PLATE I

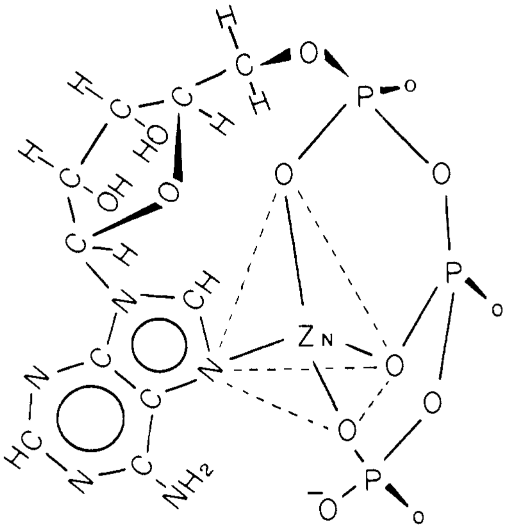
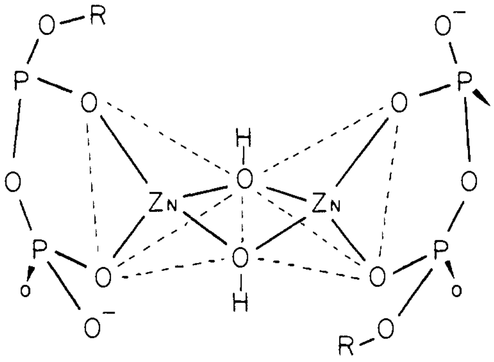


PLATE II



R = ADENOSINE RESIDUE

Similar reasoning would seem to apply to the analogous Zn(II) complexes, although the corresponding Zn(II) complex of ATP does not form a binuclear species. The Zn(II)-ADP chelate, like the Zn(II)-ATP chelate, seems to have enough stability to keep the metal ion from precipitating in the weakly basic pH range, but unlike the latter system, the stability apparently is not enough to prevent hydrolysis and dimerization reactions. This behavior of the zinc(II)-ADP chelate at high pH may be interpreted on the basis of the difference in the donor capacity of ADP and ATP with octahedral and tetrahedral models of the hydrated metal ions. With the tetrahedral zinc(II) ion, ADP and ATP seem to give terdentate and quadridentate structures, respectively, in which the nitrogen at position 7 of the purine ring may take part in metal coördination by folding of the ligand molecule. A model of such a structure for the zinc(II)-ATP chelate is illustrated in Plate I. The additional stability that one would expect from such a quadridentate Zn(II)-ATP chelate correlates with the observed lack of hydrolysis at higher pH.[3]

With respect to the relative dimerization tendencies of Cu(II)-ADP and Zn(II)-ADP chelates, the dimerization constant of Cu(II)-ADP is slightly higher. The small difference may be due to a number of factors, such as the difference in the stereochemistry of the two ions, square planar copper being more favorable for dimer formation than tetrahedral zinc, as well as the fact that Cu(II) generally has stronger coördinating tendencies than does Zn(II). The probable structure of the Zn(II)-ADP chelate dimer is shown in Plate II.

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

Influence of Metal Ions and of Metal Complexes on the Hydrolysis of Salicyl Phosphate[1]

BY ROBERT HOFSTETTER,[2a] YUKITO MURAKAMI,[2b] GEORGE MONT[2c] AND ARTHUR E. MARTELL[2d]

RECEIVED NOVEMBER 30, 1961

The first order hydrolysis of salicyl phosphate was studied at 30.3° at 0.10 *M* ionic strength in the presence of, and in the absence of various salts and metal chelate compounds. The order of increasing catalytic activity for metal salts is Cu(II) < UO_2(VI) < VO(IV) < ZrO(IV), Fe(III), while salts of Ni(II), Co(II), Zn(II) and Cd(II) were found to be inactive. In general it was found that the reaction rates in the presence of metal chelates are considerably lower than the rates for the corresponding aquo metal ions. In the absence of metal ions, the variation of rate of hydrolysis with hydrogen ion concentration shows first order dependence on the individual ionic species of the substrate.

Introduction

Earlier work in these Laboratories on the catalytic effects of metal ions and of metal chelates on solvolysis reactions[3,4] led to studies of the influence of metal compounds on solvolysis of a variety of esters. Since it was found that the hydrolysis of salicyl acetate is not metal-catalyzed, the discovery that salicyl phosphate hydrolysis is metal-catalyzed seemed worthy of detailed investigation. In this paper are reported our studies on the first order hydrolysis of salicyl phosphate under conditions of varying *p*H and in the presence of various metal salts and metal chelate compounds.

