

TABLE II  
CLASSICAL ACTIVATION ENERGIES (KCAL.)

Reaction	$\Delta E^a$	DIM- ap- prox. <sup>b</sup>	DIM- acc. <sup>c</sup>	Expt. <sup>d</sup>	E.-S- E. <sup>e</sup>	Sato/ <sup>f</sup>	J.-P. <sup>g</sup>
H <sub>2</sub> + H = H + H <sub>2</sub>	0	6.7	13.0	7.7	7.9	5.4	10
H <sub>2</sub> + F = H + HF	-31	5	5	7.5	6.3	0.5	2
H + HCl = H <sub>2</sub> + Cl	-3	6	7	4.5	11.4	4.7	5
H + HBr = H <sub>2</sub> + Br	-19	6	4	1.2	10.4	0.7	2
H + HI = H <sub>2</sub> + I	-35	5	3	1.5	7.7	0.3	1
F <sub>2</sub> + H = F + FH	-103	2					
Cl <sub>2</sub> + H = Cl + ClH	-49	2		2	2.7		
Br <sub>2</sub> + H = Br + BrH	-44	2		1.2	2.1		
I <sub>2</sub> + H = I + IH	-38	2		0	1.8		

<sup>a</sup>  $\Delta E$  for over-all reaction; zero-point energies not included. Note that the classical activation energy for the reverse reaction may be obtained by subtracting  $\Delta E$  from the classical activation energy for the forward reaction. <sup>b</sup> Present method, using potential energy curves obtained by Hulburt-Hirschfelder formula for ground states and eq. 17 for excited states. <sup>c</sup> Present method, using accurate potential energy curves for H<sub>2</sub> but approximate curves for HX. <sup>d</sup> First reaction from A. Farkas and L. Farkas, *Proc. Roy. Soc. (London)*, **A152**, 124 (1935); all others from list given in ref. 5. <sup>e</sup> Ref. 5. <sup>f</sup> Ref. 6. <sup>g</sup> Ref. 7.

one evident in the H<sub>3</sub> complex were deepened seriously for high values of  $p$ ; in fact, complexes ABC stable relative to AB + C and to A + BC were sometimes obtained. The cause is obvious: as  $p$  is increased, the triplet state energy  $E_{2e}$  is lowered according to eq. 16, which leads to an increased resonance energy in the activated complex. For  $p = 0.15$ , the energy basins disappeared for all reactions 1-3 except for those involving H<sub>3</sub> and H<sub>2</sub>Cl; these two cases are exceptional in that reactants and products are either exactly or almost

degenerate ( $\Delta E \sim 0$ ). For H<sub>3</sub>, the deep basin can be eliminated almost completely by decreasing the parameter  $p$  into the negative range.

### Conclusions

Diatomics in molecules theory applied to reactions 1-3 even with the necessary use of approximate diatomic potential curves leads to good predictions for classical activation energies. However, the Hulburt-Hirschfelder ground state potentials introduce deviations (up to about 5 kcal.) in the contours when one of the end bonds is significantly longer than its equilibrium length, and our roughly approximated excited state curves cause potential energy depressions or basins (up to about 13 kcal.) when the two end bond energies are equal or nearly equal.

Research is now in progress on a new modified atoms-in-molecules model for making fairly rapid and more accurate predictions of diatomic excited (and ground) state potential energy curves.<sup>14</sup> This will make possible applications of diatomics in molecules theory with a minimum set of assumptions; rate constants will also be computed. Even then, it must be recognized that activation energy calculations (and the customary accompanying discussions of existence or nonexistence of potential energy "basins") constitutes the most severe test of any theory of molecular electronic structure; no methods of practical value have yet been developed that yield polyatomic energies more accurate than 5 to 10 kcal.

(14) F. O. Ellison, *J. Chem. Phys.*, to be submitted.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY, WORCESTER, MASSACHUSETTS]

## Kinetic Studies of the Catalytic Hydrolysis of 1,3-Dicarboxyphenyl 2-Phosphate and 1-Methoxycarbonyl-3-carboxyphenyl 2-Phosphate<sup>1</sup>

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RECEIVED JULY 29, 1963

First-order hydrolysis studies of two salicyl phosphate analogs, 1,3-dicarboxyphenyl 2-phosphate (DCPP) and 1-methoxycarbonyl-3-carboxyphenyl 2-phosphate (MCP), are reported. Maximum rates of spontaneous hydrolysis of DCPP and of MCP occur at  $-\log [H^+] = 3.90$  and  $5.50$ , respectively. The rate constants for hydrolysis of the mono-, di-, and triionic species are evaluated. The 1:1 dipyriddy-Cu(II) chelate system was found to have a strong catalytic effect on the hydrolysis of DCPP in neutral and in alkaline solutions where neither the un-ionized nor the monoionic species is present. The catalytic effect of vanadyl ion on the hydrolysis of MCP is evaluated from the data obtained in the low pH region. Possible reaction mechanisms involving the formation of cyclic activated complexes are discussed.

This paper describes an extension of the investigation of metal ion and metal chelate catalysis in the hydrolysis of salicyl phosphate reported in preliminary communications.<sup>4</sup> As an approach to the study of the mechanism of catalysis, two analogs of salicyl phosphate, 1,3-dicarboxyphenyl 2-phosphate and 1-methoxycarbonyl-3-carboxyphenyl 2-phosphate were studied

so that the influence of metal ions on these substances might be compared with the effects observed with the parent compound. The work reported up to the present time on monophosphate esters indicates that the un-ionized and the completely ionized phosphate species undergo hydrolysis more slowly than do the intermediate forms. Accordingly, the rate profile has a peak in the middle pH region,<sup>5-11</sup> where the observed

(1) This investigation was supported by a grant from the Esso Education Foundation, Linden, N. J., and by Research Grants G-9998 and G-21055 from the National Science Foundation.

(2) Abstracted in part from a dissertation submitted by Y. Murakami to the faculty of Clark University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1959.

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(4) (a) R. Hofstetter, Y. Murakami, G. Mont, and A. E. Martell, *J. Am. Chem. Soc.*, **84**, 3041 (1962); (b) Y. Murakami and A. E. Martell, *J. Phys. Chem.*, **67**, 582 (1963).

(5) M. C. Bailly, *Bull. soc. chim. France*, [5] **9**, 314 (1942).

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(9) J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, **74**, 4347 (1952).

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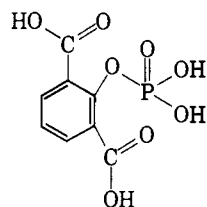
(11) J. D. Chanley and E. Feagson, *ibid.*, **77**, 4002 (1955).

kinetics are generally first order. Most organic phosphates, however, undergo acid-catalyzed hydrolysis in the extreme acid region.<sup>5-8,12</sup>

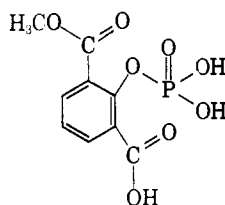
No studies of the metal ion catalyzed hydrolysis of organic phosphates have been published, with the exception of the preliminary investigation carried out in this laboratory<sup>4</sup> on the catalytic effects of chelates of metal ions.

### Experimental

**Reagents.**—The organic phosphates, 1-methoxycarbonyl-3-carboxyphenyl 2-phosphate (MCP) and 1,3-dicarboxyphenyl 2-phosphate (DCPP) were synthesized by Dr. David Todd of Worcester Polytechnic Institute, Worcester, Mass. The purity of these compounds was checked by analysis for phosphorus content and by potentiometric titration.



I, 1,3-dicarboxyphenyl 2-phosphate (DCPP)



II, 1-methoxycarbonyl-3-carboxyphenyl 2-phosphate (MCP)

Copper(II), nickel(II), and cobalt(II) solutions were prepared from their nitrate salts and were standardized by titration in ammoniacal solution with standard disodium salt of ethylenediaminetetraacetic acid, with murexide as an indicator.<sup>13</sup>

A stock solution of vanadyl sulfate was prepared from Fisher certified material and was standardized by means of oxidation-reduction titration with potassium permanganate.<sup>14</sup> Since the vanadyl solution is unstable above  $-\log [H^+] = 3.50$ , enough free acid (HCl) was added to the stock solution to bring the  $-\log [H^+]$  value down to approximately 2.0.<sup>7</sup>

A high purity sample of  $\alpha, \alpha'$ -dipyridyl was obtained from S.A.F. Hoffman-La Roche and Co. Ltd., Basle, Switzerland, and was used without further recrystallization.

Disodium pyrocatechol-3,5-disulfonate (Tiron) was purchased from the LaMotte Chemical Products Co., Baltimore, Md., and was used without further purification after establishment of its purity by potentiometric titration.

2-Hydroxyisophthalic acid (HIPA) and 2-acetoxyisophthalic acid (AIPA) were prepared by Dr. Todd.

**Potentiometric Measurements.**—The dissociation constants of the organic phosphates and the formation constants of the metal chelates were determined by potentiometric measurements. A Beckman Model GS pH meter with expanded scale was used with extension glass and calomel electrodes. The pH meter was calibrated in terms of hydrogen ion concentration with acetic acid buffer as well as with standard hydrochloric acid and sodium hydroxide solutions. The ionic strength was maintained at approximately 0.100 M with  $KNO_3$  during the measurements. A nitrogen atmosphere was maintained in the titration cell to avoid atmospheric carbon dioxide.

**Kinetic Measurements.**—The pH value of an experimental solution was maintained constant during each run with a Beckman automatic titrator fitted with extension glass and calomel electrodes. It was calibrated with acetic acid buffer and by titration of standard hydrochloric acid and sodium hydroxide solutions. The ionic strengths of the experimental solutions were maintained at approximately 0.100 M with  $KNO_3$ . The rate of hydrolysis was determined by measuring the amount of phosphoric acid liberated in the course of the hydrolysis.

