to the benzene solution, and the mixture was stirred magnetically for 2 days. Crude salol phosphate crystallized as a pasty mass which was filtered off and recrystallized several times from benzene; m.p. 91–92°, reported[12] m.p. 88°. The yield of pure salol phosphate was of the order of 5% (based on salol). Salol phosphate was not stable; fresh ester was prepared just before each set of kinetic measurements, if these were carried out more than 2 weeks apart.

Salicylaldehyde phosphate was prepared from salicylaldehyde (Matheson Coleman and Bell, from the bisulfite compound, 12.2 g., 0.1 mole) and phosphorus pentachloride (30 g., 0.14 mole) according to the method of Manaka.[13] The solution was made alkaline, and the solution was saturated with solid ammonium chloride. Nonacidic materials were extracted with ether. The aqueous solution was acidified until the solution was approximately normal in hydrochloric acid. The solution was extracted with ether (3 × 100 ml.); the ether extract was dried with anhydrous magnesium sulfate and evaporated under reduced pressure overnight. The product, a pasty mass of crystals of salicylaldehyde dihydrogen phosphate, was recrystallized by dissolving it in the minimum of cold ether, adding a relatively large volume of benzene (but not enough to cause precipitation), and evaporating solvent under reduced pressure. The yield of salicylaldehyde dihydrogen phosphate after two recrystallizations was 2.5 g., 12.5%, of light brown crystals, m.p. 124.5–126.5°. Treatment with Norit failed to remove the coloration. The ester produced a silver mirror when warmed with ammoniacal silver nitrate. The phosphomolybdate test and the ferric chloride test were both negative at room temperature. The dicyclohexylammonium salt had a melting point of 171–172°.

Naphthalene-1,8-diol.—Sodium 8-hydroxynaphthalene-1 sulfonate (Eastman, Tech., 100 g., 0.4 mole) was fused with sodium hydroxide (200 g., 5 moles) and potassium hydroxide (100 g., 1.8 moles) under nitrogen. The yield of buff needles was 22 g., 32%, m.p. 140–141°, reported[14,15] m.p. 140°. A sample of the diol was further purified for spectrophotometric measurements by recrystallization from benzene–heptane solvent. The purified compound was pale yellow and this color was not removed by vacuum sublimation or by treatment with Norit; m.p. 141.5–143°. The yellow color was probably due to traces of oxidation products. An aqueous solution of the diol produced a gray-green precipitate when treated with aqueous ferric chloride.

Naphthalene-1,8-diol Cyclic Phosphate.—Naphthalene-1,8-diol, dissolved with a large excess of sodium hydroxide in water, was treated with an excess of phosphorus oxychloride at 0°. The solution—still alkaline—was extracted with ether, and the aqueous phase was saturated with ammonium chloride. The mixture was neutralized to congo red, then made 2 *N* in acid with concentrated hydrochloric acid, and cooled in ice. Much of the cyclic phosphate crystallized as pale brown plates which were filtered and washed with cold 2 *N* hydrochloric acid. The yield from 2 g. of diol was 2.3 g., 83%. The cyclic phosphate was dissolved in the minimum volume of water, treated with Norit, and filtered. The filtrate was made 2 *N* in hydrochloric acid and cooled in ice. The cyclic phosphate crystallized as colorless plates which were filtered, dried, and recrystallized from acetone-benzene; m.p. 280–284°. The material contained no inorganic phosphate or free phenolic groups.

Anal. Calcd. for $C_{10}H_7O_4P$: C, 54.05; H, 3.17; P, 13.95. Found: C, 54.21; H, 3.31; P, 13.92. Dicyclohexylammonium salt, m.p. 234–235.5°. *Anal.* Calcd. for $C_{22}H_{30}NO_4P$: C, 65.49; H, 7.50; N, 3.47; P, 7.68. Found: C, 65.62; H, 7.56; N, 3.57; P, 7.82.

8-Hydroxyl-1-naphthyl Dihydrogen Phosphate.—Naphthalene-1,8-diol cyclic phosphate was dissolved in aqueous sodium hydroxide to give a strongly alkaline solution. A saturated solution of barium chloride (1.5 moles of barium chloride to 1 mole of cyclic phosphate) was added to the alkaline solution of

(6) F. R. Atherton, Chemical Society, Spec. Publ. No. 8, London, 1957, p. 77.
(7) T. Marakami, Ph.D. Thesis, Clark University, 1959.
(8) W. W. Butcher and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2420 (1955).
(9) C. A. Vernon, Chemical Society Special Publ. No. 8, London, 1957, p. 17.
(10) E. B. Herr, Jr., and D. E. Koshland, Jr., *Biochim. Biophys. Acta*, **25**, 219 (1957).
(11) G. DiSabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4400 (1961).
(12) A. Michaelis and W. Kerkhof, *Ber.*, **31**, 2174 (1898).
(13) C. Manaka, *J. Biochem.* (Tokyo), **14**, 481 (1932).
(14) H. Erdmann, *Ann.*, **247**, 356 (1888).
(15) G. Heller and H. Kretzschmann, *Ber.*, **54**, 1100 (1921).

cyclic phosphate, and the mixture was heated to 100°. As the temperature approached 100° a copious precipitate was formed. The mixture was cooled and filtered. The precipitate was washed with cold water and dissolved in hydrochloric acid. The acid solution was saturated with solid ammonium chloride and then extracted with ether. The ether extract was dried and then evaporated under reduced pressure to yield a crystalline residue. The crude product was recrystallized from ether–benzene. The fluffy, buff needles of product began to sinter at 150° and finally melted near 280°—dehydration to the cyclic phosphate was indicated. The yields were of the order of 50% based on the cyclic phosphate. The buff coloration of the crystals was not removed by treatment with Norit. An aqueous solution of the purified material developed an intense magenta color when treated with aqueous ferric chloride. The ester was not contaminated with inorganic phosphate.

Anal. Calcd. for $C_{10}H_9O_5P$: C, 50.00; H, 3.79; P, 12.91. Found: C, 50.26; H, 4.13; P, 12.70. Dicyclohexylammonium salt, m.p. 212–213.5°. *Anal.* Calcd. for $C_{22}H_{32}NO_5P$: C, 62.69; H, 7.65; N, 3.32; P, 7.36. Found: C, 62.37; H, 7.37; N, 3.38; P, 7.43. Only one amine molecule per molecule of the dibasic acid is involved in the formation of the crystalline salt. This stoichiometry is no doubt caused by the bulk of the amine.