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[1] This investigation was supported by a grant from the Esso Education Foundation, Linden, New Jersey.

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[3] R. C. Courtney, R. L. Gustafson, S. J. Westerback, H. Hyytiainen, S. C. Chaberek and A. E. Martell, *J. Am. Chem. Soc.*, **79**, 3030 (1957).

[4] A. E. Martell, R. L. Gustafson and S. C. Chaberek, "Metal Chelate Compounds in Homogeneous Aqueous Catalysis." in *Advances in Catalysis and Related Subjects*, **9** (1957).

Previous work[5-7] on the hydrolysis of salicyl phosphate in the absence of metal ions has described *p*H dependence and established the probability of the intramolecular mechanism involving nucleophilic attack of the carboxyl group on the phosphate ester linkage. The catalysis of this reaction by metal ions, however, has not been reported previously.

Experimental

Materials.—The metal salts used in this investigation were ACS Reagent grade nitrates, with the exception of that of Ce(III), which was prepared from the pure oxide, purchased from Matheson, Coleman and Bell Co., East Rutherford, New Jersey. The metal nitrates were employed in the form of 0.10 *M* stock solutions.

Salicyl phosphate was obtained as a pure sample from the California Foundation for Biochemical Research at Los Angeles. Its analysis corresponded closely to the theoretical value.

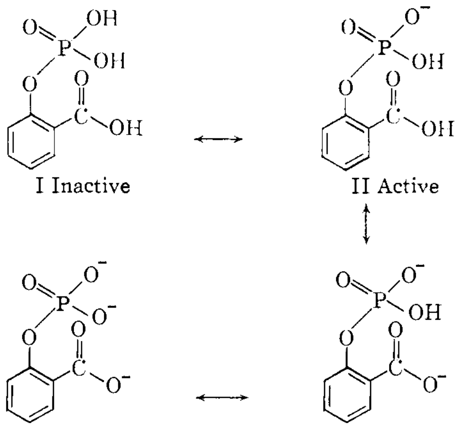
The ligands used in the metal chelate catalysis studies, salicylic acid (SAL), ethylenediamine (EN), N,N'-dimethyl ethylenediamine (DMEN), N-hydroxyethylethylenediamine (HEN), N,N'-dihydroxyethylethylenediamine (DHEN), N-hydroxyethyliminodiacetic acid (HIMDA), ethylenediaminetetraacetic acid (EDTA), N-hydroxyethylethylenediaminetriacetic acid (HEDTA), disodium pyrocatechol-3,5-disulfonate (PDS), disodium 1,8-dihydroxynaphthalene-3,5-disulfonate (DNS) and citric acid (CIT), were obtained and handled in the same manner as is described in previous publications.[8,9]

Potentiometric Measurements.—The dissociation constants of salicyl phosphate at 30° were measured potentiometrically by the standard method and apparatus described previously,[8] with the exception that the data for the intermediate *p*H region of salicyl phosphate were obtained by rapid titrations of a number of samples to the various *p*H regions of interest. In this way the effect of slight initial hydrolysis of the ester prior to the equilibrium measurements was minimized.

Kinetic Studies.—Kinetic runs were carried out at 30° in the standard potentiometric apparatus previously described,[3] the rate of reaction being determined by frequent withdrawal of samples for analysis of orthophosphate by the method of Chanley and co-workers.[5] It was found that an automatic titrator could not be used for rate measurements in the manner formerly used for the hydrolysis of Sarin[3]; however, in this case the Beckman automatic titrator (Model K) was used to keep the hydrogen ion concentration constant during hydrolysis studies. The resulting elimination of the necessity to use buffers to control *p*H greatly simplified the system under investigation, since most buffers have specific effects on hydrolysis rates and frequently bind metal ions quite strongly.