The analytical method employed for the analysis of phosphoric acid was essentially that of Chanley and co-workers.<sup>9</sup> The molyb-

date reagent required consisted of a mixture of 139 ml. of concentrated  $H_2SO_4$  (Baker analyzed, 96.7%) and 25.0 g. of ammonium molybdate,  $(NH_4)_6(Mo_7O_{24}) \cdot 4H_2O$  (Fisher certified), dissolved in sufficient distilled water to give 1 l. of solution. ANS reagent was prepared by adding a solution of 2.0 g. of  $Na_2SO_3$  (Fisher certified) and 1.0 g. of 1-amino-2-naphthol-4-sulfonic acid (Eastman Kodak) in 100 ml. of distilled water to a solution of 53.4 g. of  $Na_2S_2O_5$  (meta) (Fisher certified) in 300 ml. of distilled water. This mixture solution was allowed to stand overnight near  $0^\circ$ , and was then filtered to remove any precipitate which had formed.

To carry out phosphate analyses, a 2.0-ml. sample of the experimental solution was added to a 25-ml. volumetric flask containing 5.00 ml. of the molybdate reagent which had been cooled in an ice bath. The reaction stopped immediately because of acidification of the solution and lowering of the temperature. A 1.00-ml. sample of the ANS reagent was added, and the mixture was diluted to 25 ml. by the addition of distilled water. The volumetric flask was then placed in a constant temperature bath at  $25^\circ$  for 20 min. to develop the color. The absorbance was measured at  $660 m\mu$  with a Cary Model 14 PM recording spectrophotometer immediately after development of the molybdenum blue color. The amount of inorganic phosphate was determined with the aid of a calibration curve determined with a standard  $KH_2PO_4$  (Fisher certified) solution.

### Results

**Determination of  $pK$  Values.**—All the dissociation constants of importance in this study are summarized in Table I. 1,3-Dicarboxyphenyl 2-phosphate (DCPP)

TABLE I  
ACID DISSOCIATION CONSTANTS<sup>a</sup>

Acid	Temp., °C.	$K_1$	$K_2$	$K_3$	$K_4$
DCPP	35	...	$1.05 \times 10^{-3}$	$1.53 \times 10^{-6}$	$4.47 \times 10^{-9}$
MCP	35	...	$4.17 \times 10^{-4}$	$2.34 \times 10^{-8}$	...
SP <sup>b</sup>	30	...	$1.95 \times 10^{-4}$	$3.16 \times 10^{-7}$	...
HIPA	30	$7.40 \times 10^{-3}$	$2.98 \times 10^{-6}$	...	...
AIPA	25	$1.4 \times 10^{-3}$	$1.6 \times 10^{-4}$	...	...
Aspirin <sup>c</sup>	17	$2.72 \times 10^{-4}$	...	...	...

<sup>a</sup>  $\mu = 0.10 M (KNO_3)$ . <sup>b</sup> See ref. 4. <sup>c</sup> L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).

has four dissociation constants. The most acidic proton is completely dissociated before addition of base, and the first dissociation constant,  $K_1$ , could not, therefore, be determined under the experimental conditions employed. The second and the third dissociation constants,  $K_2$  and  $K_3$ , respectively, were determined graphically with the aid of eq. 1<sup>15</sup>

$$\frac{1}{K_2} = K_3 \frac{B}{A} - B \quad (1)$$

where

$$A = \frac{(a-1)T_s + [H^+]}{(2-a)T_s - 1} - 1 \quad B = \frac{(a-1)T_s + [H^+]}{[H^+](aT_s + [H^+])}$$

$T_s$  = the total molar concentration of all acid species and  $a$  = the number of moles of base added per mole of acid.

1-Methoxycarbonyl-3-carboxyphenyl 2-phosphate (MCP) has three dissociation constants. The first dissociation constant was not determined, as in the case of DCPP, since the free acid was completely dissociated under the reaction conditions.

(15) A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, Inc., New York, N. Y., 1952, p. 90.

(12) P. Fleury, *Compt. rend.*, **221**, 416 (1945).

(13) G. Schwarzenbach, "Die komplexometrische Titration," Ferdinande Enke Verlag, Stuttgart, 1955, pp. 65, 66, and 68.

(14) W. W. Scott, "Standard Methods of Chemical Analysis," Vol. I, N. H. Furman, Ed., D. Van Nostrand Co., Inc., Princeton N. J., 1939, p. 1037.

The dissociation constants of 2-acetoxyisophthalic acid (AIPA) and of 2-hydroxyisophthalic acid (HIPA), which is a product of hydrolysis of DCP, were calculated with the aid of eq. 1.

**Kinetics of Hydrolysis of 1,3-Dicarboxyphenyl 2-Phosphate (DCPP).**—All the rates of hydrolysis of DCP were obtained at  $35.0 \pm 0.05^\circ$ , in the absence of, and in the presence of, metal ions and chelate compounds.

(a) **Spontaneous Hydrolysis.**—It was observed that the hydrolysis reaction followed first-order kinetics with respect to the total concentration of unreacted phosphate. The specific rate constants determined experimentally are listed in Table II, together with those values calculated from the values assigned to each ionic species. For the assignment of specific rates to each ionic species, fractional molar concentrations were evaluated at different hydrogen ion concentrations. The results are summarized in Table II. The assign-

TABLE II  
SPONTANEOUS HYDROLYSIS RATES AND MOLE FRACTIONS OF IONIC SPECIES OF DCP AT  $35^\circ$  AND 0.100 M IONIC STRENGTH ( $\text{KNO}_3$ )<sup>a</sup>

-log [H <sup>+</sup> ]	Fractions of ionic species				$k \times 10^3$ , sec. <sup>-1</sup>	
	DCPP <sup>-</sup>	DCPP <sup>2-</sup>	DCPP <sup>3-</sup>	DCPP <sup>4-</sup>	Obsd.	Calcd. <sup>b</sup>
2.00	0.905	0.095			2.18	2.42
2.50	0.750	0.249	0.001		5.20	5.87
3.00	0.484	0.508	0.008		10.8	11.6
3.40	0.267	0.705	0.027		15.8	16.0
3.90	0.097	0.806	0.097		19.2	18.4
4.00	0.076	0.801	0.123		..	18.3
4.50	0.020	0.661	0.319		15.1	15.3
5.00	0.004	0.394	0.602		10.4	9.56
5.30	0.001	0.246	0.753		..	6.35
5.50	0.001	0.171	0.828		5.41	4.74
6.00		0.061	0.939		2.37	2.37
6.35		0.028	0.972		..	1.65
7.00			0.957	0.043	1.01	1.01
7.50			0.875	0.125	..	0.919
8.00			0.690	0.310	0.638	0.724
8.50			0.414	0.586	..	0.435
9.00			0.183	0.817	0.178	0.192

<sup>a</sup>  $k_1 = 3.06 \times 10^{-5}$ ,  $k_2 = 2.26 \times 10^{-3}$ , and  $k_3 = 1.05 \times 10^{-4}$  sec.<sup>-1</sup>, where  $k_1$ ,  $k_2$ , and  $k_3$  are the first-order rate constants of DCP<sup>-</sup>, DCP<sup>2-</sup>, and DCP<sup>3-</sup>, respectively. <sup>b</sup> Calculated from assigned specific rate constants  $k_1$ ,  $k_2$ , and  $k_3$ .

ments of specific rate constants were made to the mono- and the diionic species from the data obtained in the lower pH range, and to the triionic species in the higher pH region. It was not possible to calculate the specific rate for the tetraionic species, since its value is very small in comparison with those of other species. The maximum rate was observed, as is seen in Fig. 1, at  $-\log [\text{H}^+] = 3.90$ , where the diionic species is predominant.

(b) **Dipyridyl-Cu(II) Catalysis.**—The experimental results indicate an apparent first-order rate of hydrolysis with respect to the total concentration of unreacted organic phosphate species. Therefore, it seems that dipyridyl-Cu(II) behaves as a true catalyst. In the  $-\log [\text{H}^+]$  region between 4.0 and 6.4, the reaction proceeds heterogeneously because of the formation of a precipitate, although the rate was found to be first order. Also, at both  $-\log [\text{H}^+] = 3.00$  and 7.00, a precipitate was observed after the reaction proceeded

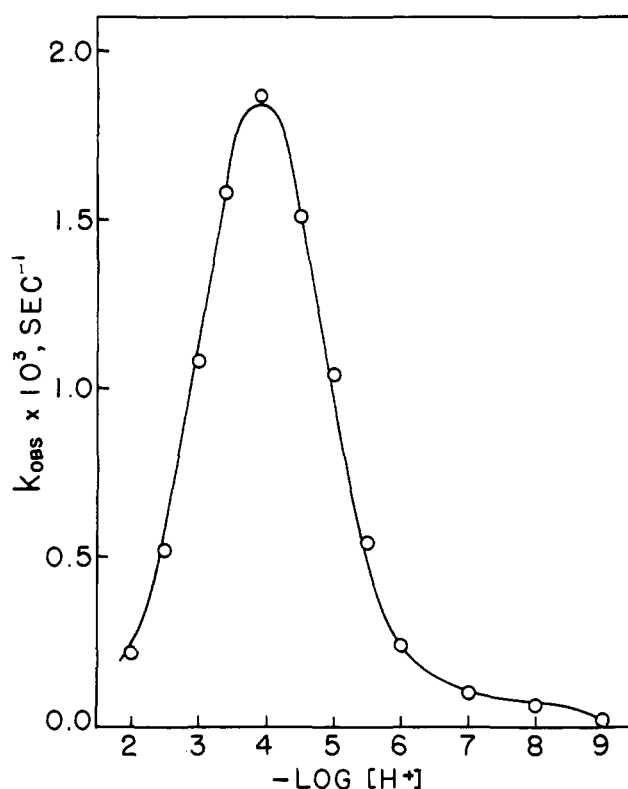


Fig. 1.—Rate profile for the spontaneous hydrolysis of DCP at  $35.0^\circ$ : O, measured rate constants; the solid curve indicates calculated rates.

for a certain time. Outside this pH region, the reaction proceeded homogeneously. All the rate data obtained on the dipyridyl-Cu(II) catalyzed hydrolysis reaction are listed in Table III, including the ratio of rate increase,  $k_{\text{obsd}}/k^0$ , which indicated qualitatively the catalytic effect. The total chelate concentration was not maintained constant in the whole pH region investigated; nevertheless, its variation is so small that the qualitative catalytic effects may be evaluated directly from the quantities listed in Table III. It can be seen that the catalytic effect of the metal chelate increases sharply in the higher pH region.