1-Hydroxy-8-methoxynaphthalene.—1-Hydroxy-8-methoxynaphthalene was prepared from naphthalene-1,8-diol (16 g., 0.1 mole), sodium hydroxide (4.5 g., 0.11 mole), and dimethyl sulfate (13 g., 0.1 mole) according to the method of Staudinger, *et al.*[16] The yield of crude phenol was 8.5 g., 68%. A sample which was recrystallized from hexane for spectrophotometric purposes melted at 53.5–55°, reported[16] m.p. 55–56°.

8-Methoxynaphthyl-1 Dihydrogen Phosphate.—Phosphorus oxychloride (15 g., 0.1 mole), pyridine (15 g., 0.2 mole), and ether (100 ml.) were placed in a flask cooled by ice. 1-Hydroxy-8-methoxynaphthalene (3.5 g., 0.02 mole) in ether (150 ml.) was added to the stirred mixture over a period of 1 hr. The reaction mixture was poured into a vigorously stirred slurry of ice and water (approximately 150 ml.), and the resulting aqueous phase was made strongly alkaline by the addition of solid sodium hydroxide. The ether layer was discarded. The aqueous layer was saturated with solid ammonium chloride, neutralized to congo red, and made 2 *N* in acid with concentrated hydrochloric acid. The phosphate monoester was extracted with ether (3 × 100 ml.). The ether solution was dried over magnesium sulfate and evaporated under reduced pressure. The crystalline residue was crystallized from acetone–benzene. The purified material, m.p. 166–168°, gave no color reaction with ferric chloride and contained no inorganic phosphate. The yield of ester after the first recrystallization was 2.5 g., 69%.

Anal. Calcd. for $C_{11}H_{11}O_5P$: C, 51.97; H, 4.37; P, 12.19. Found: C, 51.68; H, 4.68; P, 12.27. Dicyclohexylammonium salt, m.p. 206–207.5°. *Anal.* Calcd. for $C_{23}H_{34}NO_5P$: C, 63.28; H, 8.08; N, 3.21; P, 7.10. Found: C, 63.51; H, 7.96; N, 3.21; P, 7.05.

Synthesis and Reactions of Salicyloyl Phosphate.—Silver dihydrogen phosphate was prepared from trisilver phosphate and 86% phosphoric acid at 100°, followed by precipitation of the product with acetone. Salicyloyl chloride was prepared from salicylic acid and excess thionyl chloride at 60°. The excess thionyl chloride was removed under reduced pressure, and the residue of salicyloyl chloride was used without further purification. Salicyloyl chloride (from 1 g. of salicylic acid) was added, in 100 ml. of ether, to a large excess of dried silver dihydrogen phosphate (20 g.) in a flask fitted with a calcium chloride tube. The mixture was swirled vigorously for 20 min., filtered, and the filtrate was treated with dry triethylamine (1 g.). An oily suspension was formed. This oily suspension, which was presumably trimethylammonium salicyloyl phosphate (heavily contaminated with the triethylammonium salts of salicylic and phosphoric acids), was shown to give a positive hydroxamic acid test on treatment with hydroxylamine buffer at pH 6 followed by treatment with 1% ferric chloride solution and sufficient hydrochloric acid to discharge the color of the ferric–salicylate complex. Attempts to isolate pure salicyloyl phosphate yielded only a mixture of salicylic and polyphosphoric acids. Attempts to prepare pure tertiary amine salts of salicyloyl phosphate also proved abortive because they were obtained initially as pastes or oils which rapidly decomposed.

A similar treatment was given to salicyl phosphate to ascertain whether salicyloyl phosphate was formed during the hydrolysis of the former. Salicyl phosphate was dissolved in ether and treated with trimethylamine. The resulting oil was dissolved in the hydroxylamine buffer. This solution (approximately pH 6) was kept at room temperature for 30 hr. to allow the ester to hydrolyze. An aliquot of the hydrolysate was treated with ferric chloride solution and hydrochloric acid solution, as above, but no hydroxamic acid was observed.

Determination of Ionization Constants.—The second and third ionization constants of salicyl phosphate in water and in deuterium oxide were required for the analysis of the kinetic data. The pK_2's of the naphthalene derivatives were also measured. The ionization constants were obtained by measuring the pH's of the appropriate half-neutralization points estimated from titration curves. When pK's below 4.5 were to be determined, the form of the Henderson equation that included the hydrogen ion concentration was employed. The titration curves for salicyl phosphate were obtained by the use of a Radiometer TTT1 automatic titrator coupled with a Radiometer SBR2c Titragraph recorder. A Radiometer 4c pH meter and a micrometer buret were used to obtain the titration curves of 8-hydroxy- and 8-methoxy-1-naphthyl dihydrogen phosphates. All titrations were carried out under nitrogen and all water used was carbon dioxide-free.

Determination of Rates of Hydrolysis.—The extent of hydrolysis of each of the phosphates examined was determined by ultraviolet spectrophotometry. All the hydrolyses were first order with respect to the organic phosphate; the rate constants were calculated from the usual integrated equation using graphical methods. The spectrophotometers employed were a Cary 14 PM recording spectrophotometer and a Beckman DU spectrophotometer, each of which was equipped with a thermostated cell compartment.

Hydrolysis of Salicyl Phosphate and Salicyloyl Cyclic Phosphate.—Salicyl phosphate and salicyloyl cyclic phosphate were hydrolyzed in buffer solutions at 25.00 ± 0.02°. The reaction solutions were initially 10^{-3} to 10^{-4} *M* in substrate. At pH 1 and 2, the compounds were hydrolyzed in 0.1 *N* and 0.01 *N* hydrochloric acid, respectively. The hydrolyses were carried out in acetate buffers between pH 3 and 5.6. From pH 5.8 to 7.4, phosphate buffers were employed. The ionic strengths of the buffer solutions were adjusted to $\mu = 1$ with potassium chloride. All the buffer materials were reagent grade. The pH's of the reaction solutions were measured with a Radiometer pH meter at the beginning and end of each kintic run; the differences between the initial and final pH's were ±0.02 pH unit or less. To determine pD, 0.40 was added to the pH meter reading.[17]

Solutions of salicyl phosphate were prepared by dissolving approximately 2 mg. of the ester in 100 ml. of buffer solution contained in a volumetric flask, which had been equilibrated at 25.00° in a constant temperature bath. The stoppered flask was shaken vigorously and then returned to the bath. The flask was left to re-equilibrate for at least 15 min. before any measurements were made. Samples of the reaction mixture were withdrawn at appropriate time intervals and placed in a 1-cm. cuvette; the absorption at 296 mμ of each sample was measured immediately.

