[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE MOUNT SINAI HOSPITAL]

The Mechanism of the Hydrolysis of Organic Phosphates. II. *o*-Carboxynaphthyl Phosphates[1]

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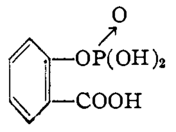
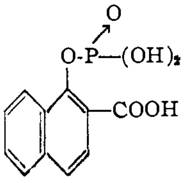
The rates of the hydrolyses of 2-carboxy-1-naphthyl phosphate (II), 3-carboxy-2-naphthyl phosphate (III) and 1-carboxy-2-naphthyl phosphate (IV), to the corresponding parent acid and phosphoric acid have been investigated in the *p*H region of 2–10. These orthocarboxynaphthyl phosphates show the same striking *p*H dependency on hydrolysis as observed in the case of salicyl phosphate (I).[2] They are most unstable at *p*H *ca.* 5–6, are very stable in the extreme acid region and completely stable in strong alkali up to 75°. The ease and unusual *p*H dependency on hydrolysis, observed with compounds II, III and IV, support the assumption of a mechanism involving the formation of a cyclic transition state as first proposed in the study on the hydrolysis of salicyl phosphate.[2] The variations in rates of hydrolysis of the aforementioned compounds are discussed and the entropies and heats of activation evaluated.

We have previously reported on the mechanism of the hydrolysis of salicyl phosphate (I).[2] In continuation of this work we have investigated the hydrolysis of three related *o*-carboxy-aryl phosphates: 2-carboxy-1-naphthyl phosphate (II), 3-carboxy-2-naphthyl phosphate (III) and 1-carboxy-2-naphthyl phosphate (IV) to the corresponding parent acid and phosphoric acid.



I



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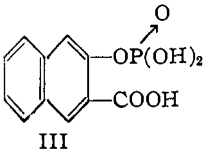

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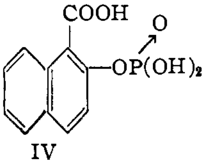


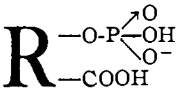
IV

As with salicyl phosphate the three carboxynaphthyl phosphates exhibit the same striking *p*H dependency on hydrolysis. They are most rapidly hydrolyzed at that *p*H (*ca.* 5–6) where the compound exists mainly in the di-ionic form, are very stable in the extreme acid region and completely stable in strong alkali up to 75°. The half-life periods at 37° and *p*H *ca.* 5.7 for the hydrolysis of the four aforementioned compounds I, II, III and IV are 2.2, 0.5, 4.3 and 84 hours, respectively. This ease of hydrolysis is in marked contrast to the behavior of phenyl phosphate,[2] α-naphthyl phosphate, β-naphthyl phosphate,[3] salicyl aldehyde phosphate[4a] and *m*- and *p*-carboxyphenyl phosphate,[4b] which remain virtually unchanged at *p*H 2–10 under the mild conditions which effect the complete hydrolysis of the aforementioned carboxy phosphates.

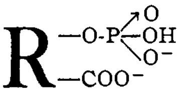
***p*H Dependency.**—We have determined the rates of hydrolysis of compounds II, III and IV at 37° over the *p*H range 2–10 in buffered medium of ionic strength $\mu = 0.1$ by analysis for liberated phosphoric acid. In each instance first-order kinetics obtained throughout the course of the reaction. The same analysis, as given for salicyl phosphate,[2] was employed in the elucidation of *p*H dependency for the hydrolysis of compounds II, III and IV. The rate equation deduced to describe the observed rate of hydrolysis at any *p*H is

$$k_{\text{obsd.}} = k_1M_1 + k_2M_2 \qquad (1)$$

where k_1 and k_2 are the specific rate constants for the hydrolysis of the mono-ionic form and di-ionic form and M_1 and M_2 are the respective mole fractions for each of the forms at the particular *p*H



M_1



M_2

R = naphthyl (1,2-, 2,3-, or 2,1-substituted)

The specific rate constants k_1 and k_2 were obtained in exactly the same manner as already described.[2] The determination of the three ionization constants K_1, K_2, K_3 (at $\mu = 0.1$) (see Table II) of compounds II, III and IV makes possible the calculation of M_1 and M_2 at any *p*H. From the observed rate constants at *p*H *ca.* 5.7, k_2 was evaluated; and at *p*H 2.3 k_1 was obtained.