Results

Salicyl Phosphate Hydrolysis.—The rates of hydrolysis of salicyl phosphate as a function of hydrogen ion concentration in the absence of metal ions was reinvestigated as a basis for comparison with the metal-ion and metal-chelate catalyzed reactions. The reactions were found to be first order with respect to salicyl phosphate concentration, and, as reported previously,[5] the plot of rate *vs.* hydrogen ion concentration was found to increase sharply with increase in hydrogen ion concentration, with a maximum at $-\log[H^+] = 5.10$. At higher *p*H the rate decreased rapidly to very low values. This variation may be accounted for, if the rate is considered to be much higher for the mono- and di-ionic forms of salicyl phosphate than for either the un-ionized or fully ionized ester, as is indicated by the equilibria


I Inactive

II Active

III Active

IV Inactive

If one assumes that II and III are the only forms that have significant rates of hydrolysis, the observed rate is related to the specific rate constants of the mono- and di-ionic species by the relationship $k_{obs} = k_1X_{Sp^-} + k_2X_{Sp^{2-}}$, where X represents the corresponding fractional values of the total salicyl phosphate species present. The dissociation constants of salicyl phosphate, determined under the conditions employed in these reactions ($pK_2 = 3.72$; $pK_3 = 6.505$), were then used to calculate the values of X_{Sp^-} and $X_{Sp^{2-}}$ as a function of *p*H, and the values of k_1 and of k_2 were determined graphically. An analysis of the kinetic behavior of salicyl phosphate as a function of hydrogen ion concentration is given in Table I. A plot of the data in the right-hand columns of Table I would give a typical "bell-shaped curve" of the type usually observed for intramolecular nucleophilic (intramolecular base-catalyzed) reactions involving a rate-determining rearrangement of the reaction molecule or ion. In this case the bell-shaped curve is unsymmetrical as the result of the fact that there are two reacting species with different rates. In the absence of interfering ionization reactions, a single reactive species (or two or more species with the same activities) would give a symmetrical rate profile.

The relative rates of mono- and di-anionic species may be understood on the basis of the ionic species present in solution as a function of *p*H. There can be little doubt that the monoanionic form is principally structure II, with a carboxyl group, while the di-ionic form has a negative carboxylate group (III). Since the carboxylate group has considerably higher nucleophilic activity than does the carboxyl group, the higher value of $k_{Sp^{2-}}$ would, therefore, seem reasonable.

Catalysis by Metal Salts.—The rate of hydrolysis of salicyl phosphate was measured at various *p*H values in the presence of equivalent concentrations of various metal salts. The instances in which positive catalysis was observed are listed in Table II. Since the *p*H values employed are not strictly parallel, a precise comparison of relative catalytic

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

(6) J. D. Chanley and E. M. Gindler, *ibid.*, **75**, 4035 (1953).

(7) J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955).

(8) A. E. Martell, S. Chaberek, R. C. Courtney, S. Westerback and H. Hyytiainen, *ibid.*, **79**, 3036 (1957).

(9) R. C. Courtney, R. Gustafson, S. Chaberek and A. E. Martell, *ibid.*, **80**, 2121 (1958).

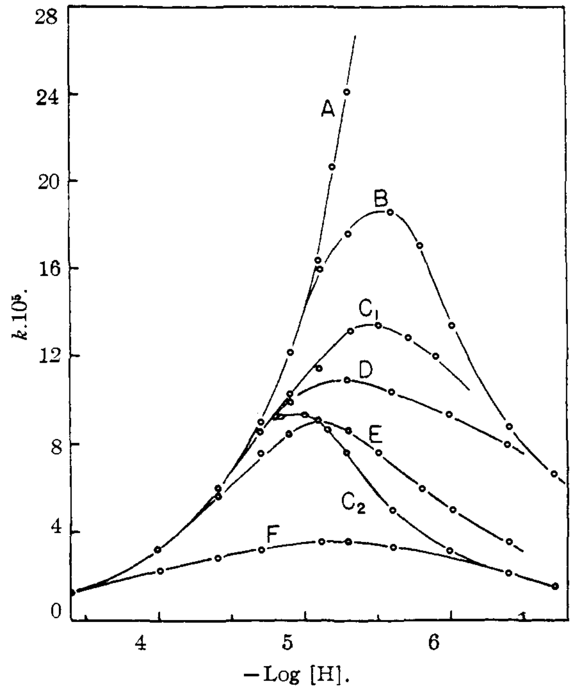

Fig. 1.—Rate profiles for 1.00 × 10^{-3} *M* salicyl phosphate hydrolysis in the presence of 1.00 × 10^{-3} *M* Cu(II) nitrate, 0.100 *M* KNO_3, and the following concentrations of ligands: A, no ligand; B, 1.00 × 10^{-3} *M* dimethylethylenediamine; C_1, 1.00 × 10^{-3} *M* ethylenediamine; C_2, 2.00 × 10^{-3} *M* ethylenediamine; D, 1.00 × 10^{-3} *M* hydroxyethylethylenediamine; E, 1.00 × 10^{-3} *M* dihydroxyethylethylenediamine; F, no Cu(II) salt or ligand.