The hydrolysis of salol phosphate[4] can be analyzed in terms of three reactions: (1) intramolecular nucleophilic attack by phosphate dianion to produce a cyclic acyl phosphate, salicyloyl cyclic phosphate; (2) hydrolysis of the cyclic acyl phosphate to yield salicyl phosphate; and (3) hydrolysis of salicyl phosphate to salicylate and phosphate. The first process is complete in a few minutes. In order to determine the relative magnitudes of the rate constants of the second and third reactions, the kinetics of hydrolysis of the cyclic acyl phosphate were determined. Solutions of the cyclic acyl phosphate for kinetic runs at pH 5 and higher pH's were prepared in the same manner as the salicyl phosphate solutions, by dissolving salol phosphate in the appropriate buffer, except that the solutions were allowed to re-equilibrate for 25 min. to permit the complete conversion of salol phosphate to the cyclic acyl phosphate. At pH's below 5 the rate of conversion of salol phosphate to the cyclic acyl phosphate is too slow to permit the direct addition of salol phosphate to the buffer. These solutions were prepared by dissolving salol phosphate in water, adjusting the pH to 5 or 6, and maintaining that pH for 35 min.; at that time the solution of the cyclic acyl phosphate was mixed with the appropriate buffer. The isosbestic point in the hyrolysis of salicyl phosphate fortunately occurs at a wave length at which there is a large absorption change in the hydrolysis of the cyclic acyl phosphate. The hydrolysis of the cyclic acyl phosphate was therefore measured at the wave length of the isosbestic point of the salicyl phosphate hydrolysis; in this way it was possible to avoid absorption changes caused by the secondary hydrolysis of salicyl phosphate. Simple first-order kinetics were observed. The wave length of the isosbestic point was pH-dependent, and it was necessary to determine the position of the isosbestic point at each pH at which the cyclic acyl phosphate was hydrolyzed. For example, at pH 5.81, the isosbestic point occurred at 245 mμ, and at pH 1.78 it occurred at 252.2 mμ. The rate constants obtained from duplicate runs generally differed by 1 to 2%.

Hydrolysis of 8-Hydroxy- and 8-Methoxy-1-naphthyl Dihydrogen Phosphates.—1,8-Naphthalenediol and 8-methoxy-1-naphthol (and salicylaldehyde) were very sensitive to the presence of oxygen at the temperatures (80 and 100°) used for the kinetic

(16) H. Staudinger, E. Schlenker, and H. Goldstein, *Helv. Chim. Acta*, **4**, 334 (1921).

(17) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

studies, particularly at high pH's. It was therefore necessary to conduct the hydrolyses of the phosphates of these compounds in sealed ampoules. At pH 10, borate was leached from the Pyrex ampoules in sufficient quantities to combine with 1,8-naphthalenediol. The buffer also acted on the Pyrex glass to produce flakes of solid which were difficult to remove. Hydrolyses at pH 10 were therefore conducted with degassed samples in ampoules of alkali-resistant glass (Corning No. 7280). It was necessary to add sodium ethylenediaminetetraacetate to the solutions of the naphthol derivatives in order to minimize side reactions with, or catalyzed by, metal ions in the solutions.

An acetate buffer was employed at pH 3, and a carbonate buffer was used at pH 10. The actual pH's of a carbonate buffer at 80° and at 100° are not known, but it is known that the change in pH between 25 and 60° is small.[18] The ionic strengths of the buffers were $\mu = 0.2$, and the concentrations of sodium ethylenediaminetetraacetate in the buffers was 0.001 *M*. In spite of these precautions the plots of log $(A_\infty - A_t)$ were scattered and the values of A_∞ were frequently as much as 10–20% too low. Because the experimental values of A_∞ were unreliable, calculated values were used, except for the 8-methoxy compound at pH 3. The results were particularly poor in the hydrolysis of 8-methoxy-1-naphthyl dihydrogen phosphate at pH 10 at 80°, but the value of the rate constant obtained is probably reliable within a factor of 2; duplication of other hydrolyses gave results which agreed to 4% or better.

Hydrolysis of Salicyl Phosphate in $H_2{}^{18}O$.—Salicyl phosphate (120 mg.) and anhydrous sodium acetate (460 mg.) were dissolved in 4 ml. of $H_2{}^{18}O$ (1.84 atom % ^{18}O). The solution (pH 5.2) was allowed to stand at 30° for 24 hr. The solution was chilled and acidified with concentrated hydrochloric acid. The precipitated salicylic acid was washed with water and recrystallized from heptane; m.p. 159–160°. The oxygen of the salicylic acid was converted to carbon dioxide by the method of Rittenberg and Ponticorvo.[19] The ratio of $C^{16}O^{18}O$, measured on a Consolidated 21–130 mass spectrometer, was found to be 4.03×10^{-3}.

Salicylic acid (140 mg.) and anhydrous sodium acetate (200 mg.) were dissolved in 4 ml. of $H_2{}^{18}O$ and another 140 mg. of anhydrous sodium acetate was added to bring the solution to pH 5.2. The solution was allowed to stand at 30° for 24 hr. and the salicylic acid isolated as before. The ratio of $C^{16}O^{18}O$ to $C^{16}O^{16}O$ was 4.03×10^{-3}, exactly the same as the ratio found for the carbon dioxide derived from the salicylic acid formed in the hydrolysis of salicyl phosphate. The isotopic ratio, obtained from the carbon dioxide derived from the salicylic acid samples, was also the same within experimental error as the ratio obtained from tank carbon dioxide.

Results

The Hydrolysis of Salicyl Phosphate.—The effect of deuterium oxide on the kinetics of hydrolysis of salicyl phosphate was determined. The kinetics results are presented in Table I and Fig. 1. The smooth curves in Fig. 1 were calculated on the basis of the ionization constants of salicyl phosphate in water and in deuterium oxide which are shown in Table II, and from estimated values for the rate constants of the hydrolysis of the individual ionic species. The values of k_1 (for the monoanion) and k_2 (for the dianion) which gave the best approximation to the experimental curve were accepted as the required rate constants. The values derived for k_2 are $2.3 \pm 0.1 \times 10^{-5}$ sec.$^{-1}$ and $2.4 \pm 0.1 \times 10^{-5}$ sec.$^{-1}$ for the reaction in water and deuterium oxide, respectively.[20] The deuterium oxide solvent isotope effect in the hydrolysis of salicyl phosphate dianion $(k_2^{H_2O}/k_2^{D_2O})$ is therefore 0.96.