These particular *p*H's were chosen since the only reactive species present at *p*H 5.7, the di-ionic form, is almost at a maximum; at *p*H 2.3 the mono-ionic form to the over-all rate is small and may be accounted for. The evaluation of k_1, k_2, M_1 and M_2 enabled us to compute from equation (1) the theoretical values for the rate constants at various *p*H's (see Table I). The agreement between observed and calculated values for the rate constants is satisfactory. In general the greatest deviations occur at the high *p*H's, since slight changes in *p*H effect a considerable percentage change in the mole fraction of the di-ionic group. This point is discussed in detail in the first paper of this series.[2]

The particular shape of the *p*H *vs.* hydrolysis rate curves (see Fig. 1) will be governed (1) by the

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(1) This work was supported in part by a grant from the National Science Foundation. The material was presented in part at the Annual Meeting of the American Chemical Society, Division of Organic Chemistry, on September 17, 1952. For the first paper in this series see reference (2).

(2) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).

(3) The half-life periods of α- and β-naphthyl phosphate over the *p*H range 2–6 are *ca.* 4300 and 1200 hours, respectively, the rate of hydrolysis dropping off rapidly above *p*H 6 to be reported in a subsequent communication.

(4) (a) C. Manaka, *J. Biochem.*, **14**, 481 (1932); (b) **14**, 191 (1931).

(4a) As with salicyl phosphate (*cf.* ref. **2**) we have observed that at *p*H values above 10 compounds II, III and IV undergo no measurable hydrolysis during 6 hours at 75°.

TABLE I

HYDROLYSIS OF *o*-CARBOXYNAPHTHYL PHOSPHATES[a]

	2-Carboxy-1-phosphate (II)				3-Carboxy-2-phosphate (III)				1-Carboxy-2-phosphate (IV)			
pH	M_1	M_2	$k_{obsd.}$ hr.$^{-1}$ × 1000	$k_{calcd.}$ hr.$^{-1}$ × 1000	M_1	M_2	$k_{obsd.}$ hr.$^{-1}$ × 1000	$k_{calcd.}$ hr.$^{-1}$ × 1000	M_1	M_2	$k_{obsd.}$ hr.$^{-1}$ × 1000	$k_{calcd.}$ hr.$^{-1}$ × 1000
2.34	0.91	0.03	166	(166)	0.85	0.04	22.3	(22.3)	0.84	0.12	3.57	(3.57)
2.94	.86	.13	257	286	.83	.14	42.2	44	.65	.34	5.62	5.43
3.71	.54	.46	756	671	.50	.50	112	112	.24	.76	8.66	8.91
4.82	.08	.92	1300	1200	.07	.91	188	188	.02	.93	10.1	10.1
5.67	.01	.99	1300	(1300)	..	.82	169	(169)	..	.76	8.32	(8.32)
5.94	..	.99	1300	1300								
6.22									..	.44	5.40	4.83
6.57					..	.37	90.0	77.0				
6.69	..	.95	1300	1280								
7.22	..	.86	1280	1120	..	.13	30.5	26.3	..	.04	0.72	0.44
7.90	..	.55	814	711	..	.03	8.7	6.8				
8.50	..	.24	297	313	..	.006	1.9	1.2				

[a] Computations based on figures in parentheses; t is 37.2°.

three ionization constants for the particular phosphate since these constants determine the mole fractions of M_1 and M_2, (2) by the relative values of k_1 and k_2. However, since the first ionization constants all fall around $pK = 1.2$ and k_2 is larger than k_1, the contours of the curves will be governed principally by pK_2 and pK_3, in the region of pH 2–10. The further apart the latter are, the flatter and wider the maximum region, conversely the closer these pK's, the sharper will be the maximum region. This is indeed the case. Figure 1 shows the log of the experimental rate constants as plotted against the pH. The curves for compounds I, III and IV are nearly identical in shape, since the difference between pK_2 and pK_3 is almost a constant value (see Table II). In contrast, 2-carboxy-1-naphthyl phosphate (II), which has an unexpectedly high pK_3 (7.99) and a "normal" pK_2 (3.78), exhibits a much broader maximum. Calculations show that the mole fraction of its di-ionic form is *ca.* 96% over the pH range 5–7.

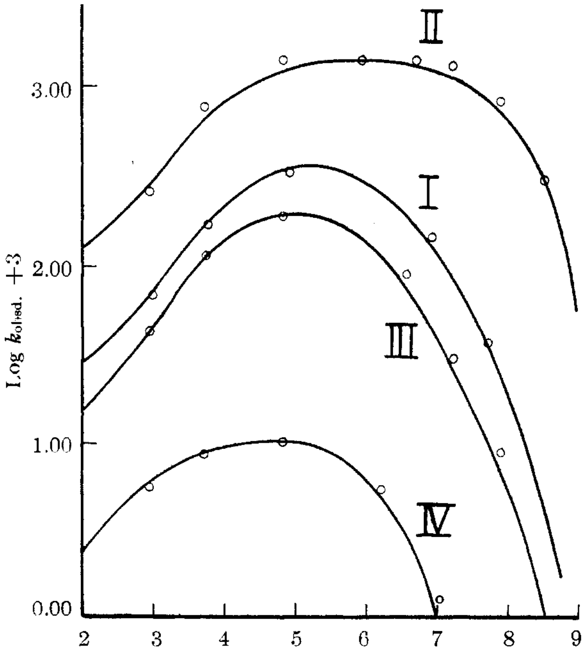

Fig. 1.—Logs of observed rates of hydrolysis in hours^{-1} at 37.2° for compounds I, II, III and IV at various pH values. The solid curve is derived from the values of k_1 and k_2 obtained at pH 2.34 and 5.67, respectively.