TABLE III  
RATES OF THE DIPYRIDYL-CU(II)-CATALYZED HYDROLYSIS OF DCP AT  $35.0^\circ$  AND 0.100 M IONIC STRENGTH ( $\text{KNO}_3$ )

$-\log [\text{H}^+]$	$T_M, M^{a,b}$	$k_{\text{obsd}}, \text{sec.}^{-1c}$	$k^0_{\text{obsd}}, \text{sec.}^{-1d}$	$\frac{k_{\text{obsd}}}{k^0}$
2.00	$1.30 \times 10^{-3}$	$2.46 \times 10^{-4}$	$2.18 \times 10^{-4}$	1.13
3.00	$1.28 \times 10^{-3}$	$1.47 \times 10^{-3}$	$1.08 \times 10^{-3}$	1.36
4.00	$1.27 \times 10^{-3}$	$2.3 \times 10^{-3}$	$1.83 \times 10^{-3}$	1.28
5.30	$1.33 \times 10^{-3}$	$2.5 \times 10^{-3}$	$6.35 \times 10^{-4e}$	3.94
6.35	$1.29 \times 10^{-3}$	$1.6 \times 10^{-3}$	$1.65 \times 10^{-4e}$	9.70
7.00	$1.09 \times 10^{-3}$	$9.63 \times 10^{-4}$	$1.01 \times 10^{-4}$	9.53
	$1.47 \times 10^{-3}$	$1.03 \times 10^{-3}$		10.21
7.50	$1.12 \times 10^{-3}$	$1.03 \times 10^{-3}$	$9.19 \times 10^{-6e}$	11.2
8.00	$1.24 \times 10^{-3}$	$8.29 \times 10^{-4}$	$6.38 \times 10^{-5}$	13.0
8.50	$1.23 \times 10^{-3}$	$7.25 \times 10^{-4}$	$4.35 \times 10^{-5e}$	16.7
9.00	$1.12 \times 10^{-3}$	$6.17 \times 10^{-4}$	$1.78 \times 10^{-5}$	34.6
9.50	$1.05 \times 10^{-3}$	$5.13 \times 10^{-4}$		

<sup>a</sup>  $T_M$  = total molar concentration of the chelate species. <sup>b</sup> Ratio of  $T_M$  to total molar concentration of the phosphate species maintained at unity. <sup>c</sup>  $k_{\text{obsd}}$ , observed rate of the catalyzed reaction. <sup>d</sup>  $k^0_{\text{obsd}}$ , observed rate of the spontaneous reaction. <sup>e</sup> Calculated value.

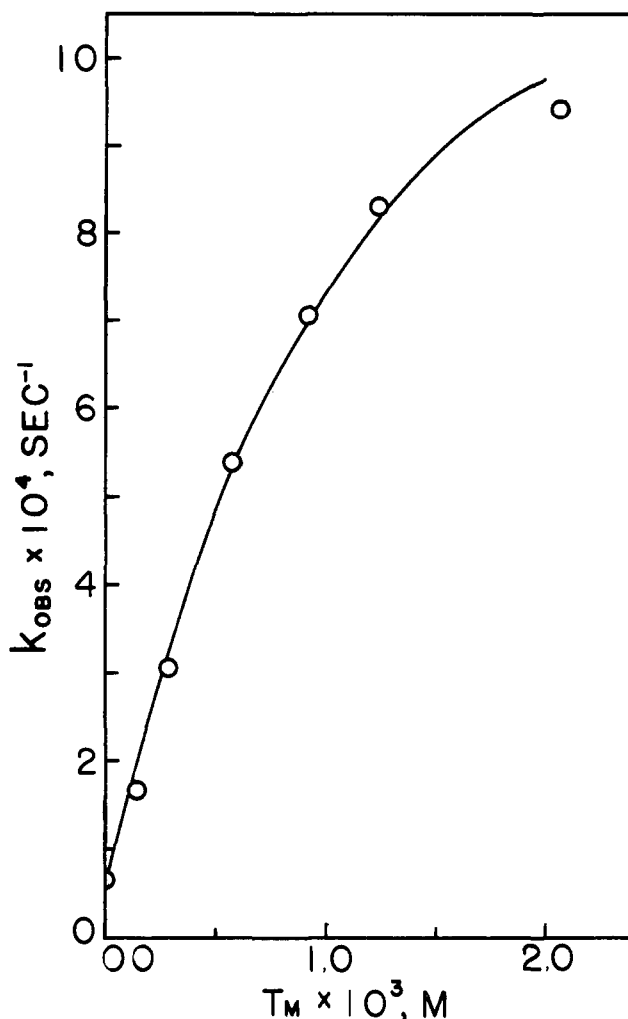


Fig. 2.—Variation with dipyriddy-Cu(II) catalyst concentration of the first-order hydrolysis constants of DCPD at  $-\log [H^+] = 8.00$ ,  $35.0^\circ$ ;  $T_M$  = total concentration of the dipyriddy-Cu(II) chelate species.

The results of a study of the effect of catalyst concentration at  $-\log [H^+] = 8.00$  are illustrated in Fig. 2. The rate constants obviously do not show a linear relationship to the total concentration of the catalyst.

(c) **Other Chelates and Metal Ions.**—The catalytic activities of a few other metal ions and of the Co(II)-dipyriddy chelate (Co-Dipy) were also investigated and the results are summarized in Table IV. Both nickel(II) and copper(II) ions do not have any catalytic effect at low pH. On the other hand, the vanadyl ion has considerable catalytic activity in this pH region.

TABLE IV

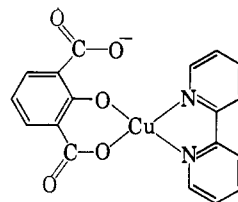
EFFECTS OF METAL IONS AND CHELATES ON THE HYDROLYSIS OF DCPD AT  $35.0^\circ$  AND  $0.100 M$  IONIC STRENGTH ( $KNO_3$ )

$-\log [H^+]$	Catalyst <sup>a</sup>	$T_M, M^b$	$k_{obsd}, sec^{-1}$	$k_{obsd}, sec^{-1}$
2.00	VO(IV)	$1.64 \times 10^{-3}$	$7.13 \times 10^{-4}$	$2.18 \times 10^{-4}$
2.00	Ni(II)	$1.40 \times 10^{-3}$	$2.09 \times 10^{-4}$	...
2.00	Cu(II)	$1.43 \times 10^{-3}$	$2.25 \times 10^{-4}$	...
7.00	Dipyriddy-Cu(II)	$1.14 \times 10^{-3}$	$6.67 \times 10^{-4}$	$1.01 \times 10^{-4}$

<sup>a</sup> If ligand is not specified, catalyst is aquo metal ion. <sup>b</sup> Ratio of total concentrations of metal to substrate species maintained at unity.

At neutral pH the dipyriddy-Co(II) chelate has a catalytic effect which is comparable to dipyriddy-Cu(II). However, the Co(II) chelate undergoes a slow disproportionation reaction at  $-\log [H^+]$  values above 7.5. Thus, the components of the solution, and the reactions occurring at higher pH, are not clearly defined. This chelate system was found to be stable at  $-\log [H^+]$  values below 5.5 where no hydrolyzed metal chelate species exist in significant amounts.

(d) **Interaction between Dipyriddy-Cu(II) and 2-Hydroxyisophthalic Acid (HIPA).**—One of the hydrolysis products of DCPD is 2-hydroxyisophthalic acid. A mixture of cupric salt, dipyriddy hydrochloride, HIPA, and standard base, in a 1:1:1:4 ratio, was titrated with standard hydrochloric acid solution. The solution was clear and yellowish green in the higher pH region. The titration curve shows a good inflection at  $m = 4.0$  where the  $-\log [H^+]$  value is approximately 8.5. Lowering the pH of the solution by adding acid beyond this inflection results in the formation of a precipitate. Both the color in the higher pH region (dipyriddy-Cu(II) itself is deep blue in this region) and the inflection at  $m = 4.0$  suggest the formation of the mixed chelate.



III

**Kinetics of Hydrolysis of 1-Methoxycarbonyl-3-carboxyphenyl 2-Phosphate (MCPD).**—The experiments described below were carried out at  $35.0 \pm 0.05^\circ$ .

(a) **Spontaneous Hydrolysis.**—The observed and calculated first-order rate constants and mole fractions of the three ionic species at different pH values are listed in Table V, together with the assigned rate con-

TABLE V

SPONTANEOUS HYDROLYSIS RATES AND MOLE FRACTIONS OF EACH IONIC SPECIES OF MCPD AT  $35.0^\circ$  AND  $0.100 M$  IONIC STRENGTH ( $KNO_3$ )<sup>a</sup>

$-\log [H^+]$	Fraction of ionic species			$k \times 10^3, sec^{-1}$	
	MCPD <sup>-</sup>	MCPD <sup>2-</sup>	MCPD <sup>3-</sup>	Obsd.	Calcd. <sup>b</sup>
2.00	0.962	0.038		2.26	(2.26)
3.00	0.704	0.296			8.87
3.10	0.656	0.344		9.90	10.1
3.50	0.431	0.569		16.6	15.9
4.00	0.193	0.807		22.0	22.0
5.00	0.023	0.974	0.003	26.3	26.2
5.50	0.007	0.986	0.007	26.5	(26.5)
6.00	0.003	0.974	0.023	26.3	26.2
7.00		0.810	0.190	23.0	22.4
7.50		0.575	0.425	17.2	16.7
8.10		0.253	0.747	8.87	(8.87)

<sup>a</sup>  $k_1 = 1.29 \times 10^{-5}$ ,  $k_2 = 2.69 \times 10^{-4}$ , and  $k_3 = 2.74 \times 10^{-5} sec^{-1}$ , where  $k_1$ ,  $k_2$ , and  $k_3$  are the specific first-order rate constants for MCPD<sup>-</sup>, MCPD<sup>2-</sup>, and MCPD<sup>3-</sup>, respectively.