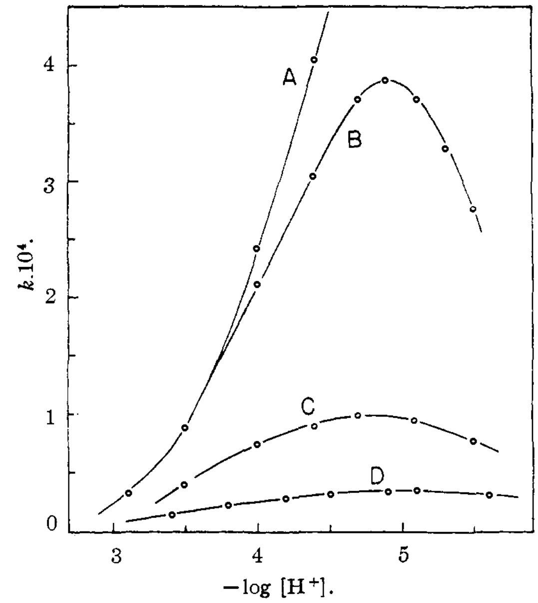

Fig. 2.—Rate profiles for the hydrolysis of 1.00 × 10^{-3} *M* salicyl phosphate, 0.100 *M* KNO_3, 1.00 × 10^{-3} *M* vanadyl ion and the following ligand concentrations: A, no ligand, B, 1.00 × 10^{-3} *M* salicylic acid; C, 1.00 × 10^{-3} *M* hydroxyethyliminodiacetic acid; D, no metal ion or ligand.

activities of the metal ions investigated is not possible from the data on hand. If one takes into account the rapid increase of catalytic activity with *p*H, as is illustrated in Figs. 1 and 2 for Cu(II), and VO(II) salts, respectively, it can be seen that the hydrolyzed polynuclear form of Zr(IV) seems to be much more active than the other metal species listed in Table II. Of the remaining metal salts, it is seen that the order of activity is roughly: VO(IV) > UO_2(VI) > Cu(II). The catalytic activity of Fe(III) was measured at a very low *p*H, so that it cannot be compared very well with the other metal ions. Because of the strong *p*H dependence of these metal ion-catalyzed solvolysis reactions, however, it appears that the catalysis by the Fe(III) ion may be of the order of magnitude of that of ZrO(IV).

TABLE I

CORRELATION OF HYDROLYSIS RATES WITH CONCENTRATIONS OF IONIC FORMS OF SALICYL PHOSPHATE (Sp)

	Mole fraction			Rate constant, sec.$^{-1}$ × 10^5	
−log [H⁺]	Sp^-	Sp^{-2}	Sp^{-3}	Measd.	Calcd.[a]
6.60		0.446	0.554	1.52	1.65
6.50		.502	.498	1.62	1.86
6.20		.670	.330	2.26	2.48
6.00		.763	.237	2.66	2.82
5.80		.830	.170	2.84	3.07
5.60		.890	.110	3.26	3.29
5.10	0.038	.926	.072	3.46	3.44
4.90	.060	.917	.036	3.46	3.42
4.50	.144	.854	.003	3.20	3.22
4.20	.248	.752		2.81	2.89
3.90	.398	.602		2.46	2.41
3.80	.454	.546		2.22	2.22
3.70	.511	.489		2.12	2.04
3.50	.623	.377		1.70	1.67
3.40	.676	.324		1.50	1.50
3.20	.767	.233		1.20	1.20
3.00	.840	.160		0.99	0.97

[a] $k_{Sp^-} = 4.5 \times 10^{-6}$; $k_{Sp^{2-}} = 3.70 \times 10^{-5}$.

TABLE II

CATALYTIC EFFECTS OF METAL SALTS

$t = 0°$; $\mu = 0.10$ *M* (KNO_3)

Metal ions[a-c]	−log [H⁺]	$t_{1/2}$ (min.)
None	3.4	768
	5.1	334
Cu(II)	3.4	768
	5.1	48
Fe(III)	2.2	~165
VO(IV)	3.3	130
	4.5	21
ZrO(IV)	3.3	~ 60
UO_2(VI)	3.3	~200

[a] No effects with Co(II), Ni(II), Cd(II) and MoO_2(VI). [b] Precipitates obtained with Ce(III) and Th(IV). [c] 1.0 × 10^{-3} *M* concentrations of metal ions and substrate.