TABLE I

THE HYDROLYSES OF SALICYL PHOSPHATE IN WATER AND DEUTERIUM OXIDE[a]

Water				Deuterium oxide	
pH	$k_{obsd} \times 10^5$, sec.$^{-1}$	pH	$k_{obsd} \times 10^5$, sec.$^{-1}$	pD	$k_{obsd} \times 10^5$, sec.$^{-1}$
0.99	0.146	4.94	2.03	4.17	1.51
2.00	.226	4.94	1.99	4.61	1.97
2.01	.223	5.50	1.61	4.80	2.00
3.05	.776	5.51	1.61	4.83	2.01
3.08	.756	5.81	1.25	5.00	2.14
3.88	1.68			5.00	2.09
3.89	1.70	5.82	1.26	6.04	1.67
3.95	1.75			6.05	1.65
3.96	1.70			6.76	0.70
4.94	2.04			6.77	0.695

[a] 25.00°, $\mu = 1.0$.

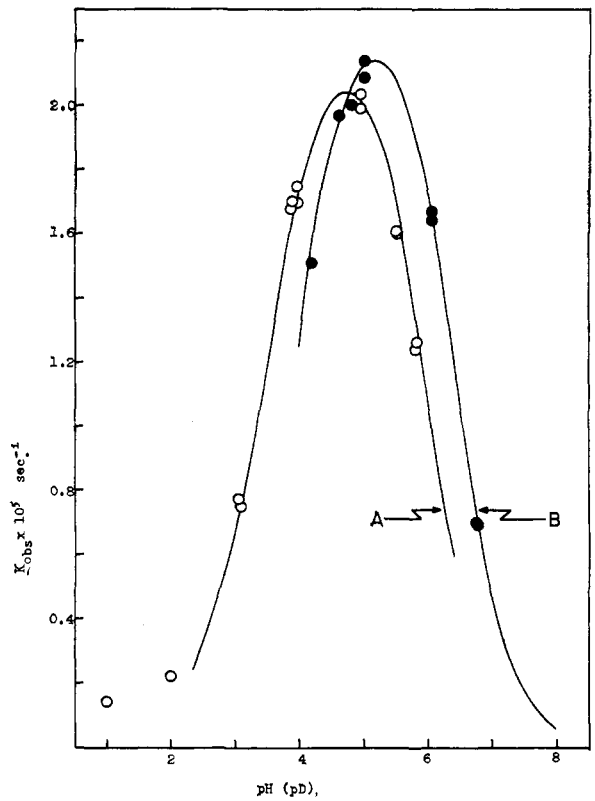


Fig. 1.—Hydrolysis of salicyl phosphate in water (curve A) and in deuterium oxide (curve B) at 25° and $\mu = 1$. The curves were calculated from the experimental data.

TABLE II

IONIZATION CONSTANTS OF PHOSPHATE ESTERS

Ester	Solvent	Ionic strength	pK_2	pK_3
Salicyl phosphate[a]	Water	1.0	3.51 ± 0.04	6.03 ± 0.02
Salicyl phosphate	D_2O	1.0	4.01 ± .02	6.46 ± 0.02
8-Hydroxy-1-naphthyl dihydrogen phosphate	Water	0.2	4.74 ± .04	
8-Methoxy-1-naphthyl dihydrogen phosphate	Water	0.2	6.42 ± .01	

[a] Chanley, Gindler, and Sobotka[5a] report $pK_2 = 3.87$ and $pK_3 = 6.74$ at $\mu = 0.16$. The differences between these two sets of results can be attributed to the difference in ionic strength.

An extrapolation of the results of Chanley, *et al.*,[5] to 25.0° gives a value of 2.03×10^{-5} sec.$^{-1}$ for k_2, in reasonable agreement with the present results, considering the difference in ionic strength and the necessary extrapolation.

The Hydrolysis of Salicyloyl Cyclic Phosphate.—The kinetics of hydrolysis of salicyloyl cyclic phosphate (II) are shown in Table III. The pH–rate profiles of the

(18) I. M. Kolthoff and C. Rosenblum, "Acid–Base Indicators," The Macmillan Co., New York, N. Y., 1937.

(19) D. Rittenberg and L. Ponticorvo, *J. Appl. Radiation Isotopes*, **1**, 208 (1956).

(20) This analysis did not permit an accurate determination of k_1 because the rate constant for the neutral molecule was not known, and k_1 itself was relatively small. However, the estimation of k_2, the rate constant of interest, was not significantly affected by the inaccuracy in k_1 because the monoanion reacted at about one-tenth the rate of the dianion ($k_1 \cong 0.2 \times 10^{-5}$ sec.$^{-1}$ in both water and deuterium oxide).

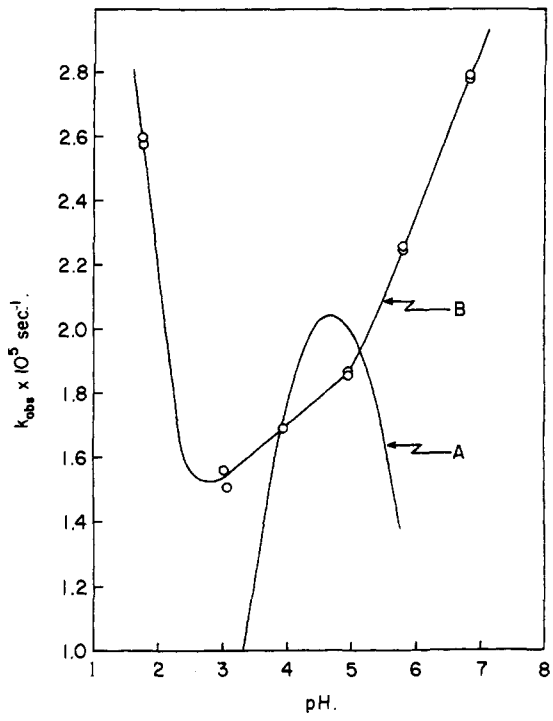


Fig. 2.—Hydrolysis of salicyl phosphate (curve A, calcd.) and of salicyloyl cyclic phosphate (curve B) at 25° and μ = 1.

cyclic acyl phosphate and acetyl phosphate are quite similar. The hydrolyses of acyl dihydrogen phosphates are catalyzed by a number of buffer anions, notably acetate and phosphate ions,[11] and the hydrolysis of the cyclic anhydride should also show buffer catalysis. However, for present purposes it was necessary that the rate constants include the buffer catalysis contributions in order to compare the above rates with those of salicyl phosphate hydrolyzed under exactly the same conditions as the cyclic anhydride. The results of such a comparison are presented in graphical form in Fig. 2.