<sup>b</sup> Calculated from the assigned specific rate constants  $k_1$ ,  $k_2$ , and  $k_3$ .

stant of each ionic form of the phosphate. The rate-pH profile, shown in Fig. 3, is quite symmetrical, with the maximum rate at  $-\log [H^+] = 5.50$ . At this value of  $-\log [H^+]$  the diionic species reaches its highest mole fraction.

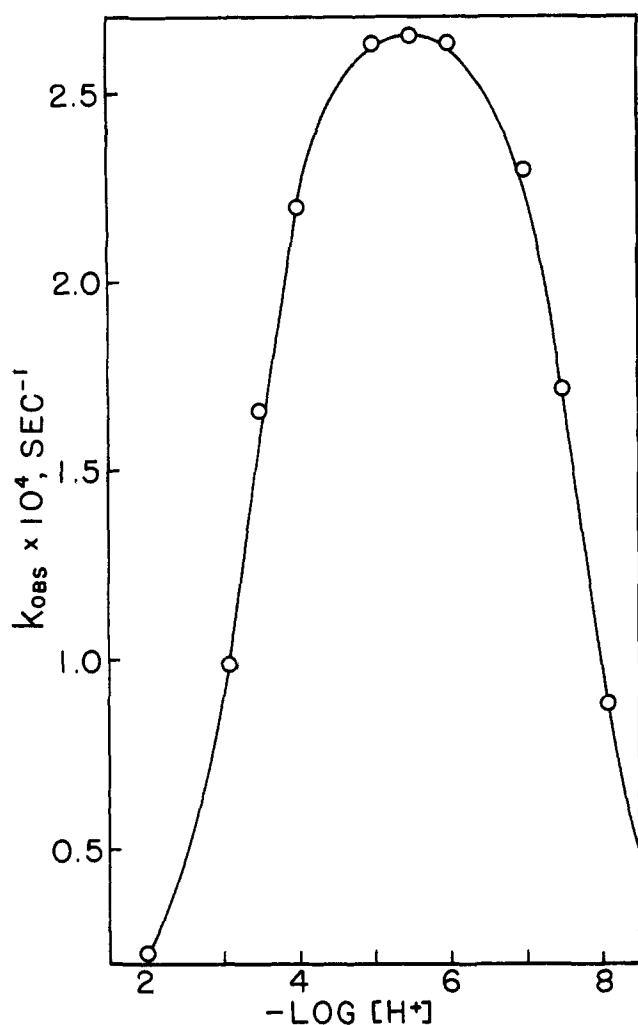


Fig. 3.—Rate profile for the spontaneous hydrolysis of MCPP at 35.0°: O, observed rates; the solid curve indicates calculated rates.

(b) **Catalytic Hydrolysis.**—The hydrolytic tendencies of the vanadyl ion made it necessary to perform the rate experiments at hydrogen ion concentrations greater than  $10^{-3.50}$ . The observed first-order rates are summarized in Table VI. As has been observed

TABLE VI  
VO<sup>2+</sup>-CATALYZED HYDROLYSIS OF MCPP AT 35.0° AND 0.100 M IONIC STRENGTH (KNO<sub>3</sub>)

$-\log [H^+]$	$T_M^a \times 10^3, M$	$k_{obsd}, \text{sec.}^{-1}$
2.00	1.97	$4.03 \times 10^{-5}$
2.50	1.86	$9.67 \times 10^{-5}$
3.50	1.91	$5.53 \times 10^{-4}$
4.00	1.80	$8.93 \times 10^{-4}$
4.50	1.68	Not first order

<sup>a</sup>  $T_M$  = total molar concentration of vanadyl species; ratios of total molar concentrations of vanadyl to phosphate species were maintained at unity.

for DCPD, vanadyl ion has a catalytic effect which is much greater than that of the copper(II) ion. Figure 4 shows that the reaction at  $-\log [H^+] = 4.50$  does not follow first-order kinetics, no doubt because of hydrolysis of vanadyl ion, which would cause the concentration of active species to decrease with time. Also, at  $-\log [H^+] = 4.00$ , the rate curve seems to indicate

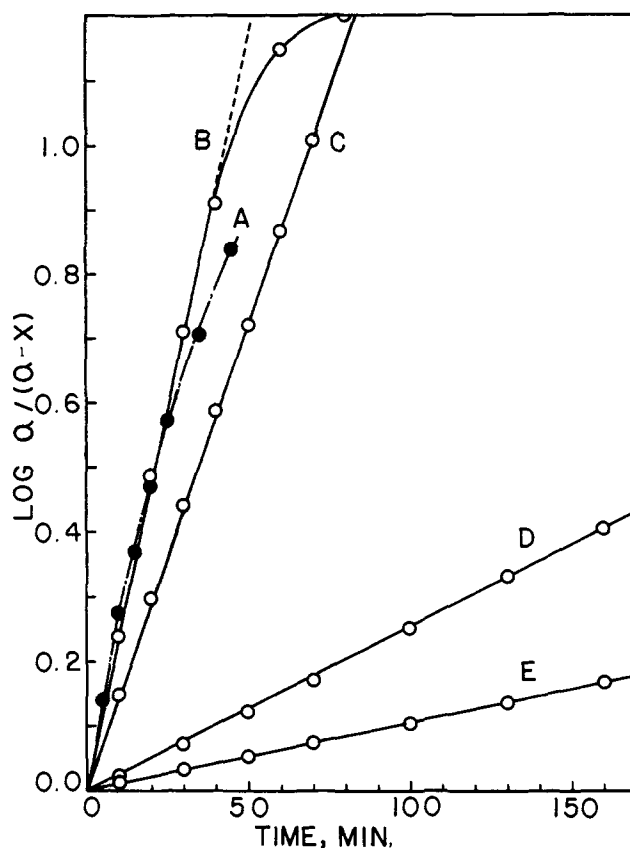


Fig. 4.—VO<sup>2+</sup>-catalyzed hydrolysis of MCPP at 35.0° at  $-\log [H^+]$  of: A, 4.50; B, 4.00; C, 3.50; D, 2.50; E, 2.00.

hydrolysis of vanadyl ion after the reaction was nearly complete.

The concentration effect of vanadyl ion was studied at two hydrogen ion concentrations:  $-\log [H^+]$  values of 2.00 and 3.00. The results are summarized in Table VII, and the rate-concentration profiles are shown in Fig. 5. At both hydrogen ion concentrations, the ob-

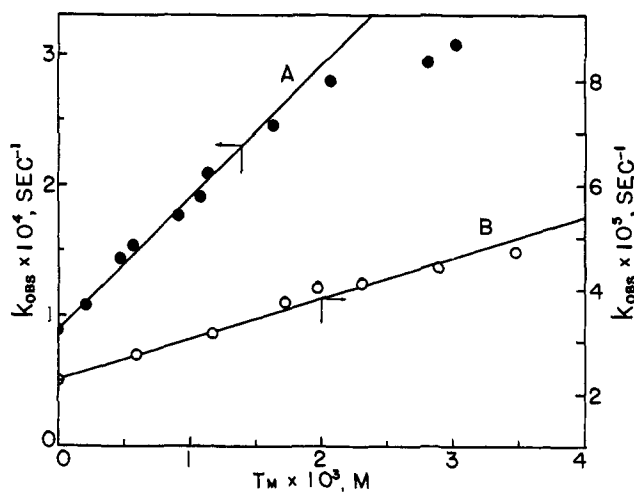


Fig. 5.—VO<sup>2+</sup>-catalyzed hydrolysis of MCPP, at  $-\log [H^+]$  values of: A, 3.00; B, 2.00;  $T_M$  = total concentration of VO<sup>2+</sup>.

served rates show a linear relationship with the concentrations of vanadyl ion. However, at  $-\log [H^+] = 3.00$  the observed rates begin to level off in the higher concentration region.