To account both for the extreme rapidity of the hydrolysis as compared with *p*- and *m*-carboxyphenyl phosphate and for the observed pH dependency[5] the participation of the *o*-carboxylate ion in the removal of the phosphate group has been postulated.[2] The essential feature of the mechanism suggested was the attack of the oxygen of the carboxyl group on the phosphorus with the formation of a cyclic transition state and the latter's subsequent rapid breakdown to salicyclic and phosphoric acids. The fact that a completely analogous type of hydrolysis is again encountered in three *o*-carboxy aromatic phosphoric acid esters emphasizes the role that participation of the *o*-carboxyl group must play in the hydrolysis. Indeed both the speed of the hydrolysis and its peculiar pH dependency would appear to admit of no other interpretation. The variations in rates, particularly the relatively slow rate of hydrolysis of 1-carboxy-2-naphthyl phosphate lends support to the hypothesis of participation. We have found that β-naphthyl phosphate hydrolyses approximately 3.5 times as fast as α-naphthyl phosphate. If the carboxy groups were not involved in the hydrolysis, one might anticipate that 1-carboxy-2-naphthyl phosphate (IV) would hydrolyze faster than 2-carboxy-1-naphthyl phosphate (II). Actually, the reverse is found. 2-Carboxy-1-naphthyl phosphate hydrolyzes more than 100 times faster than 1-carboxy-2-naphthyl phosphate. A reasonable explanation of this observation is offered by a participation mechanism. This point will be further elucidated in the section devoted to the variation in rates. The mechanism proposed for the hydrolysis of the three *o*-carboxynaphthyl phosphates is the same as that given for salicyl phosphate, and is illustrated in the instance of 2-carboxy-3-naphthyl phosphate. The question as to whether scheme A or B is correct has been discussed in the first paper and no decision has as yet

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[5] The extremely slow hydrolysis of *p*-carboxyphenyl phosphate shows a different type of pH dependency, to be discussed in a subsequent communication.

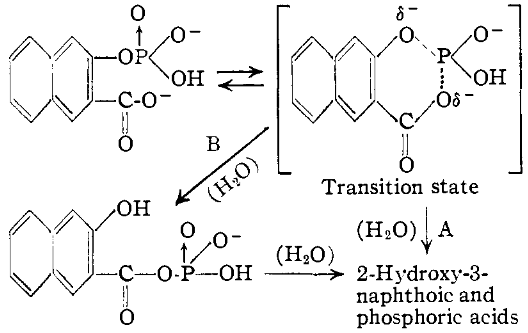
TABLE II

DISSOCIATION CONSTANTS AND REACTION RATES

	Dissociation constants				Calcd. specific rate constants of hydrolysis hr.$^{-1}$ × 1000					
				pH of	37.2°		31.0°	ΔH^{+},	ΔS^{+},	
Compound	pK_1	pK_2	pK_3	reaction	k_1	k_2	k_2	kcal./mole	e.u.	pK_A[8a]
I	1.30	3.73	6.51	5.67	32.7	369[370][b]	180	23.5	−1.2	9.20
II	1.12	3.78	7.99	5.73	.....	1410[1380][b]	....	..	...	7.90
II (monohydrate)				5.72	[134][b]	[1350][b]	[604][b]	23.9	+2.6	
III	1.46	3.70	6.34	5.63	17.2	203[202][b]	85.2[84.9][b]	24.8	+4.4	9.88
IV	1.00	3.18	6.12	5.64	264	10.9	264[c]	28.0	+6.5	8.27

[a] pK_A relates to the corresponding hydroxyaldehydes (see text). [b] Figures in brackets refer to determinations carried out in the presence of 4% methanol. [c] This value was obtained at 60°.

been reached. It already has been demonstrated that if one assumes scheme B to be correct, both the first-order kinetics and the pH dependency can only be accounted for by postulation of the formation of the mixed anhydride (Z) as the rate determining step. Furthermore, in our method of determining phosphate a molybdate reagent is employed, and since acyl-phosphates are hydrolyzed extremely rapidly in the presence of this reagent[6] our observed rate of hydrolysis is a measure only of the formation of the mixed anhydride. In any event the essential feature of "participation" as the driving force in the hydrolysis is contained in both schemes.