TABLE III

HYDROLYSIS OF SALICYLOYL CYCLIC PHOSPHATE[a]

pH	$k_{obsd} \times 10^5$, sec.$^{-1}$	pH	$k_{obsd} \times 10^5$, sec.$^{-1}$
1.78	2.59	4.94	1.86
1.79	2.58	4.94	1.87
3.03	1.56	5.81	2.26
3.07	1.51	5.81	2.25
3.94	1.69	6.86	2.79
3.94	1.69	6.87	2.78

[a] 2.50°, μ = 1.0.

The Hydrolysis of Other Phosphate Esters.—The kinetics of the hydrolysis of 8-hydroxy- and 8-methoxy-1-naphthyl dihydrogen phosphates was followed at 80 and 100°. The results are presented in Table IV.

Salicylaldehyde dihydrogen phosphate has been reported[13] to hydrolyze with a rate constant approximating those of unsubstituted aryl dihydrogen phosphates. This fact was of interest in connection with the mechanistic arguments presented later, and verification of this result was thought to be desirable. The kinetics were carried out at 100° and μ = 0.2. The results were not very accurate because of experimental difficulties. At pH 3.05, $k_{obsd} = 1.7 \pm 0.1 \times 10^{-3}$ sec.$^{-1}$; at pH 3.94, $k_{obsd} = 2.2 \times 10^{-3}$ sec.$^{-1}$; and at pH 5.20, $k_{obsd} = 1.0 \times 10^{-3}$ sec.$^{-1}$.

For comparison with other dianions, the rate constant for the hydrolysis of *p*-nitrophenyl dihydrogen phosphate at pH 9.99 was determined at 100° at μ = 0.2. It was found that $k_{obsd} = 6.24 \times 10^{-5}$ sec.$^{-1}$.

TABLE IV

HYDROLYSIS OF 8-HYDROXY- AND 8-METHOXY-1-NAPHTHYL DIHYDROGEN PHOSPHATES

8-Hydroxy ester		8-Methoxy ester	
pH	k_{obsd}, sec.$^{-1}$	pH	k_{obsd}, sec.$^{-1}$
Hydrolysis at 80°, μ = 0.2			
9.86	2.06×10^{-5}[b]	9.87	1.49×10^{-6}[b]
9.88	1.98×10^{-3}[b]	9.87	1.23×10^{-6}[b]
Hydrolysis at 100°,[a] μ = 0.2			
7.38	1.7×10^{-4}	9.86	$\sim 1 \times 10^{-5}$[b]
7.32	2.0×10^{-4}		
10.00	2.07×10^{-4}[b]		

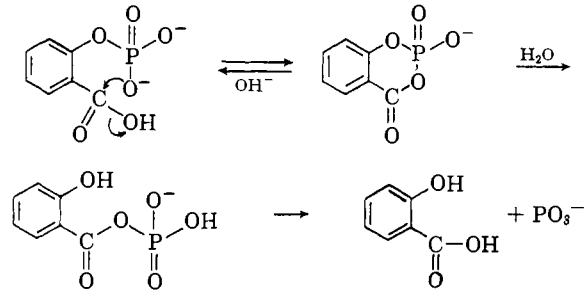
[a] The data at 100° should be considered to be less reliable because Pyrex ampoules were employed in these determinations (see Experimental). [b] Sodium ethylenediaminetetraacetate used in these runs to prevent metal ion-catalyzed decomposition.

Discussion

The dianion of salicyl phosphate, the species of interest, can exist in two kinetically indistinguishable forms. From a comparison of the pK_a's of salicyl phosphate with those of ordinary phosphates and benzoic acids, the dianion of salicyl phosphate must contain one proton almost entirely associated with the phosphate group. However, the position of the proton is not usually decisive to a mechanistic argument, since proton transfer from one position to another can be more rapid than other bond-breaking reactions. Furthermore, the higher concentration of one form of the ion must be compensated by the higher free energy of the less abundant form.

The available evidence demands that in the hydrolysis of salicyl phosphate the carboxyl group must participate in some direct manner with the phosphate ester linkage resulting in an enhancement of the rate of hydrolysis. Three possibilities will be considered for the mechanism of this interaction: (1) intramolecular nucleophilic catalysis by carboxylate ion; (2) intramolecular nucleophilic catalysis; or (3) intramolecular electrophilic catalysis by the carboxylic acid group. It will be shown that the first two possibilities are not in accord with the experimental facts, whereas the last hypothesis is in accord with all the presently available evidence.

Nucleophilic Attack by the Phosphate Dianion.—The phosphate group in its dianionic form could attack the *o*-carboxylic acid group to expel hydroxide ion and produce a cyclic acyl phosphate as shown in eq. 2.

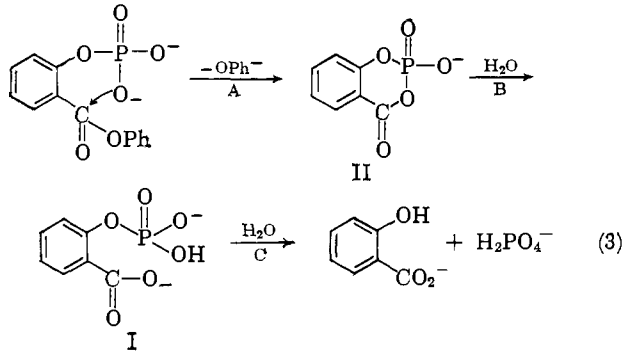


(2)

This intermediate might then decompose to salicylate and inorganic phosphate by routes analogous to those proposed by Chanley[5] (eq. 1).