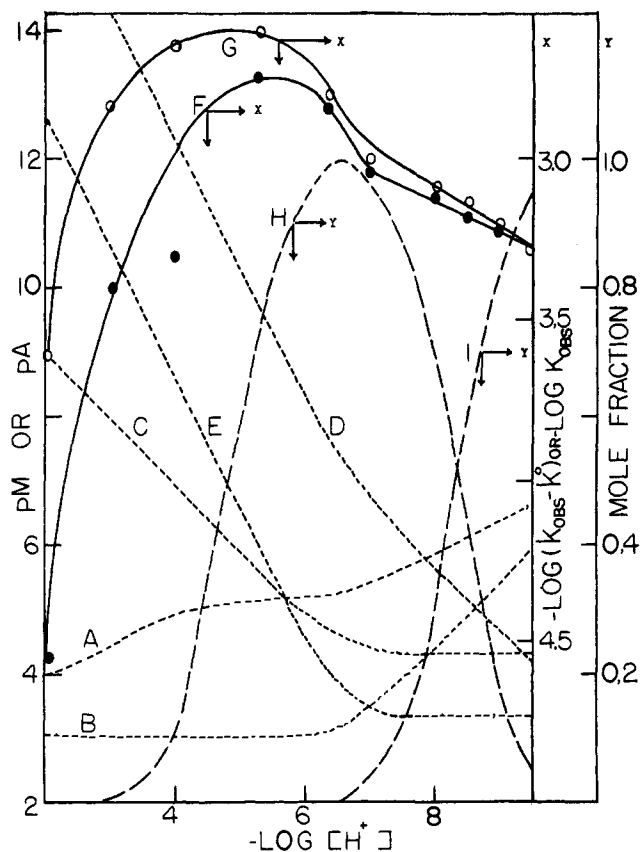


Fig. 6.—I. Distribution of Cu(II)-dipyridyl (Dipy) chelate species as a function of  $-\log [H^+]$  at  $35.0^\circ$ : A,  $Cu^{2+}$ ; B,  $Cu$ -Dipy; C,  $Cu(OH)Dipy$ ; D,  $Cu(OH)_2Dipy$ ; E,  $[Cu(OH)Dipy]_2$ ; total concentration is  $1.00 \times 10^{-3} M$ . II. F:  $\log$  of catalytic effect,  $k_{obsd} - k^0$ , as a function of  $-\log [H^+]$  at  $35.0^\circ$ ;  $k_{obsd}$  is the measured rate constant of the catalyzed reaction;  $k^0$  is the spontaneous rate constant. III. G:  $\log$  of the observed rate constant,  $k_{obsd}$ , for the catalyzed reaction as a function of  $-\log [H^+]$ . IV. Mole fraction of the triionic and tetraionic species of DCPD as a function of  $-\log [H^+]$ : H,  $DCPP^{3-}$ ; I,  $DCPP^{4-}$ .

(c) **Other Metal Ions and Chelates.**—An attempt was made to determine the catalytic effects of the dipyridyl-Cu(II) chelate at  $-\log [H^+]$  values of 5.50

TABLE VII

$VO^{2+}$ -CATALYZED HYDROLYSIS OF MCPD AT  $35.0^\circ$  AND 0.100 M IONIC STRENGTH ( $KNO_3$ )

$-\log [H^+]$	$T_M^a \times 10^3, M$	$k_{obsd} \times 10^5, \text{sec.}^{-1}$	
2.00	0	2.26	
	0.585	2.75	
	1.17	3.15	
	1.72	3.76	
	1.97	4.03	
	2.31	4.12	
	2.89	4.43	
	3.48	4.73	
	3.00	0	8.87
		0.210	10.8
0.468		14.4	
0.571		15.4	
0.910		17.7	
1.08		19.1	
1.13		20.9	
1.63		24.6	
2.07		28.0	
2.81		29.5	
3.02		30.8	

<sup>a</sup>  $T_M$  = total concentration of vanadyl ion species.

and 8.00. While this chelate compound showed considerable catalytic activity with DCPD, the formation of a precipitate under these conditions precluded further study of the system. The results of other investigations are shown in Table VIII. Cupric ion has almost no catalytic effect below  $-\log [H^+] = 4.00$ .

TABLE VIII

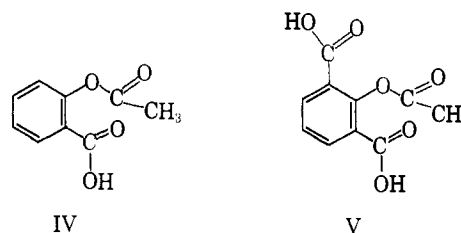
EFFECTS OF COPPER(II) ION AND A COPPER(II) CHELATE ON THE HYDROLYSIS OF MCPD AT  $35.0^\circ$  AND 0.100 M IONIC STRENGTH ( $KNO_3$ )

$-\log [H^+]$	Catalyst	$T_M, M^a$	$k_{obsd}, \text{sec.}^{-1}$	$k^0, \text{sec.}^{-1}$
3.0	Cu(II)	$1.64 \times 10^{-3}$	No effect	
4.0	Cu(II)	$1.82 \times 10^{-3}$	$2.60 \times 10^{-4}$	$2.20 \times 10^{-4}$
8.0	Cu(II)- Tiron	$1.65 \times 10^{-3}$	$1.30 \times 10^{-4}$	$9.97 \times 10^{-5}$

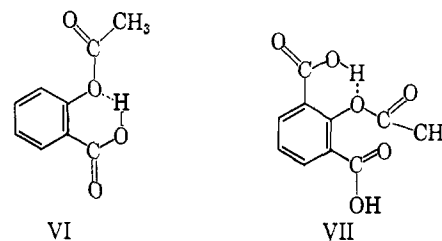
<sup>a</sup>  $T_M$  = total molar concentration of metal ion; ratios of total molar concentrations of metal ion to MCPD maintained at unity;  $k^0$  = spontaneous hydrolysis rate.

### Discussion

**Acid Dissociation Constants.**—The  $pK$  value of aspirin (IV) is 0.72 unit greater than the  $pK_1$  of AIPA (V). Both compounds may form weak intramolecular

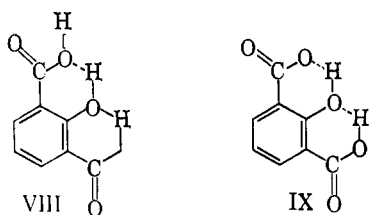


hydrogen bonds to give the structures VI and VII.



The probable formation of a hydrogen bond in aspirin would increase its  $pK$  value to a certain extent over what would be expected in the absence of hydrogen bonding, since the proton of the carboxyl group is involved in bond formation. On the other hand, the proton which dissociates first in AIPA (as shown in VII) is not involved in hydrogen bond formation. Moreover, the inductive effect of the carboxyl group should increase the dissociation constant over and above a statistical effect of  $0.3 \log K$  unit, which results from the fact that there are two carboxyl groups in the molecule.

The  $pK_1$  value of HIPA (VIII) is lower than that of AIPA (V) by 0.72  $pK$  unit. The proton which dissociates first in HIPA does not take part in hydrogen bond formation, as shown in VIII, and the dissociated form IX further stabilizes the hydrogen bonds. Thus, the decrease in  $pK$  is primarily due to the increased stabilization of the dissociated form IX by intramolecular hydrogen bonding. Similar behavior has been



noted for salicylic acid.<sup>16</sup> The increase in the  $pK_2$  value of HIPA by 0.73  $pK$  unit over that of AIPA is accounted for by the fact that the hydrogen bond shown in IX is more stable than that of structure VII, in which the donor power of the acetoxy oxygen is reduced by the adjacent carbonyl group.

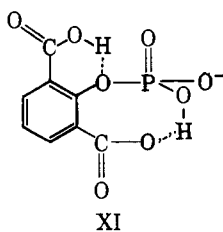
Careful consideration of the  $pK$  values of the acids listed in Table IX indicates that the substituent effects of the phosphate and acetoxy groups on the dissociation constants are comparable. However, the  $pK_3$  value of DCPD increases more than the expected value of about 3.9, calculated under the assumption that relative  $pK$  values of Ib and Va in Table IX would

TABLE IX

STRUCTURES AND  $pK$  VALUES OF SALICYL PHOSPHATE ANALOGS

No.	Structure	$pK$	No.	Structure	$pK$
X		3.71	IV		3.57
Ia		2.98	V		2.85
Ib		4.82	Va		3.80

be about the same as those of X and IV, and of Ia and V, respectively. This significant stabilization of the third proton in DCPD is rather anomalous. A satisfying explanation for this effect is not obvious at the present time, although it is conceivable that the electronic shift resulting from the second hydrogen-bonded ring in XI would influence  $pK_3$  in the right direction.



XI

The somewhat lower  $pK_2$  (3.38) of MCPP (II) as compared to SP (X) is accounted for by considering the

(16) Y. K. Syrkin and M. E. Dyatkina, "Structure of Molecules and Chemical Bond," Butterworth Scientific Publications, London, 1950, p. 283.

inductive effect ( $-I$  effect) of the methoxycarbonyl group.

The relative values of the dissociation constants of the most strongly bound hydrogen of the phosphate groups in DCPD, MCPP, and SP are

$$pK_4 \text{ of DCPD}^{3-} > pK_3 \text{ of MCPP}^{2-} > pK_3 \text{ of SP}^{2-}$$

$$8.35 \qquad 7.63 \qquad 6.50$$

The high  $pK_4$  value of DCPD is expected on the basis of the greater negative charge of the dissociating anion. The higher  $pK_3$  of MCPP over that of SP is probably due to the inductive influence of the methoxycarbonyl group, as well as its possible influence on hydrogen bonding of the proton on the phosphate group.

**Spontaneous Hydrolysis.**<sup>16a</sup>—Previous studies<sup>7,8</sup> indicated that hydrolysis of the monoionic form of monoalkyl phosphates occurs through phosphorus-oxygen bond fission. Chanley and co-workers<sup>9</sup> also proposed a mechanism for the hydrolysis of salicyl phosphate on this basis. Therefore, in the present investigation it is assumed that the ionized forms of salicyl phosphate analogs also undergo phosphorus-oxygen cleavage.