The variation of Cu(II) and of VO(IV) catalysis as a function of *p*H is illustrated in Figs. 1 and 2. Although the curves cannot be extended to high *p*H because of extensive metal ion hydrolysis above $-\log[H^+] = 5$ for Cu(II) and $-\log[H^+] = 4.5$ for VO(IV), the behavior of salicyl phosphate seems to be entirely different in the presence of these metal ions. It would be of interest, but of course not possible, to determine if a maximum would exist at high *p*H to give a rate profile similar to that of salicyl phosphate. (The pronounced maximum for the latter is not readily apparent in Figs. 1 and 2 because of the expansion of the scale necessitated by the increased rates observed in the presence of metal ions and metal chelates.)

All of the catalytic rates described above and listed in Table II were measured at 1.0×10^{-3} M concentration of catalyst and of salicyl phosphate. The reactions were all found to be first order in substrate concentration under conditions which maintained constant catalyst concentration. In the case of Cu(II), however, the concentration was varied from 1.0×10^{-4} to 2.0×10^{-3} M at constant salicyl phosphate concentration. The results of these runs indicate first order behavior over the whole range of catalyst concentration. If the variation of the first order rate constants, listed in Table III, are compared with the corresponding catalyst concentrations, it is readily seen that the relationship is not a linear one. A plot of $k_{\text{obsd.}}$ *vs.* $[Cu^{2+}]$ would show a saturation effect, with decreasing slope at higher concentrations. With the data on hand, it is not possible to show whether this effect is due to a change in the nature of the catalyst or whether it is due to a more complicated cause, such as a change in the mechanism of the reaction.

TABLE III

VARIATION OF REACTION RATE WITH Cu(II) CONCENTRATION

(t = 30°; $-\log[H^+]$ = 5.1; salicyl phosphate = 1.0×10^{-3} M)

Cu^{2+}, $M \times 10^3$	$k_{\text{obsd.}}$, sec.$^{-1} \times 10^5$
0.10	6.5
.25	11.2
.50	17.6
.75	21.8
1.0	24.8
1.25	27.5
2.0	32.1

Catalysis by Metal Chelates.—The variation of the observed rate constant as a function of pH in the presence of Cu(II) chelates is illustrated in Fig. 1. It is noted that all four Cu(II) chelates again show an increase in the rate of reaction, as pH is increased, to a maximum value, followed by a decrease as the pH is further increased in the alkaline range. Thus the rate profiles are similar to that of the substrate in the absence of metal ions but with much higher maxima. On the other hand, the catalytic effects of the metal chelate systems are always equal to or lower than that of the free metal ion.

The rate profiles of the vanadyl ion and of vanadyl chelates, illustrated in Fig. 2, are similar to those of the analogous Cu(II) systems, with the exception that the observed catalytic effects are considerably greater for the vanadyl compounds.

Nature of Metal Ion.—The results of a study of the catalytic effects of a wide variety of metal chelates on salicyl phosphate hydrolysis at the pH (5.1) of the maximum spontaneous rate, and at other pH values, are given in Table IV. The metal chelates which showed no catalytic activity are not listed. Thus various chelates of Ni(II), Co(II), Cd(II) and MoO_2(VI) were found not to influence the rate of hydrolysis of salicyl phosphate. It is interesting that complexes of oxo metal ions such as ZrO(IV), UO_2(VI) and VO(IV) have higher catalytic reactivity than the complexes of a highly-charged metal ion such as Th(IV). In general, if the oxo ions are compared and if the effects of the divalent ions are compared, the metal ions and complexes that would be expected to interact strongly with the substrate seem to show considerable activity.

Discussion

The fact that the chelate and free metal ion curves coincide at low pH, where the chelates are highly dissociated, indicates that the catalysis is due to the free metal ion in this range. In the region near and above the maxima of the chelates, the effect is not so simple, because of the presence of a number of species, such as the chelates with 1:1 and 1:2 molar ratios of metal ion to ligand, and possibly some free metal ion as well as hydrolytic forms of the free metal ion and of the chelate. It is possible that mixed chelates consisting of the metal ion, the substrate and one of the ligands are also formed. Further elucidation of these systems would require careful and detailed equilibrium and kinetic studies under conditions where ratios and concentrations of all species are varied. Such

TABLE IV

CATALYTIC EFFECTS OF METAL CHELATES ON SALICYL PHOSPHATE HYDROLYSIS[a]