To test this hypothesis it was decided to synthesize the cyclic acyl phosphate intermediate by an independent route and to observe its hydrolytic behavior. Arai[4] found that the formation of phenol from salol phosphate increased with increasing pH up to pH 6; at higher pH's the rate was independent of hydrogen ion concentration. The reaction at pH 5 was very rapid; the release of phenol was complete within 10 min. at 37°. If salol phosphate is dissolved in water,

and the pH of the solution is adjusted to pH 4 or 5, there is a rapid rise in pH. These experimental facts clearly point to the nucleophilic attack of the phosphate dianion on the carbonyl carbon atom of the ester with the expulsion of phenoxide ion, leading to the formation of cyclic acyl phosphate (step A of reaction 3). The pH–rate profile obtained by Arai for the formation of salicylate and inorganic phosphate during the hydrolysis of salol phosphate resembles markedly the pH–rate profile for the hydrolysis of salicyl phosphate. However, Arai found that the rate of production of salicylate and inorganic phosphate from the cyclic



acyl phosphate II was slower than that from salicyl phosphate. *Therefore salicyl phosphate I rather than being the precursor of the cyclic acyl phosphate II must be an intermediate in its hydrolytic decomposition.* We have confirmed this conclusion by measurement of the rate of disappearance of the cyclic acyl phosphate as a function of pH. The pH–rate profile of the cyclic acyl phosphate actually passes under the pH–rate maximum for the hydrolysis of salicyl phosphate (Fig. 2). Further evidence confirming the intermediacy of salicyl phosphate in the hydrolysis of the cyclic acyl phosphate stems from the spectrophotometric behavior of the system discussed in the Experimental section.

A variant of eq. 2 has been suggested by Atherton.[6] His suggestion that the tetrahedral addition compound formed by the nucleophilic attack of the phosphate dianion on the carboxylic acid group decomposes directly to products ignores the point that the ester linkage would not be weakened by this transformation. Furthermore, one would predict on this basis that the dianion of salicylaldehyde phosphate should hydrolyze faster than the dianion of salicyl phosphate, since nucleophilic addition to an aldehyde group should occur much more readily than to a carboxylic acid group. However, salicylaldehyde phosphate dianion behaves as an ordinary aryl phosphate with respect to its rate of hydrolysis and the position of the maximum in its pH–rate profile.

It therefore appears that one can unequivocally rule out nucleophilic attack by phosphate dianion (eq. 2) as the mechanism for the facile hydrolysis of salicyl phosphate.

Nucleophilic Attack by the Carboxylate Anion.—One of the two routes proposed by Chanley and co-workers[5] for the mechanism of the hydrolysis of salicylate phosphate involves the intermediate formation of salicyloyl phosphate (eq. 1). It should be possible to trap this intermediate by the use of nucleophilic reagents. Acyl phosphates acylate many nucleophiles, including most amine bases in aqueous solution.[21,22] The acylation of hydroxylamine has been used to measure the concentration of acyl phosphates in aqueous solution.[21,22b,d,e]

Triethylammonium salicyloyl phosphate (heavily contaminated with the triethylammonium salts of salicylic and phosphoric acids) when dissolved in a hydroxylamine buffer (pH 6) very rapidly produced a considerable quantity of a hydroxamic acid. However, when the triethylammonium salt of salicyl phosphate was hydrolyzed in the presence of the same hydroxylamine buffer, no hydroxamic acid was detected. This result indicates the absence of the acyl phosphate as an intermediate in the hydrolysis of salicyl phosphate. Similar evidence is available in the literature. The methanolysis of salicyl phosphate dianion yields methyl phosphate but no methyl salicylate.[5a] The reaction of the bis-(triethylammonium) salt of salicyl phosphate with aniline in acetonitrile solution produces N-phenylphosphoroamidate but no salicylanilide.[6]

Salicyl phosphate was hydrolyzed in $H_2{}^{18}O$ at an initial pH of 5.2. It was found that no ^{18}O was incorporated into the salicylic acid isolated after the hydrolysis. The hydrolysis of acetyl phosphate under similar conditions produced acetate in which approximately 9%[25a] or ~10%[26] of its oxygen content was derived from the medium. The difference between these tracer experiments can be interpreted most simply by saying that salicyloyl phosphate is not an intermediate in the hydrolysis of salicyl phosphate.

The formation of the anhydride depicted in eq. 1 is analogous to the mechanism proposed for, and well-documented for, the formation of the anhydride in the hydrolysis of aspirin in neutral solution. In the hydrolysis of aspirin anion in $H_2{}^{18}O$ it has been found that the salicylic acid product contains about 6% of the ^{18}O of the solvent,[23] whereas in the present reaction no ^{18}O is found in the hydrolysis product. Furthermore, in the hydrolysis of the former compound it is found that k^{H_2O}/k^{D_2O} is 1.8,[24] whereas in the hydrolysis of the latter compound it is found that k^{H_2O}/k^{D_2O} is 0.96. It is believed that the isotope effect in the aspirin hydrolysis is a secondary deuterium isotope effect. Certainly, if anhydrides were formed in both these reactions, similar ^{18}O tracer results and similar deuterium oxide solvent isotope effects would be observed. Since this is not the case, serious doubt must be cast on eq. 1 as a mechanism for the hydrolysis of salicyl phosphate. In summary, it appears that there exist a number of pieces of evidence which are inconsistent with a mechanism for the hydrolysis of salicyl phosphate involving nucleophilic attack by *o*-carboxylate ion.[24a]

Internal Proton Transfer by the Carboxylic Acid Group.—Mechanisms invoking intramolecular nucleophilic attack have been considered thus far, and it is seen that neither is consistent with the experimental evidence. A more satisfactory approach involving proton transfer can be developed from Westheimer's[8] suggestion for the hydrolysis of monoanions of phosphate monoesters. Assistance of the proton transfer from the hydrogen phosphate group to the ester oxygen by the *o*-carboxyl substituent is proposed. The mechanism is suggested *a priori* by the fact that the carboxyl group is in an excellent position to form a hydrogen bond with, or to effect a hydrogen transfer to, the ester oxygen atom. The reaction scheme may be drawn formally as shown in eq. 4.

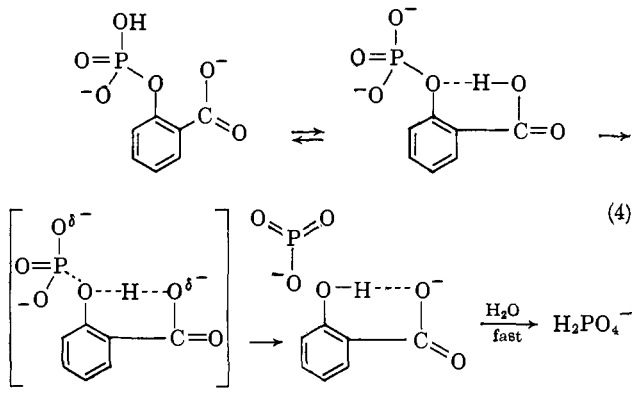
(21) G. DiSabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4400 (1961).