Variation in Rates.—Our discussion concerning the variation in rates of hydrolysis for compounds I, II, III and IV will be related almost exclusively to the specific rate constant, k_2, associated with the hydrolysis of the di-ionic form of the particular phosphate. This choice was made for the following reasons: (a) k_2 is known more accurately than k_1, (b) the rapid hydrolysis of the aforementioned compounds in the pH region studied is associated principally with the di-ionic form and (c) primarily because the participating group associated with the k_2 rate must be the carboxylate anion.[2] A simple relationship between structure and rate of hydrolysis for all four compounds is not to be expected, since we are dealing with one phenyl and three naphthyl derivatives and since within the naphthyl series there are two β-naphthol and one α-naphthol derivatives. However, since the same mechanism is postulated in each instance, and the compounds are closely related, it may be anticipated that the observed variations in rates could at least be qualitatively accounted for within the frame of the postulated mechanism. We reason therefore that, as a first rough approximation, the formation of the transition state and consequently the rate of hydrolysis[7] will be governed primarily by (a) the nucleophilic power of the carboxylate anion in the particular phosphate and (b) by the ease with which the phosphorus of the parent phosphate will accept the electron pair from the carboxylate ion. It follows that the stronger the carboxylate anion is as a base (nucleophilic power) and the relatively more positive the phosphorus atom is in each particular instant, the faster will be the rate of hydrolysis. The basicity of the carboxylate anion in any particular carboxy phosphate is taken here as the inverse of its second ionization constant ($1/K_2$). The nucleophilic power of the carboxylate anion is the same in each of the three compounds I, II and III, as the pK_2's for the three acids are very close together. The second ionization constant of compound IV is significantly different, a point to be taken up further below. We may anticipate that the rates of hydrolysis of compounds I, II and III will be principally governed by the relative electropositive character of the phosphorus atom. The ease with which the phosphorus atom will accept the electron pair from the carboxylate ion will be mirrored by the capacity of the phenolic oxygen to hold the electron pair it shares with the phosphorus, when the bond between it and the phosphorus is stretched in the process of attaining the transition state. As a measure of the relative propensity of the phenolic oxygen for the electron pair, we have selected the ionization constants pK_A of the four related ortho-hydroxy aldehydes (last column of Table II),[8,9] salicylaldehyde, 1-hydroxy-2-naphthaldehyde, 2-hydroxy-3-naphthaldehyde and 2-hydroxy-1-naphthaldehyde. The stronger an acid the hydroxy aldehyde is, the relatively more positive will the phosphorus be in the corresponding phosphate ester and, consequently, the faster its hydrolysis. That this is actually the case, may be seen in Table II. When one plots the log of the rate constant k_2 against pK_A a straight line relationship is indicated (Fig. 2).[10]

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(6) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945). *Cf.* H. Chantrenne, *Compt. rend., trav. Lab. Carlsberg*, **26**, 297 (1948); *Biophys. Biochim. Acta*, **2**, 286 (1948).

(7) According to the activated state theory the rate of decomposition of the transition state is the same in all instances, and we assume that the so-called transmission coefficient is one.

(8) R. T. Arnold and J. Spring, THIS JOURNAL, **60**, 1163 (1938); **61**, 2475 (1939).

(9) The corresponding parent acids, salicylic acid, etc., are unsuitable for comparison since in their case the picture is complicated by hydrogen bonding.

(10) In the related hydrolysis of substituted phenyl sulfates, a similar plot of the log of the rate constants *versus* the pK of the parent phenols gives a straight line, the rate increasing with increasing strength of the parent phenol. *Cf.* G. N. Burkhardt, W. G. K. Ford and E. Singleton, *J. Chem. Soc.*, 17 (1936). G. N. Burkhardt, C. Horrax and D. I. Jenkins, *ibid.*, 1649, 1654 (1936).