Ligand	Cu(II)		Th(IV)		VO(IV)		ZrO(IV)		UO_2(IV)	
	$-\log[H^+]$	$t_{1/2}$	$-\log[H^+]$	$t_{1/2}$	$-\log[H^+]$	$t_{1/2}$	$-\log[H^+]$	$t_{1/2}$	$-\log[H^+]$	$t_{1/2}$
SAL	5.1	48			4.5	31				
EN	5.1	88			3.0	203				
	3.4	768								
DMEN	3.4	697								
	5.1	65								
HEN	3.8	330			3.0	241				
	5.1	104								
DHEN	3.8	327			3.3	292				
	5.1	132			4.5	116				
HIMDA			5.1[b]	60	5.1	~150	5.1	~150		(p)[c]
EDTA	5.1	n.e.[c]	5.1	n.e.	5.1	n.e.	5.1	~100 (t)[c]	5.1	n.e.
HEDTA	5.1	n.e.	5.1	n.e.	5.1	n.e.	5.1	~140 (t)	5.1	n.e.
PDS[d]			5.1	140 (t)	5.1	290	5.1	~230	5.1	n.e.
DNS[e]			5.1	70 (t)	5.1	130			5.1	Very fast (p)
CIT			5.1[b]	n.e.	5.1	n.e.	5.1	~200	5.1	~200

[a] Conditions: μ = 0.10 (KNO_3); t = 30.0°, salicyl phosphate 0.10 M; $t_{1/2}$ in minutes; ratio of ligand to metal = 1:1 except where otherwise specified. [b] 2:1 ratio. [c] p = precipitate; t = turbidity; n.e. = no effect. [d] For 1:1 Fe(III) chelate at pH 5.1, $t_{1/2}$ = 578 minutes. [e] For 1:1 Fe(III) chelate at pH 5.1, $t_{1/2}$ = 678 minutes.

studies are now underway in these Laboratories, and it is hoped to describe the results in a later communication.

Mechanistic Considerations.—On the basis of the data available in Fig. 1, it is seen that the catalytic activities of the metal chelate systems decrease with increasing stability. Thus, it is quite possible that the free metal ion is the most important catalytically active species even at high *p*H. The observed variation with the stability would, therefore, be due to the lowering of the concentrations of free metal ion in equilibrium with the chelate, as the *p*H is raised, and as the stability of the chelate is increased. With this type of behavior the main function of the chelating agent would be to prevent the metal ion from precipitating and thus maintain a homogeneous system in which it is possible to make measurements.

Since most of the chelates formed have uncoördinated positions on the metal ion, it is possible that they also function as Lewis acids and have, therefore, some residual catalytic activity, lower than that of the aquo Cu(II) ion, but sufficient to influence the rate.

The fact that the catalytic effect of the 2:1 ethylenediamine–Cu(II) system rapidly decreased to the spontaneous (metal ion-free) rate shows that the Cu(II) ion must not be fully coördinated (tetracoördinate) in order to have catalytic activity. All of the other chelates, which retain considerable activity even at high *p*H, have uncoördinated positions in the metal ion. It is seen that the results presented in this paper, therefore, are in accord with the reaction mechanisms of Plates I–II.

It is interesting to note that the reaction mechanisms outlined above would predict somewhat different paths for the metal-free and metal-catalyzed systems. The monoprotonated form III may be considered analogous to the complex VI in which the metal ion is bound to the phosphate group, with no protons present on either functional group. On the other hand, the observed reaction of the diprotonated form may be visualized as occurring through a rearrangement of the proton (to give IIb), since the neutral carboxyl group should have very little nucleophilic activity. There is no counterpart for species IIb with the metal ion bound to the substrate, since a rearrangement of the proton to the phosphate group would tend to displace the metal ion. Thus, one would predict that a metal ion that greatly accelerates the rate at low *p*H would react through the formation of a non-protonated species.