(22) (a) R. Bentley, *ibid.*, **70**, 2183 (1948); (b) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945); (c) H. Chantrenne, *Compt. rend. trav. lab. Carlsberg, ser. chim.*, **26**, 231 (1948); (d) D. E. Koshland, Jr., *J. Am. Chem. Soc.*, **73**, 4103 (1951); **74**, 2286 (1952); (e) J. L. Kurz and C. D. Gutsche, *ibid.*, **82**, 2175 (1960).

(23) M. L. Bender, F. Chloupek, and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5384 (1958).

(24) M. L. Bender, E. J. Pollock, and M. C. Neveu, *ibid.*, **84**, 595 (1962).

(24a) NOTE ADDED IN PROOF—Dr. J. D. Chanley (personal communication) suggests that nucleophilic attack by the carboxylate anion to give a pentacovalent phosphorus intermediate which decomposes directly to products may be an alternative mechanism.

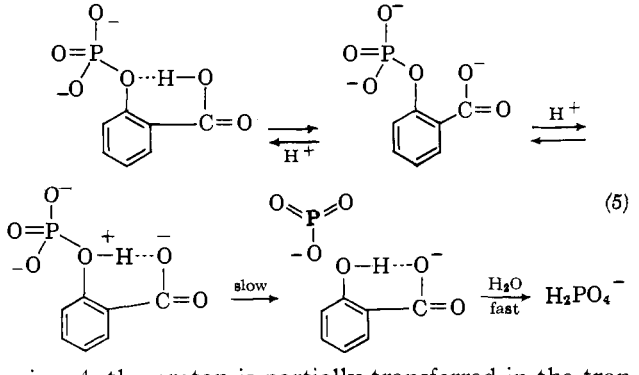


(4)

There are a number of pieces of evidence which are consistent with this mechanism. They will be discussed in turn: (1) Mechanism 4 does not require the formation of an acyl phosphate or any other intermediate that could acylate a nucleophile. The absence of hydroxamic acid in the hydrolysis of salicyl phosphate in the presence of hydroxylamine is consistent with mechanism 4 as is the lack of introduction of oxygen-18 into the salicylic acid on hydrolysis of the ester in $H_2{}^{18}O$.

(2) To discuss the effect of deuterium oxide on the rate of hydrolysis of salicyl phosphate it is advantageous to consider the following related reactions: the hydrolyses of (1) acetyl hydrogen phosphate monoanion,[21] (2) methyl hydrogen phosphate monoanion,[25] (3) 2-hydroxyphenyl-1-3-dioxane,[26] and (4) salicyl hydrogen phosphate dianion.[5] These four compounds have in common the positioning of an acidic hydroxyl group contiguous with the reaction center. Previous work indicates that all these hydrolyses involve the particular species mentioned or a kinetic equivalent thereof. The reaction of these systems can be written mechanistically as reactions in which the proton transfer is slow and is concerted with the decomposition to products (eq. 4), or alternatively as involving a pre-equilibrium proton transfer to give a zwitterionic form of the substrate which decomposes in a slow step to products (eq. 5). In the slow proton-transfer reactions there is formed in all four reactions an unstable intermediate which rapidly reacts with water to form the products (metaphosphate in the reactions of the three phosphate compounds).

Another way to describe these two mechanistic possibilities is to discuss the position of *the* proton in the transition state. In the slow proton-transfer mech-



(5)

anism 4, the proton is partially transferred in the transition state from the ground state oxygen atom to the final state oxygen atom. On the other hand, in the transition state of the pre-equilibrium proton-transfer mechanism 5, the proton is completely transferred to the final-state oxygen atom. These alternative transition states and their respective deuterium kinetic isotope effects have been considered by Westheimer,[27] who discussed the magnitude of deuterium kinetic isotope effects in terms of the symmetrical and antisymmetrical stretching vibrations in the transition state in which the proton (deuteron) is transferred. He showed that when the system A···H···B is indeed symmetric (when the proton is partially transferred), the isotope effect is at a maximum, but when the system is not symmetric (when the proton is not transferred or is fully transferred), the isotope effect decreases markedly. Thus mechanism 4 should lead to a large deuterium kinetic isotope effect while mechanism 5 should lead to a negligible kinetic isotope effect. The latter argument can alternatively be stated in terms of the pre-equilibria in eq. 5. It would be anticipated that the deuterium oxide isotope effect on the two equilibria in eq. 5 would be equal in magnitude but opposite in sense to one another, and thus would cancel. Therefore the whole reaction consisting of two equilibria and one rate step would have an isotope effect of 1. The deuterium oxide isotope effects for these four reactions including that of salicyl phosphate are shown in Table V.

TABLE V

DEUTERIUM OXIDE KINETIC ISOTOPE EFFECTS IN SOME HYDROLYTIC REACTIONS OF COMPOUNDS CONTAINING AN ACIDIC GROUP

Hydrolysis	k^{H_2O}/k^{D_2O}	Reference
Methyl phosphate monoanion	0.87	25
Acetyl phosphate monoanion	1.1	21
2-Hydroxyphenyl-1,3-dioxanes	1.26, 1.33, 1.29	26
Salicyl phosphate dianion	0.96	[a]

[a] This research.

In none of the reactions in Table V does a large deuterium oxide isotope effect appear. One can therefore accept the view that the pre-equilibrium protonation picture in eq. 5 is the correct one.

The question may be asked whether there is some independent evidence which supports the formulation of these reactions in terms of eq. 5. In the hydrolysis of the acetals, it was possible to demonstrate such an independent piece of evidence by moving the phenolic hydroxyl group from the *o*-position to the *p*-position, where the concerted reaction would be impossible, but where the pre-equilibrium proton transfer could still occur. When this was done, it was found that exactly the same pH–rate profile and exactly the same D_2O effect occurred.[26] This result indicates that the pre-equilibrium proton-transfer mechanism is certainly correct for the acetal hydrolyses and possibly correct for the other three reactions. It might be argued by analogy that in the salicyl phosphate hydrolysis a carboxyl group in the *p*-position should be just as effective as in the *o*-position. This is, of course, not found experimentally. There is a difference, however, between the salicyl phosphate hydrolysis (where the *o*-carboxyl group is mandatory) and the acetal hydrolysis (where the *o*-phenolic group is not mandatory). In the former reaction the anion must hydrogen bond to the proton in the transition state; in the latter reaction all the anion need do is provide the resonance stabilization which can be effected either from the *o*- or *p*-position.

The lack of a deuterium oxide isotope effect further indicates the absence of a nucleophilic water molecule in the transition state of these reactions, for deuterium oxide and water would be expected to have different nucleophilicities.