The differences in  $pK_2$  values,  $\Delta pK_2$ , between salicyl phosphate and each of its analogs are a measure of the inductive effect and hydrogen bonding of the substituent groups in each analog. The differences in rate constant values,  $\Delta(-\log k)$ , shown in Table X, display

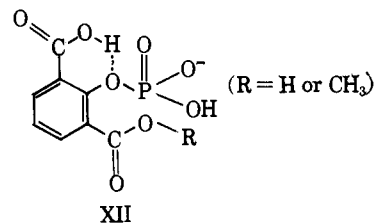
TABLE X

RELATIONSHIP BETWEEN ACID DISSOCIATION CONSTANTS AND RATE CONSTANTS OF ORGANIC PHOSPHATES

Phosphate	$pK_2^a$	$\Delta pK_2$	$-\log k_1^b$	$\Delta(-\log k_1)$	$-\log k_2^c$	$\Delta(-\log k_2)$
SP	3.71 <sup>d</sup>	...	5.17 <sup>e</sup>	..	4.10 <sup>e</sup>	..
MCPP	3.38	0.33	4.89	0.28	3.57	0.53
DCPD	2.98	0.73	4.51	0.66	2.65	1.45

<sup>a</sup>  $K_2$  = second dissociation constant of organic phosphate. <sup>b</sup>  $k_1$  = first-order rate constant of monoionic species. <sup>c</sup>  $k_2$  = first-order rate constant of diionic species. <sup>d</sup> Value obtained at 30.0° by Hofstetter, *et al.*<sup>4</sup> <sup>e</sup> Value interpolated from the data of Chanley, *et al.*<sup>9</sup>

the same trend as the  $\Delta pK_2$  values. Thus, it seems that the second carboxyl group in DCPD (I) and the methoxycarbonyl group in MCPP (II) may participate in acceleration of the hydrolysis rate of the monoionic phosphates, MCPP<sup>-</sup> and DCPD<sup>-</sup>, by withdrawing electrons from the O-P bond which undergoes fission. The electronic effect of the substituent may take place through inductive-resonance interaction, and through the electrostatic effect of the hydrogen bond, as is indicated in XII.



XII

(16a) NOTE ADDED IN PROOF.—While this paper was in press, an alternative reaction mechanism for the hydrolysis of salicyl phosphate was proposed by M. L. Bender and J. M. Lawlor [*J. Am. Chem. Soc.*, **85**, 3010 (1963)]. This mechanism, involving a hydrogen-bonded proton interposed between the carboxylate group and the phenolate ester oxygen, cannot be related to the hydrolysis of the nonprotonated species described in this paper. Its relationship to metal ion catalysis of hydrolysis of protonated species is now under study and will be reported in detail later.

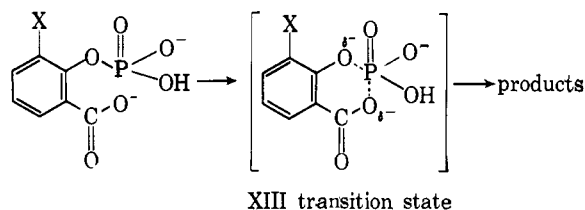
TABLE XI

CONCENTRATIONS (*M*) OF Cu(II) AND DIPYRIDYL-Cu(II) CHELATE SPECIES AT 35.0° AND 0.100 *M* IONIC STRENGTH (KNO<sub>3</sub>)<sup>a</sup>

$-\log [H^+]$	$[Cu^{2+}]$	$[CuL^{2+}]$	$[Cu(OH)L^+]$	$[Cu(OH)_2L]$	$[(Cu(OH)L)_2^{2+}]$
2.00	$1.08 \times 10^{-4}$	$8.92 \times 10^{-4}$	$1.12 \times 10^{-9}$	$5.13 \times 10^{-17}$	$2.52 \times 10^{-13}$
3.00	$3.62 \times 10^{-5}$	$9.64 \times 10^{-4}$	$1.21 \times 10^{-8}$	$5.54 \times 10^{-16}$	$2.96 \times 10^{-11}$
4.00	$1.33 \times 10^{-5}$	$9.87 \times 10^{-4}$	$1.24 \times 10^{-7}$	$5.67 \times 10^{-13}$	$3.08 \times 10^{-9}$
5.00	$7.68 \times 10^{-6}$	$9.90 \times 10^{-4}$	$1.25 \times 10^{-6}$	$5.69 \times 10^{-11}$	$3.10 \times 10^{-7}$
6.00	$6.68 \times 10^{-6}$	$9.30 \times 10^{-4}$	$1.17 \times 10^{-5}$	$5.35 \times 10^{-9}$	$2.73 \times 10^{-5}$
7.00	$3.86 \times 10^{-6}$	$3.18 \times 10^{-4}$	$4.00 \times 10^{-5}$	$1.8 \times 10^{-7}$	$3.20 \times 10^{-4}$
8.00	$1.33 \times 10^{-6}$	$3.80 \times 10^{-5}$	$4.79 \times 10^{-5}$	$2.85 \times 10^{-6}$	$4.57 \times 10^{-4}$
8.50	$7.6 \times 10^{-7}$	$1.22 \times 10^{-5}$	$4.86 \times 10^{-5}$	$7.02 \times 10^{-6}$	$4.70 \times 10^{-4}$
9.00	$4.2 \times 10^{-7}$	$3.85 \times 10^{-6}$	$4.85 \times 10^{-5}$	$2.21 \times 10^{-5}$	$4.68 \times 10^{-4}$
9.50	$2.4 \times 10^{-7}$	$1.20 \times 10^{-6}$	$4.78 \times 10^{-5}$	$6.90 \times 10^{-5}$	$4.55 \times 10^{-4}$

<sup>a</sup> Total concentrations of metal ion and ligand =  $1.00 \times 10^{-3}$  *M*;  $K_{ML} = [CuL^{2+}]/[Cu^{2+}][L]$ ;  $K_{M(OH)L} = [Cu(OH)L^+][H^+]/[CuL^{2+}]$ ;  $K_{M(OH)_2L} = [Cu(OH)_2L][H^+]^2/[CuL^{2+}]$ ;  $K_{[M(OH)L]_2} = [(Cu(OH)L)_2^{2+}][H^+]^2/[CuL^{2+}]^2$ ; where  $\log K_{ML} = 6.33$ ;  $pK_{M(OH)L} = 7.9$ ;  $pK_{M(OH)_2L} = 17.24$ ;  $pK_{[M(OH)L]_2} = 10.50$ .

The rate constants of the diionic phosphates, SP<sup>2-</sup>, MCP<sup>2-</sup>, and DCP<sup>2-</sup>, are much greater than those of the corresponding monoionic forms as is seen in Table X. Under the assumption that a simple solvolysis mechanism applies to both mono- and diionic species, a somewhat slower rate would be expected for the diionic form. The anomalous increase in the reaction rate of the diionic form may be explained by means of a reaction mechanism involving nucleophilic attack of the phosphate by the neighboring carboxylate group to give an activated complex of the type indicated by XIII. Two factors were cited by Chanley, *et al.*,<sup>9</sup> in proposing intramolecular interaction which would be in accord with the observed acceleration. The *ortho* carboxyl group is assumed to participate in the hydrolysis by coordinating directly with the phosphorus atom to produce an anhydride, which then undergoes rapid hydrolytic cleavage, in accordance with the following reaction scheme.



The substituent X, a carboxyl group for DCP<sup>2-</sup> and a methoxycarbonyl group for MCP<sup>2-</sup>, acts as an electron-withdrawing group and thus increases the rate of hydrolysis of the diionic forms of MCP<sup>2-</sup> and DCP<sup>2-</sup> over the rate of hydrolysis of unsubstituted SP. This effect is illustrated by the rate constants,  $pK_2$ , in Table X.

The rate constant ( $k_3$ ) for the hydrolysis of the trinegative form of DCP<sup>3-</sup>, which has a second negative carboxylate group in the *ortho* position, is somewhat greater than the corresponding rate constant,  $k_2$ , of SP. Since the second carboxylate group can also form the reactive intermediate of the type indicated by XIII, it is reasonable to expect that the reaction rate would be increased. There is also the possibility that the very slight  $-I$  effect<sup>17</sup> of the second carboxylate group also tends to increase the rate.

The rate constant for the hydrolysis of fully ionized form of MCP<sup>3-</sup> ( $k_3 = 2.74 \times 10^{-5}$  sec.<sup>-1</sup> at 35.0°) is considerably larger than that of SP ( $k_3 = 4 \times 10^{-8}$

sec.<sup>-1</sup> at 30.0°). The corresponding rate constant of the fully ionized form of DCP<sup>3-</sup> was not evaluated because the reaction proceeded too slowly under the experimental conditions employed. The slow hydrolysis rates of the fully ionized forms of DCP<sup>3-</sup> and SP may be ascribed to the accumulated negative charge around the O-P bond. Since in these cases the reaction probably involves a nucleophilic attack of the phosphorus atom by hydroxyl ion rather than interaction with adjacent groups, the rate would be decreased by negative substituents adjacent to the phosphate ester group. The faster rate of hydrolysis of the fully ionized species of MCP<sup>3-</sup> over the rate of the corresponding SP species may be accounted for by the inductive effect of the methoxycarbonyl group in MCP<sup>3-</sup>.

**Catalytic Hydrolysis of 1,3-Dicarboxyphenyl 2-Phosphate.** (a) **Dipyridyl-Cu(II).**—Cupric ion and dipyridyl in aqueous solution in a 1:1 ratio form the complexes Cu-Dipy, Cu(OH)Dipy, Cu(OH)<sub>2</sub>Dipy, and [Cu(OH)Dipy]<sub>2</sub>. The relative amounts of these substances are dependent on the hydrogen ion concentration and total concentration of the metal species.<sup>18</sup> Although cupric ion undergoes hydrolysis to yield Cu(OH)<sup>+</sup> and Cu<sub>2</sub>(OH)<sub>2</sub><sup>2+</sup>,<sup>19</sup> these species are not present in significant concentrations under the conditions of this investigation. The concentration of the five forms of Cu(II) in the region of  $-\log [H^+]$ , 2.00–9.50, in a total concentration of metal ion of  $1.00 \times 10^{-3}$  *M*, were calculated and are listed in Table XI. Analysis of the data in Table II, which gives compositions of the substrates at different hydrogen ion concentrations, and in Fig. 6, which shows the catalytic effects and concentrations of metal ion and metal chelates as a function of the hydrogen ion concentration, makes it possible to estimate the catalytic activities of the various Cu(II) species present. From the plot of the catalytic effect ( $k_{\text{obsd}} - k^0$ ), it is seen that the rate constant increases to a maximum, and then decreases to a lesser extent. At about pH 9.5, where the tetraionic form is the only important substrate species, the observed rate seems to be approaching a constant value. In Fig. 6, it is seen that the monohydroxo form of the metal chelate has reached a constant value, whereas the concentration of the aquo metal chelate is decreasing rapidly and is already much smaller than that of the monohydroxo chelate. Thus it seems that the rate of the pH 9.5 may be assigned to the catalytic effect of the monohydroxo

(17) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 72.