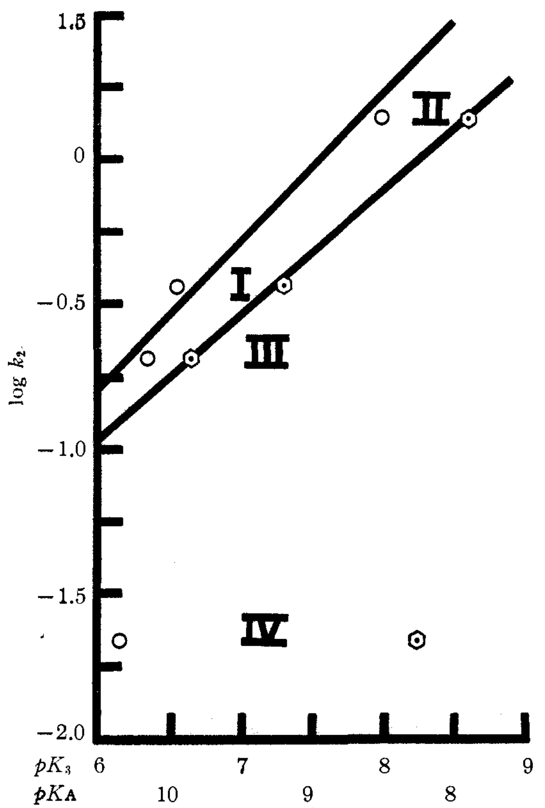

Fig. 2.—Logarithms of the specific rate constants (k_2) for compounds I, II, III and IV as plotted against pK_3 and pK_A: ○ and ⊙ refer to pK_3 or pK_A, respectively.

In looking for an alternative measure of the factor (b) we plotted the log of the rate constant k_2 against pK_3 and found again a straight line for compounds I, II and III; moreover, the line (plotted with the abscissa in reverse) is almost parallel to the log k_2 *versus* pK_A plot, indicating that the variations of pK_3 and pK_A from compound to compound are not only of the same sense, but numerically about equal. Thus, either of them will provide a measure of the ease with which the phosphorus will accept the electron pair, as both affect, although in the opposite sense, the same phenomenon to approximately the same extent. Why the numerical value of pK_3 should increase, *i.e.*, the dissociation of the second hydrogen ion from the phosphoryl group decrease with increasing acidity (lower pK_A) of the parent phenol group, invites speculation. Column 2 in Table II shows that the pK_1 values run in a direction opposite to the pK_3 values.

The points relating to 1-carboxy-2-naphthyl phosphate obviously fall out of line in both plots. The slowness of hydrolysis of compound IV seems to be not only a result of the high acidity (pK_2) of the carboxyl group (weaker nucleophilic power), but a steric factor also must play an important role. Models of the carboxy phosphates show that the restriction in rotation of the carboxylate group is greatest in case of 1-carboxy-2-naphthyl phosphate. We presume that this hindrance of rotation by the hydrogen on the C_8-position of the naphthalene ring makes it relatively more difficult to attain the transition state in compound IV than in the other three compounds.

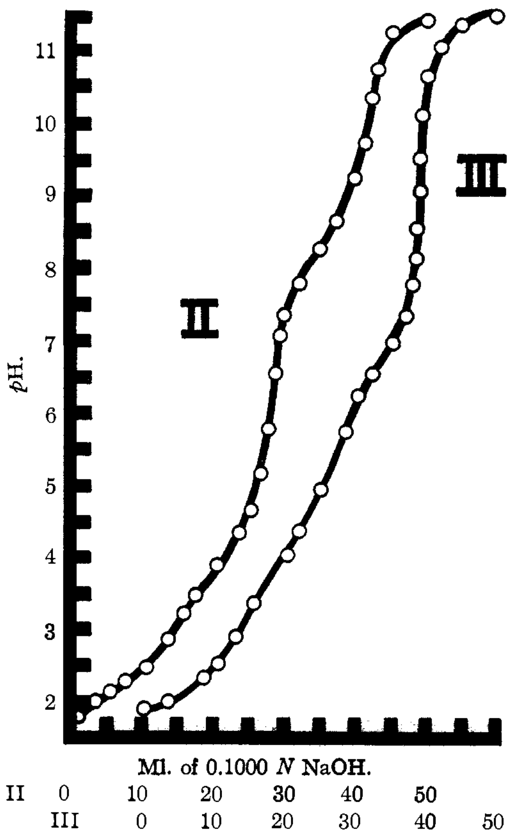

Fig. 3.—Potentiometric titration of compounds II and III.

We have measured the rates of hydrolysis for compounds I, II and III at 31° and compound IV at 60° (see Table I) and have calculated the heat of activation $\Delta H^{\ddagger}$ and the entropy of activation $\Delta S^{\ddagger}$ employing the well-known Eyring equation.[11]

$$k = \frac{kT}{h} e^{\Delta S^{\ddagger}/R} e^{-\Delta H^{\ddagger}/RT}$$

The results are indicated in Table II. The observed variation in rates of hydrolysis roughly follows the varation in $\Delta H^{\ddagger}$, since $\Delta S^{\ddagger}$ exhibits a tendency to become more positive the slower the reaction. It might be noted at this point that since a straight line plot is observed for log k_2 *versus* pK_3 or pK_A, we would infer that the factor which makes $\Delta S^{\ddagger}$ vary with $\Delta H^{\ddagger}$ must be operating equally in the rate constants and the corresponding pK_A's and pK_2's for compounds I, II and III and that such is not the case with 1-carboxy-2-naphthyl phosphate. The observed positive values for $\Delta S^{\ddagger}$ are in contrast to the negative values encountered in reactions involving a cyclic transition state. An examination of Fischer–Hirschfelder models of these *o*-carboxy phosphates reveals that there is no hindrance to the approach of the oxygen to the phosphorus atom, but indicates that the carboxyl and phosphate groupings are hindered in their rotation by each other. This would suggest that in the postulated transition state there is not as great a relative loss in degrees of freedom as encountered in reactions such as Claisen type rearrangements,