It is of further interest to note that a chelate compound involving the combination of the phosphate and carboxylate groups of the substrate with the metal ion would not be a pathway for the reaction, since such a combination would tie up the reacting groups in a way that would be sterically unfavorable for the reaction and would decrease the donor activity of the carboxylate group. There is also the possibility of the combi-

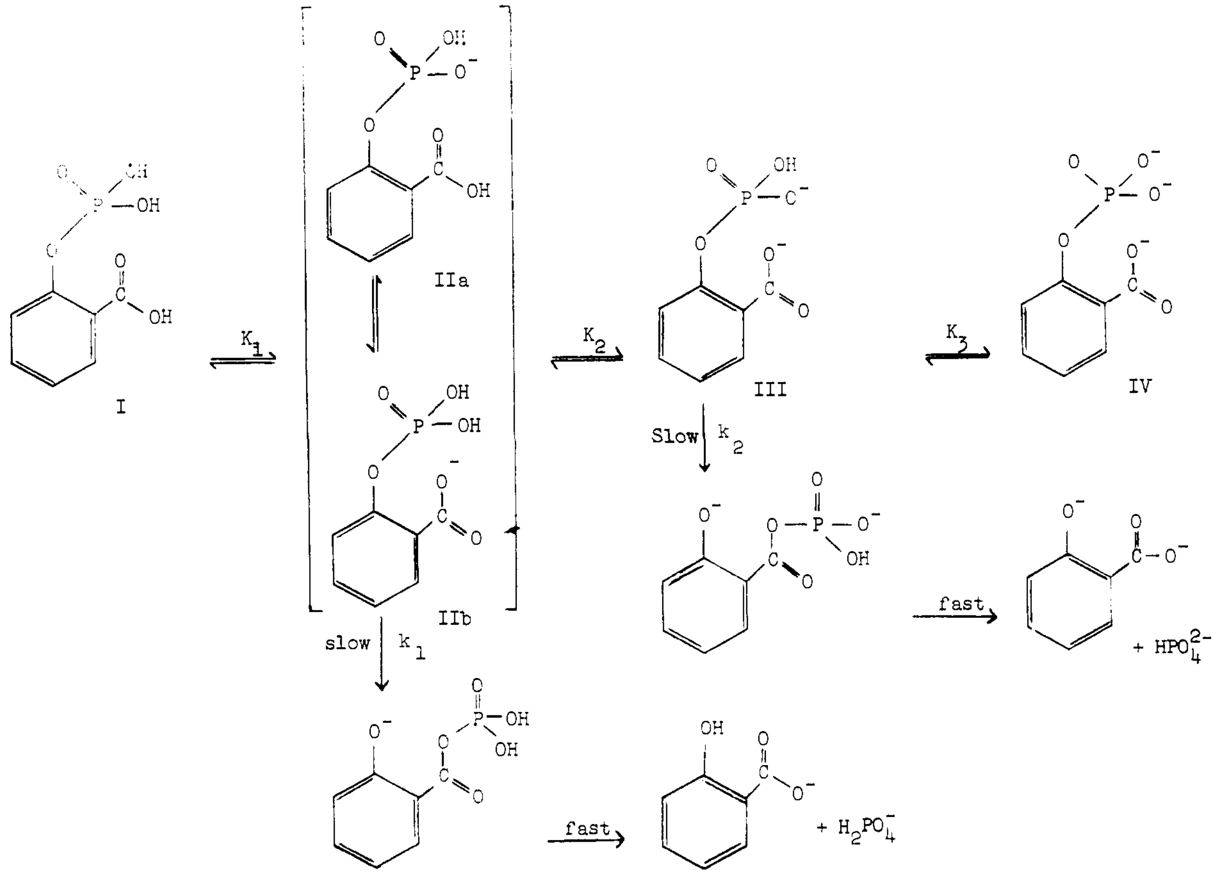

PLATE I

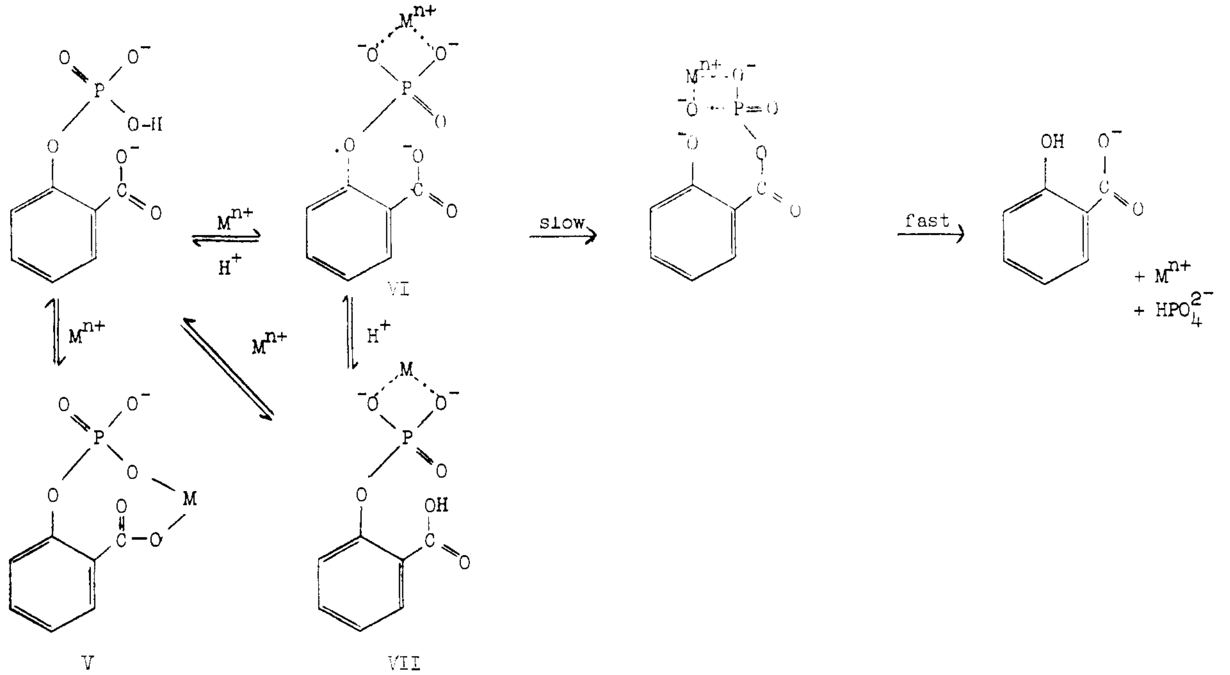

PLATE II

nation of a metal ion with the substrate in two different ways, as indicated above, to produce an unreactive species competing with the reactive coördination intermediate.

Effect of Metal Ion.—One would not expect direct correlation between the half times listed in Table IV and the stabilities of analogous chelates of a series of metal ions, since the interactions with the ligand as shown in formulas VI and VII would depend on a balance between various factors such as the residual coördinating tendency of the metal ion in the catalytic metal chelate, the tendencies of the metal ion and the metal chelate to hydrolyze and the relative tendencies of metal ions and metal chelates to form coördination compounds having linkages to the substrate of the type illustrated in V.

Detailed studies of these various factors are now being undertaken and will be reported in a subsequent communication.

[CONTRIBUTION FROM THE MELLON INSTITUTE, 4400 FIFTH AVENUE, PITTSBURGH 13, PA.]

Transition Metal Complexes of Secondary Phosphines. I. Palladium(II) and Diphenylphosphine

BY R. G. HAYTER

RECEIVED DECEMBER 4, 1961