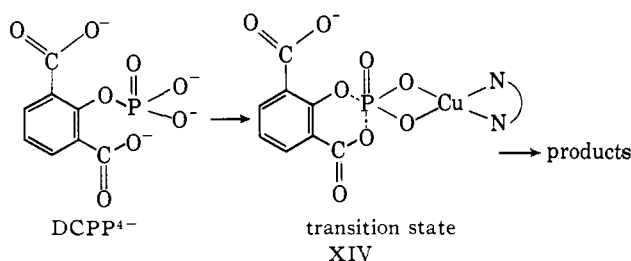
(18) R. L. Gustafson and A. E. Martell, *J. Am. Chem. Soc.*, **81**, 525 (1959).

(19) C. Berecki-Biedermann, *Arkiv Kemi*, **9**, 175 (1956).

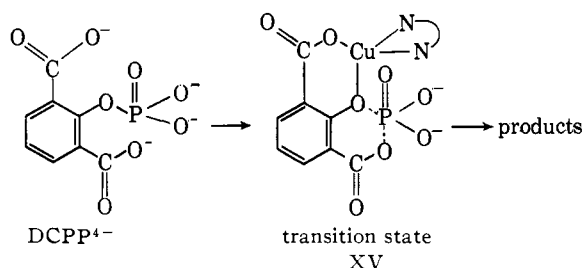


species in the hydrolysis of the tetraionic form. This approximation, however, involves the assumption that the dihydroxo chelate and the binuclear chelated complex cannot be very effective catalysts, as the data taken at high pH seem to indicate.

The nature of the variation of observed rates with pH indicates that the mechanism of the metal-catalyzed reaction must be similar to that of the uncatalyzed hydrolysis in that it involves the participation of the adjacent carboxylate ions. Thus the low rates at the extremes of pH indicate that simple acid- or base-catalyzed hydrolysis reactions do not contribute significantly to the observed reaction. Also, the fact that the measured rates are uniformly first order indicates that the reaction does not proceed through the equilibrium formation of appreciable amounts of a metal-ligand-substrate complex.<sup>20</sup> It seems, therefore, that the hydrolysis of the tri- and tetraionic forms may involve the schematic reactions



or, as an alternative



The transition state XIV is favored over XV since the influence of the metal ion would be greater in the former case, and because of the requirement of the phosphate group for metal ion catalysis in salicyl phosphate analogs.<sup>4</sup> In view of the wide pH range of the observed catalytic effects, the possibility of catalytic activity of both the normal and monohydroxo chelates must be considered. It is, of course, impossible to determine the exact site of combination of the chelate with the substrate. In any case the chelate, acting as a Lewis acid, would, in the transition state, assist the attack of the phosphorus by the neighboring carboxylate group. As has been pointed out above, the first-order intramolecular nucleophilic attack of the phosphate by the carboxylate group does not result in a significant reaction rate in the absence of metal ions or complexes.

A study of the variation of the catalytic effects at pH 8 as the concentration of catalytic metal species is varied makes it possible to determine the relative activities of the mononuclear and the binuclear chelates present. At constant pH, the ratios of concentrations of the various hydrolytic mononuclear species remain

constant, but the ratio of polynuclear to mononuclear species increases with increase of metal ion concentration. The ratio of chelate compounds to free Cu(II) ion also varies, but the concentration of Cu(II) ion is so low at pH 8 that its catalytic effect may be neglected. Therefore, if the polynuclear chelate were appreciably active, the following rate expression would apply.

$$k_{\text{obsd}} - k^0 = k_{\text{Cu(OH)L}}[\text{Cu(OH)L}^+] + k_{[\text{Cu(OH)L}]_2}[(\text{Cu(OH)L}_2^{2+})]$$

or

$$k_{\text{obsd}} - k^0 = k_{\text{Cu(OH)L}}[\text{Cu(OH)L}^+] + k_{[\text{Cu(OH)L}]_2}K_d[\text{Cu(OH)L}^+]^2 \quad (2)$$

$$k_{\text{obsd}} - k^0 = k_{\text{Cu(OH)L}}K_{\text{M(OH)L}}[\text{CuL}^{2+}]/[\text{H}^+] + k_{[\text{Cu(OH)L}]_2}K_D[\text{CuL}^{2+}]^2/[\text{H}^+]^2 \quad (3)$$

where

$$K_d = \frac{[(\text{Cu(OH)L}_2^{2+})]}{[\text{Cu(OH)L}^+]^2} \quad K_D = \frac{[(\text{Cu(OH)L})_2^{2+}][\text{H}^+]^2}{[\text{CuL}^{2+}]^2}$$

Equation 2 may be arranged to

$$\frac{k_{\text{obsd}} - k^0}{[\text{Cu(OH)L}^+]} = k_{[\text{Cu(OH)L}]} + k_{[\text{Cu(OH)L}]_2}K_d[\text{Cu(OH)L}^+] \quad (4)$$

This relationship would hold at constant pH even though CuL is also an active catalyst, since under these conditions the ratio between  $[\text{CuL}^{2+}]$  and  $[\text{Cu(OH)L}^+]$  is constant. Therefore, a plot of eq. 4 should give a straight line, with an intercept equal to  $k_{\text{Cu(OH)L}}$  and a slope equal to  $k_{[\text{Cu(OH)L}]_2}K_d$ . A small value of the slope, giving a nearly horizontal line, would indicate a small or negative catalytic effect of the binuclear chelate. Under these conditions, a plot of  $k_{\text{obsd}} - k^0$  vs.  $[\text{CuL}^{2+}]$  would approximate a straight line passing through zero. A plot of the data in Fig. 7 indicates that this is the case, and the binuclear chelate is thus considered relatively inactive. This result seems to be in accord with the structure of the binuclear metal chelate compound, since the Cu(II) ions are completely coordinated and well-shielded from interaction with additional ligands.

Thus the possible catalysts above pH 4 are  $\text{CuL}^{2+}$  and  $\text{Cu(OH)L}^+$ . It seems reasonable that  $\text{Cu(OH)}_2\text{L}$  would not be active as a catalyst, since in this complex four coordination sites of the copper(II) ion are satisfied and the chelate is itself neutral, so that the electrostatic interaction with substrate species would be relatively low. On the other hand, it is interesting that the monohydroxo complex would have considerable catalytic effect on the hydrolysis reactions of both the tri- and tetraionic species. Particularly, the hydrolysis reaction of the tetraionic species obtained represents a greatly accelerated rate over that of the metal ion free system. In accordance with the studies of Rosenblatt<sup>21a</sup> and of Bjerrum, Ballhausen, and Jørgensen<sup>21b</sup> on the configuration of the copper (II) ion in the ammonia-copper system in solution, the coordination number of copper(II) may increase to five or six.

(20) This conclusion involves the reasonable assumption that such a mixed complex would not be completely formed over the wide range of conditions employed.

(21) (a) F. Z. Rosenblatt, *Z. anorg. allgem. Chem.*, **204**, 351 (1932); (b) J. Bjerrum, C. J. Ballhausen, and C. K. Jørgensen, *Acta Chem. Scand.*, **8**, 1275 (1954).

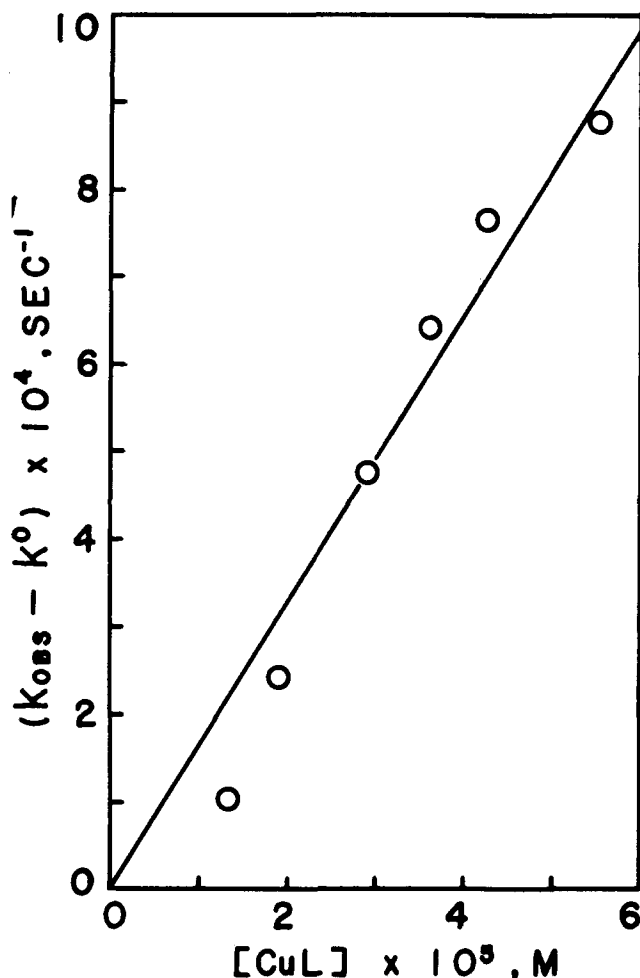


Fig. 7.—Catalytic rate constants of the hydrolysis of DCPD in the presence of Cu(II)-Dipy at  $-\log [H^+] = 8.00$  at  $35.0^\circ$ .

Thus, copper(II) is able to have a higher coordination number than four under certain conditions. It would be reasonable, therefore, to form an activated complex of the type illustrated by XIV or XV but containing an additional hydroxo group in the hydrolysis reaction of DCPD.