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[11] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941; $\Delta H^{\ddagger}$ is almost exactly equal to $Ea - RT$, where Ea is the Arrhenius activation energy.

which involve a cyclic transition state.[12] This interpretation is supported by the observation that compound IV which, as indicated previously, has the relatively largest amount of hindrance to rotation exhibits the largest positive entropy change (see Table II).

The stability of these compounds in alkaline medium at *p*H values above 8.5 at temperatures at least up to 65° may be attributed to the enormous hindrance by the large negative charge surrounding the phosphorus atom in the tri-ionic form. Thus, the approach of the carboxylate group is completely repressed. Since the splitting of the O–P bond in phenyl phosphate and α- and β-naphthyl phosphate in alkaline medium at temperatures at least up to 65° is negligible, no hydrolysis is observed with the tri-ionic form.

Experimental

The hydroxy acids 1-hydroxy-2-naphthoic acid (V) and 2-hydroxy-3-naphthoic (VI) used in the synthesis of the phosphates were obtained from Eastman Kodak Co. 2-Carboxy-1-naphthoic acid (VII) was prepared in 50% yield by carbonation[13] of the dilithium salt obtained from 1-bromo-β-napthol.[14] The procedure employed was essentially that used in the preparation of salicylic acid from 2-bromophenol.[15]

2-Carboxyl-1-naphthoic acid may be recrystallized without decarboxylation from chloroform; m.p. 173° with decomposition (when heated fairly rapidly) and 158° with decomposition (when heated slowly); reported 162.5–164°.[16] Neut. equiv., calcd. 188.2; found 188.9, 188.7 (thymolphthalein), 190.1 (phenolphthalein).

Preparation of *o*-Carboxynaphthylphosphates II, III and IV.—These compounds were prepared, with some minor modifications, essentially according to the method used for the preparation of salicyl phosphate.[2] In each instance, the crude product was of high purity as indicated by melting point and neutralization equivalent. The hydroxy naphthoic acids and phosphorus pentachloride were mixed in the molecular proportions listed below, allowed to react at room temperature until the initially vigorous reaction subsided and, finally, heated on the steam-bath for the length of time indicated in Table III. The reaction mixture was cooled, dissolved in benzene (2.5 cc. of benzene per gram of hydroxy acid) filtered, if necessary, from insoluble material and diluted with an equal volume of acetone. The requisite amount of water necessary to decompose the intermediate trichloro compound and excess phosphorus pentachloride was added slowly to the mixture with slight cooling. The mixture was then allowed to stand at room temperature for one to two hours, diluted with twice the volume of benzene in the case of 1-hydroxy-2-naphthoic acid and 2-hydroxy-3-naphthoic acid and an equal volume of benzene in the instance of 1-carboxy-2-naphthoic acid, and allowed to stand until precipitation was complete, usually 24 to 32 hours. The precipitate was removed by filtration, washed with benzene in the instance of compound II and III, also with ether, compound IV being slightly soluble in wet ether. They were dried overnight *in vacuo* over potassium hydroxide and recrystallized from acetone–benzene mixtures containing some water as indicated below.

Compound II was recrystallized by dissolving 10 g. of the crude product in 250 cc. of boiling acetone containing 3.5 cc. of water, and to the hot solution 200 cc. of boiling benzene was added. After standing several hours the pure product, a monohydrate, crystallized as colorless cube-like crystals; yield 5 g., m.p. 163–164° (with decomposition).[17]

TABLE III

Compound	Amount, g.	PCl_5, g.	Heating time hr.	Water added, ml.	Yield and compound, g.
V	42 (0.22 mole)	63 (0.30 mole)	3–4	18.0	50 II
VI	42 (0.22 mole)	100 (0.48 mole)	3–4	30.0	35 III[a]
VII	10.5 (0.056 mole)	17.4 (0.084 mole)	0.5	4.9	6.7 IV

[a] To obtain this yield it was necessary to cool in the ice-chest 12 hr.

Anal. Calcd. for $C_{11}H_9O_6P \cdot H_2O$: C, 46.16; H, 3.91; P, 10.84; neut. equiv., 95.4. Found: C, 46.61; H, 3.87; P, 11.10; neut. equiv., 94.5 (thymolphthalein used as an indicator).