The reactions of diphenylphosphine with palladium(II) halides have yielded four types of complexes, whose structures and reactions have been investigated. The binuclear complexes $[PdX(PPh_2)(HPPh_2)]_2$ (X = Cl, Br, I, SCN) are shown to have a phosphorus-bridged structure and the factors affecting the formation and stability of the bridge are discussed. The Debye-Hückel-Onsager equation has been used to show that $[Pd_2(PPh_2)_2(chelate)_2]X_2$ (chelate = $C_2H_4(PPh_2)_2$, 1,10-phenanthroline; X = Cl, ClO_4, picrate) behave as uni-bivalent electrolytes in methanol.

Introduction

This study is part of a general investigation of the transition metal complexes formed by secondary phosphines. Previous work in this field by Issleib and his co-workers[1] has shown that R_2PH (R = C_2H_5, C_6H_{11}, C_6H_5) forms stable complexes, in some cases of unusual types, with the halides of iron, cobalt, nickel, chromium and palladium. However, the properties, reactions and structures of these complexes were not investigated in detail.

Our aim has been to study the effect of the P–H hydrogen on complex formation, using the corresponding tertiary phosphine complexes for comparison. The lower steric requirements of the secondary phosphine might be expected to lead to changes in stoichiometry or structure. Also, in complexes of the type $[MX_n(HPR_2)_n]$ (where M = metal and X = acid radical) there exists the interesting possibility of inter- or intramolecular elimination of acid to give complexes derived from the anionic ligand PR_2^-. Thiols readily undergo reactions of this type to give either mer-

[1] (a) **K. Issleib** and **G. Doll**, *Z. anorg. u. allgem. Chem.*, **305**, 1 (1960); (b) **K. Issleib** and **E. Wenschuh**, *ibid.*, **305**, 15 (1960).