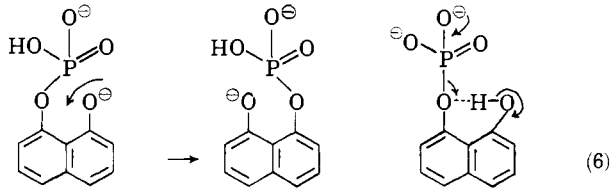
(25) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).

(26) M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **85**, 3006 (1963).

(27) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

In summary it may be stated that there is considerable similarity between the deuterium oxide solvent isotope effect in the hydrolysis of salicyl phosphate and the isotope effects in a number of other reactions involving possible internal proton transfer, and that all these reactions may be explained most readily by mechanisms analogous to eq. 5.

(3) The dianion of 8-hydroxy-1-naphthyl dihydrogen phosphate hydrolyzes approximately ten times faster than the dianion of the 8-methoxy ester. The 8-hydroxy ester cannot hydrolyze through an intermediate of the salicyloyl phosphate type (*i.e.*, by nucleophilic phenoxide ion attack at the phosphorus atom) since this reaction would only regenerate the starting material (eq. 6). Although the direction of the difference in the hydrolytic rates is that predicted by the proton-transfer mechanism, the magnitude of the difference may not be large enough to be attributed with certainty to a particular mechanism.

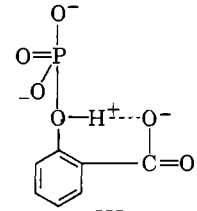


(6)

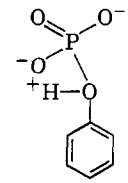
Nucleophilic attack mechanism Proton-transfer mechanism

No rate constants for the hydrolyses of aryl phosphate dianions have been reported, but it is probable that, unlike the monoanion hydrolyses, the order of reactivity is sensitive to the basicity of the phenoxide ion product. For example, the *p*-nitrophenyl phosphate dianion should hydrolyze much faster than the phenyl phosphate dianion. At 100° the dianion of *p*-nitrophenyl dihydrogen phosphate hydrolyzes faster than the dianion of 8-methoxy-1-naphthyl dihydrogen phosphate, but three times slower than the dianion of the 8-hydroxy ester. If it were not for strong intramolecular hydrogen bonding the 8-hydroxynaphthoxide ion should not differ greatly in basicity from the 8-methoxynaphthoxide ion—certainly it should be considerably more basic than *p*-nitrophenoxide. The observed order of reactivity must therefore be caused by the operation of the proton-transfer mechanism in the hydrolysis of the dianion of the 8-hydroxy ester.

The sum total of all the above arguments indicates that the best suggestion for the mechanism of the hydrolysis of salicyl phosphate is the proton transfer mechanism represented by eq. 5. Although no definitive experiment requires this conclusion, no other mechanism will satisfy the experimental criteria and, further, a large body of consistent evidence favors eq. 5. It may then be asked why proton transfer from an internal carboxylic acid group leads to a more facile reaction than proton transfer from the phosphoric acid group itself. In terms of eq. 9 it would appear that the stability of the zwitterion III is superior to that of zwitterion IV. This stability may be discussed on steric or electronic grounds. Electronically one may say that the carboxylic acid is a stronger acid than the second ionization of a phosphoric acid, and therefore the transfer of the proton to produce zwitterion III is more complete than to the zwitterion IV, or alternatively that the electrostatic stabilization of III is greater than that of IV.



III



IV

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Intramolecular Catalysis in the Hydrolysis of *p*-Nitrophenyl Salicylates[1]

BY MYRON L. BENDER,[2] FERENC J. KÉZDY, AND BURT ZERNER

RECEIVED APRIL 11, 1963

The kinetics of hydrolysis and of nucleophilic reactions of *p*-nitrophenyl salicylate, benzoate, *o*-methoxybenzoate, 5-nitrosalicylate, 3-nitrobenzoate, and 2-methoxy-5-nitrobenzoate were determined in 34.4% dioxane–water at 25°. The pH–rate profile of the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate exhibits two pH-independent reactions, one in the acid region and one in the alkaline region. The pH-independent reaction in the alkaline region may be described either as a water reaction of the ionized ester or as a hydroxide ion reaction of the un-ionized ester. Deuterium oxide solvent isotope effects do not distinguish between these possibilities. If the pH-independent reaction in the alkaline region is interpreted as the reaction of hydroxide ion with the un-ionized salicylate ester, it is calculated that hydrolysis of the salicylate esters is 213 to 458 times as fast as that of the corresponding benzoate esters. However, nucleophilic reactions of imidazole, azide ion, and sulfite ion with salicylate esters proceed essentially at the same rate as with benzoate esters. Therefore, the pH-independent hydrolysis of the salicylate esters in the alkaline region cannot be interpreted as the reaction of hydroxide ion with the un-ionized ester but rather as the reaction of water with the ionized ester, leading to a description of this facile reaction as an intramolecular general basic catalysis.

Introduction

Neighboring hydroxyl groups can catalyze the hydrolysis of carboxylic acid derivatives by direct participation in the reaction, usually by formation of an intermediate lactone (*i.e.*, nucleophilic catalysis).[3] Recently neighboring hydroxyl groups which presumably do not form lactones have been shown to accelerate the hydrolysis of carboxylic acid derivatives significantly.[3b,4–9] This rate acceleration by a neighboring

(1) This research was supported by the National Science Foundation and the U. S. Atomic Energy Commission.

(2) Alfred P. Sloan Foundation Research Fellow.

(3) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) M. L. Bender, G. R. Schonbaum, and G. A. Hamilton, *J. Polymer Sci.*, **49**, 82 (1961).

(4) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(5) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956); S. M. Kupchan and C. R. Narayanan, *ibid.*, **81**, 1913 (1959); S. M. Kupchan, W. S. Johnson, and S. Rajagopalan, *Tetrahedron*, **7**, 47 (1959); S. M. Kupchan, P. Slade, and R. J. Young, *Tetrahedron Letters*, **24**, 22 (1960); S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962); S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Am. Chem. Soc.*, **84**, 4159 (1962); S. M. Kupchan, S. P. Eriksen, and Y.-T. Shen, *ibid.*, **85**, 350 (1963).

(6) T. C. Bruice and T. H. Fife, *Tetrahedron Letters*, **8**, 263 (1961); *J. Am. Chem. Soc.*, **84**, 1973 (1962); T. C. Bruice, T. H. Fife, J. J. Bruno, and P. Benkovic, *ibid.*, **84**, 3012 (1962).