The monohydrate is slowly and difficultly soluble in water, gives no ferric chloride or free phosphate test. One gram of the above hydrate, dried *in vacuo* at 100° over phosphorus pentoxide for 12 hours, was washed with small quantities of dry ether and recrystallized by dissolving in boiling dry acetone (25 cc.), in which it is slowly soluble; to the hot filtrate 25 ml. of dry benzene was added. On standing in the ice-chest overnight the anhydrous modification was obtained as characteristic needles, m.p. 164° (decomposition). The anhydrous material is very soluble in water and gave neither ferric chloride test nor free phosphate test.

Anal. Calcd. for $C_{11}H_9O_6P$: C, 49.27; H, 3.38; P, 11.55. Found: C, 49.21; H, 3.59; P, 11.60.

Compound III was recrystallized by dissolving 25 g. of the crude reaction product in 175 ml. of boiling acetone containing 3 ml. of water, treating with Norite and subsequently adding an equal volume of benzene. On standing 17–20 g. of pure material was obtained as fine needles of m.p. 175–176°; reported 174°.[18]

Anal. Calcd. for $C_{11}H_9O_6P$: neut. equiv., 89.39. Found: neut. equiv., 89.45 (thymolphthalein), 90.2, 90.0 (phenolphthalein).

Compound IV was recrystallized by dissolving 7 g. of a crude product in boiling acetone and subsequently adding four times the volume of dry benzene. This compound exhibited a tendency to come out as a partial hydrate when recrystallized from wet solvents. On standing fine needles were obtained of m.p. 156–157° (decomposition); reported 156°.[19] The compound gave neither ferric chloride nor free phosphate tests. It is insoluble in dry ether, but moderately soluble in wet ether or U.S.P. ether containing alcohol.

Anal. Calcd. for $C_{11}H_4O_6P$: P, 11.55; neut. equiv., 89.4. Found: P, 11.55; neut. equiv., 88.8, 88.9 (phenolphthalein).

Figure 2 gives the curves obtained for the potentiometric titration of compounds II and III. The three breaks in each curve indicate three ionizable hydrogens; thymolphthalein must be used as indicator in the case of compound II.

Determination of Ionization Constants.—The *p*H determinations were obtained with the use of the Research Model Cambridge *p*H meter.[20] Our measurements of acidity are substantially activity measurements.[21] We have defined the three ionization constants of all the orthocarboxy phosphates in a semiclassical manner. The second and third ionization constants were obtained on solutions of ionic strength $\mu = 0.1$, the first ionization constant at $\mu =$ *ca.* 0.08; the temperature was 26 ± 0.5°.

$$pK_1 = p_aH + \log \frac{[\text{Un-ionized}]}{[\text{Mono-ion}]};$$

$$pK_2 = p_aH + \log \frac{[\text{Mono-ion}]}{[\text{Di-ion}]}$$

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[12] K. G. Foster, A. C. Cope and F. Daniels, THIS JOURNAL, **69**, 1893 (1947); F. W. Schuler and G. W. Murphy, *ibid.*, **72**, 3155 (1950); A. T. Blades and G. W. Murphy, *ibid.*, **74**, 1039 (1952); L. Stein and G. W. Murphy, *ibid.*, **74**, 1041 (1952); J. F. Kincaid and D. S. Tarbell, *ibid.*, **61**, 3085 (1939).

[13] H. Gilman and Sunthankar, unpublished work quoted by Jones and Gilman in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 361.

[14] W. E. Militzer, THIS JOURNAL, **60**, 256 (1938).

[15] H. Gilman and C. E. Arntzen, THIS JOURNAL, **69**, 1537 (1947).

[16] I. M. Hunsberger, THIS JOURNAL, **72**, 5626 (1950).

[17] R. Wolffenstein, *Ber.*, **21**, 1186 (1888). No melting point is given. The analytical data indicate a mixture of the anhydrous and monohydrated forms.

[18] H. Hosaeus, *Ber.*, **26**, 667 (1893).

[19] H. Rabe, *ibid.*, **22**, 392 (1889).

[20] An accuracy of ±0.02 *p*H unit has been claimed and a reproducibility of at least ±0.01 unit is observed with this instrument. The instrument was set with potassium acid phthalate buffer solution (0.05 *M*) of p_aH 4.01 ± 0.01 at 25° as recommended by the National Bureau of Standards in Research Paper RP 1495.

[21] R. G. Gates, *Chem. Revs.*, **42**, 1 (1948).

$$pK_3 = p_aH + \log \frac{[\text{Di-ion}]}{[\text{Tri-ion}]} \qquad [\ ] = \text{concn.}$$

The second and third ionization constants were obtained from the p_aH measurements of partially neutralized solutions (as described below) employing the modified Henderson equation in the calculations.[22] The p_aH was determined in six solutions all of which were finally 0.0100 *M* in acid (I, II, III, IV) and contained the exact amount of sodium hydroxide necessary to give 140, 150 and 160% (pK_2) and 240, 250 and 260% (pK_3) neutralization and to which enough potassium chloride was added to give the ionic strength μ = 0.1. The ionization constants so determined did not vary in any particular case by more than ±0.01 *p*H unit.