(b) **Other Catalysts.**—As is shown in Table IV, the vanadyl ion has a profound catalytic effect on the hydrolysis of DCPD, even at pH values as low as 2.0. Recently, Ahrlund and Noren<sup>22</sup> observed that the fluoride complexes of  $VO^{2+}$  have much greater stability than those of other divalent metal ions such as  $Ni^{2+}$  and  $Cu^{2+}$  which have similar size and higher symmetry. The high stability is attributed to the increased electrostatic force of the vanadium atom as the result of the polarity of the vanadium-oxygen linkage. Therefore, the possibility of strong interaction between the vanadyl ion and the substrate is not entirely unexpected.

**Catalytic Hydrolysis of 1-Methoxycarbonyl-3-carboxyphenyl 2-Phosphate (MCPD).** (a) **Catalysis by  $VO^{2+}$  Ions.**—Potentiometric studies were carried out to investigate the extent of hydrolysis of  $VO^{2+}$  in the concentration range,  $1.21 \times 10^{-4}$  to  $4.83 \times 10^{-3}$  M, at  $\mu = 0.100$  and  $30.0^\circ$ . The results of these experiments indicate that hydrolysis is insignificant below  $-\log [H^+] = 3.00$ . Rossotti and Rossotti<sup>23</sup> carried out extensive studies on the hydrolysis of vanadyl ion at  $25^\circ$

and  $\mu = 3.00$ . The equilibrium constants for the formation of  $VO(OH)^+$  and  $(VO)_2(OH)_2^{2+}$  indicate that these hydrolyzed species may be neglected in the low pH region where the present investigation was carried out. From studies of the oxidation-reduction potentials of the V(IV)-V(V) system at different hydrogen ion concentrations,<sup>24,25</sup> it was found that the behavior of vanadium salts is rather complex except at low pH. Accordingly, one would expect difficulties in the investigation of the vanadyl chelate system at high pH. The vanadyl chelates formed with diamines and with Tiron have been found in this laboratory<sup>26</sup> to be rather unstable in neutral and in alkaline solutions. Thus, the present study was limited to the investigation of vanadyl ion as a catalyst in acidic media.

The observed first-order rates as a function of vanadyl ion concentration at  $-\log [H^+] = 2.00$  are shown in Fig. 5. This relationship is consistent with the equation

$$k_{\text{obsd}} = k^0 + k_I[VO^{2+}] \quad (5)$$

The value of  $k_I$ , which is obtained from the slope of the straight line in Fig. 5, is  $7.87 \times 10^{-3}$  sec.<sup>-1</sup> M<sup>-1</sup>. A more detailed expression for  $k_I$  is

$$k_I = k_{I1}M_I + k_{I2}M_{II} \quad (6)$$

in which  $k_{I1}$  is the rate constant of the hydrolysis reaction of the monoionic species catalyzed by  $VO^{2+}$ ,  $k_{I2}$  is the rate constant of the hydrolysis reaction of the diionic species catalyzed by  $VO^{2+}$ ,  $M_I$  is the fraction of the monoionic species, and  $M_{II}$  is the fraction of the diionic species.

Substituting the values of  $M_I$  and  $M_{II}$ , 0.962 and 0.038, respectively, at  $-\log [H^+] = 2.00$ , the following equation is obtained.

$$0.962k_{I1} + 0.038k_{I2} = 7.87 \times 10^{-3} \quad (7)$$

A relationship which follows eq. 5 is obtained at  $-\log [H^+] = 3.00$ , except in the higher concentration region, as may be seen in Fig. 5. The lower catalytic effect in this higher concentration region is possible due to a different mode of interaction from that in relatively low concentration. The value of  $k_I$  in eq. 5 was found to be  $1.02 \times 10^{-1}$  sec.<sup>-1</sup> M<sup>-1</sup>. The values of  $M_I$  and  $M_{II}$ , 0.704 and 0.296, respectively, were substituted into eq. 6 to give

$$0.704k_{I1} + 0.296k_{I2} = 1.02 \times 10^{-1} \quad (8)$$

Calculation of  $k_{I1}$  and  $k_{I2}$  with eq. 7 and 8 yields the values

$$k_{I1} = -6.03 \times 10^{-3} \quad k_{I2} = 3.60 \times 10^{-1}$$

The negative value of  $k_{I1}$  is rather unusual. Since the absolute value of  $k_{I1}$  is much smaller than the value of  $k_{I2}$ , the  $k_{I1}$  value may be considered to be approximately zero. These results seem to indicate that the formation of structures XVI and XVII may be important in the catalytic reaction.

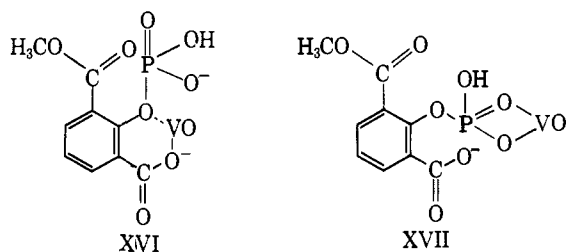
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Through the formation of structures of the type indicated by XVI and XVII, the vanadyl ion would tend to withdraw electrons from the O-P bond which undergoes cleavage, thereby accelerating the reaction. However, the formation of the activated complex between vanadyl ion and the substrate would result in less interaction if the mechanism involves XVI. If the transition state is represented by XVII, the decreased rate of reaction of the monoionic form  $k_I$ , relative to that of the diionic form  $k_{II}$ , would be expected on the basis of the weaker donor effect of the adjacent methylcarboxyl group, as compared to a carboxylate ion.

Further study of the effects of pH and concentration on this reaction would be of interest. Variation of pH, for example, could indicate whether displacement of the proton of the phosphate group would give a reac-

tion intermediate. Positive evidence on this point would favor XVII as the intermediate.

(b) **Other Catalysts.**—Free cupric ion was inert even at  $-\log [H^+] = 4.00$ . This is presumably due to the fact that the electronegativity of the Cu(II) ion is less than that of the vanadyl ion and would, therefore, have less affinity for the substrate.

The Cu(II)-Tiron chelate was found to be very slightly active as a catalyst even at  $-\log [H^+] = 8.00$ , where 70 mole % of the triionic and 30% of the diionic species are present. Since the Cu(II)-Tiron chelate has a negative charge of two, its tendency to interact with the substrate species which have charges of  $-3$  and  $-4$  is probably very weak as the result of electrostatic repulsion between the ligands and the substrate. Moreover, the high formation constant of this chelate ( $\log K_1 = 14.53$  at  $20^\circ$ )<sup>27</sup> indicates that the metal would have only very weak affinity for an additional ligand such as the substrate.

**Acknowledgment.**—The authors are indebted to Dr. David Todd of Worcester Polytechnic Institute for supplying the organic phosphates and the isophthalic acid derivatives which have been used in this work.

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[CONTRIBUTION OF THE EASTERN RESEARCH LABORATORY OF THE DOW CHEMICAL COMPANY, FRAMINGHAM, MASSACHUSETTS, THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY, WORCESTER, MASSACHUSETTS, AND THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILLINOIS]

## Copper(II) Chelates of Histidylhistidine and Related Compounds<sup>1</sup>

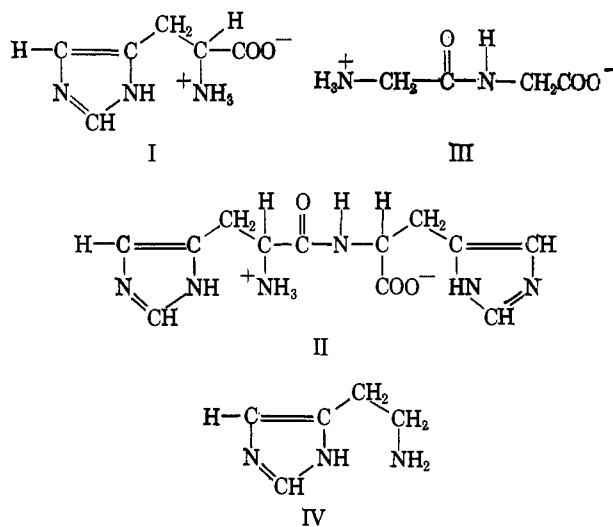
BY M. A. DORAN, S. CHABEREK, AND A. E. MARTELL<sup>2</sup>

RECEIVED AUGUST 28, 1963

The interactions of Cu(II) ions with histidylhistidine, histidine, histamine, and glycylglycine were investigated by potentiometric and spectrophotometric techniques. Acid dissociation constants of the ligands and the stability constants of the Cu(II) chelate compounds are reported. Evidence is given for a polynuclear Cu(II)-histamine complex. Probable structures of the metal chelate compounds are suggested, and their relationship to analogous metal chelate compounds occurring in biological systems is discussed.

In recent years considerable experimental evidence has accumulated which indicates that the imidazole group of histidine may serve a number of important biological functions, such as the catalytic site for hydrolytic enzymes and as an important part of the buffering action of proteins in the physiological pH range. In view of the ease with which histidine, and in particular its imidazole group, interacts with both hydrogen ions and metal ions, it seemed worthwhile to investigate the specific acid-base and metal ion interactions of histidine (I) itself, and of its dipeptide, histidylhistidine (II). For purposes of comparison, it was decided to study analogous equilibria of related compounds of glycylglycine (III), and of histamine (IV). The Cu(II) ion was chosen because of its importance in biological systems, as well as its strong coordination tendencies.

A search of the literature revealed that a limited amount of work has been reported on the metal com-



plexes of the dipeptide, histidylhistidine. Photaki, *et al.*,<sup>3</sup> have observed that in the titration of an equimolar

(1) Taken in part from a thesis submitted by M. A. Doran to the faculty of Clark University in partial fulfillment of the requirements for the Master of Arts degree, June, 1958.

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(3) I. Photaki, D. Schaefele, S. Fallab, and H. Erlenmeyer, *Helv. Chim. Acta*, **40**, 187 (1957).