The first ionization constant of all four acids pK_1 were obtained in analogous manner. However, because of the poor solubility of 2-carboxy-1-naphthyl phosphate in water and the low value of pK_1 of all four compounds the following procedure was employed. All four acids were first dissolved in a small volume of methanol, half neutralized with sodium hydroxide, and diluted with water to give a 10% methanol solution by volume and a total concentration of acid of 0.1 mole/liter. The ionic strength of these solutions is *ca.* μ = 0.08. The values obtained for the first ionization constant, although reproducible to ±0.02 *p*H unit, are not as accurate as those obtained for pK_2 and pK_3, since in our calculations, employing the Henderson equation, we have assumed that our measurement of hydrogen ion (p_aH) is substantially the same as the concentration of hydrogen ion (p_cH). This assumption results in small errors in pK_2 and pK_3, since the measured p_aH is relatively small compared with the total concentration of acid employed; however, since the measured p_aH in the determination of pK_1 is large, the above assumption leads to a greater error, which is to some extent reduced by working at total concentration of acid of 0.1 mole/liter (see Table II).

The buffer solutions employed in this work were the same as those in the first report.[2] Mole fractions M_1, M_2, etc., of the various ionic species present at any *pH* were evaluated as previously described, employing the semi-classical ionization constants determined above.

Determination of Rates of Hydrolysis.—The rates of hydrolysis were determined on analytical grade *o*-carboxy phosphates. The same procedure as already described[2] was used in the determination of the rates. Solutions containing 0.00130 mole/liter of compounds I, II, III and IV, the appropriate buffer and enough potassium chloride to bring the ionic strength up to 0.1 were employed. The *p*H determined at the start and at the end of the hydrolysis did not differ by more than ±0.03 *p*H unit. A few minor modifications were introduced. In some instances, after hydrolysis had proceeded past the half-way point, some precipitation of the hydroxy acid ensued upon development of color by the molybdate reagent. This presented little difficulty since centrifugation with a little Celite gave clear solutions. The precipitation could be avoided with no change in results, if the molybdate reagent, to which the sample was added, had not been cooled in an ice-bath as previously described. In each instance first-order kinetics were obtained throughout the course of the reaction at all *p*H's. The k_2 rates were determined from an average of at least four runs at *p*H *ca.* 5.7, while at the other *p*H's the determinations were done at least in duplicate. The average deviation in any particular run was no greater than 3% and the results in repeated runs were the same within experimental error. The rate equation used was

$$-\mathrm{d}[X]/\mathrm{d}t = k_{\text{obsd.}}\,(X_0 - P)$$

where X_0 = initial concn. and X = concn. at time t for compounds I, II, III and IV; P = concentration of phosphoric acid at time t. The rate constants were evaluated either by simple average or from the straight line plot of log X *versus* time, where $[X] = [X_0 - P]$. The rate constants, evaluated from the slope of the least square straight lines or by simple average, showed no significant differences. The rates of hydrolysis were also obtained in solutions containing 4% methanol (by vol.). The figures in brackets in Table II refer to these solutions. The final readings for phosphate were insignificantly lower in these solutions than in water. This indicates that no significant amount of methyl phosphate was formed, since methyl phosphate under the conditions of the hydrolysis is completely stable. The rate constants obtained in 4% methanol are essentially the same as those found in water (see Table II). Consequently the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ calculated for both water and dilute methanol are essentially the same.

Products of Hydrolysis.—When compounds I, II, III and IV were completely hydrolyzed at *p*H 5–6 *ca.* at 60° in the first three cases and 37° for compound IV and each of the solutions was then acidified, quantitative yields of the corresponding acids salicylic acid, 1-hydroxy-2-naphthoic acid and 2-hydroxy-3-naphthoic acid were obtained. In the case of compound IV a 60% yield of 2-hydroxy-1-naphthoic acid was obtained, the remainder being β-naphthol (insoluble in sodium bicarbonate). The decarboxylation of 2-hydroxy-1-naphthoic acid in water at moderate temperatures is well-known. However, since the theoretical amount of phosphate was obtained after complete hydrolysis, and β-naphthyl phosphate is not hydrolyzed in any appreciable extent under the conditions employed, the loss of carbon dioxide could not have preceded hydrolysis.

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New York, N. Y.

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[22] S. Glasstone, "Textbook of Physical Chemistry," Van Nostrand Co., Inc., New York, N. Y., 1943, p. 982.