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

A Kinetic Study of the Copper(II) Chelate-catalyzed Hydrolysis of Isopropyl Methylphosphonofluoridate (Sarin)[1]

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The hydrolysis of isopropyl methylphosphonofluoridate (Sarin) has been investigated in the presence of and in the absence of six copper(II)-diamine catalysts over a range of *p*H and concentration. The total catalytic activity of the various metal chelate systems decreases in the order: Cu(II)-N,N,N',N'-tetramethylethylenediamine > Cu(II)-N,N'-dimethylethylenediamine > Cu(II)-α,α'-dipyridyl > Cu(II)-1,10-phenanthroline > Cu(II)-N-hydroxyethylethylenediamine > Cu(II)-N,N'-dihydroxyethylethylenediamine. The dimers of these chelate compounds are shown to possess negligible catalytic activity, and specific rate constants are calculated for the diaquo and dihydroxo forms. Enthalpies and entropies of activation are reported, and a mechanism involving interaction between Sarin, the diaquo Cu(II) chelate, and hydroxyl ion is suggested.

The metal chelate-catalyzed hydrolysis of isopropyl methylphosphonofluoridate (Sarin) has been reported by Courtney, *et al.*,[2] who examined various metal ions with a wide variety of ligands. It was shown that, in general, copper(II) chelates of diamines have the highest catalytic activity, although certain chelates of VO(IV), ZrO(IV) and MoO_2(VI) are also quite active. It is the purpose of this investigation to study in detail the catalytic effects of six structurally-related copper(II) chelates on the hydrolysis of Sarin. On the basis of previous work in this Laboratory, the ligands chosen are N,N'-dimethylethylenediamine (DMEN), N,N,N',N'-tetramethylethylenediamine (TMEN), N-hydroxyethylethylenediamine (HEN), N,N'-dihydroxyethylethylenediamine (2-HEN), α,α'-dipyridyl (DIPY) and 1, 10-phenanthroline (PHEN).

It should be noted that a related investigation has been reported by Wagner-Jauregg, *et al.*,[3] who studied copper(II) chelates of amino acids and amines as catalysts for the hydrolysis of diisopropylphosphorofluoridate (DFP), and have suggested a mechanism for the reaction. More recently Fowkes, *et al.*,[4] have described the catalytic hydrolysis of DFP in the presence of Cu(II)-dipyridyl chelates.

Experimental

Reagents.—A sample of Sarin was supplied through the courtesy of the Army Chemical Center. The accompanying analysis showed that the sample contained 13.13% fluorine and 22.06% phosphorus, as compared to theoretical values of 13.56 and 22.12%, respectively. A seven-gram sample of Sarin was diluted to one liter with spectro grade anhydrous isopropyl alcohol to produce a 0.05 molar stock solution.

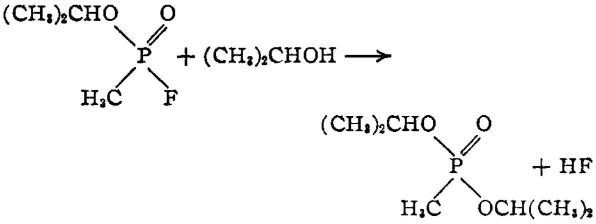
Standardization of this solution was carried out with a Beckman automatic titrator in two ways: 1, by neutralization with standard base of the acid produced when an aliquot of Sarin was introduced into a 0.1 *M* potassium nitrate solution at *p*H 10.0; and 2, neutralization of the acid produced by catalytic hydrolysis in the presence of 1:1 dipyridyl–Cu(II) at *p*H 7.0. In the former case, hydrolysis was complete after approximately forty minutes, while in the latter case, no further uptake of base was recorded after sixty minutes when approximately a five to one molar ratio of Sarin to copper dipyridyl was used.

The cupric nitrate and ligand solutions were prepared and standardized as outlined in a previous publication.[2] In all cases copper(II) chelate solutions containing equimolar amounts of metal ion and ligand were employed.

Kinetic Measurements.—The liberation of hydrogen ions during the course of the hydrolysis of Sarin was measured as a function of time with the aid of a Beckman automatic titrator, which maintained the experimental solution at constant hydrogen ion concentration by automatic addition of standard potassium hydroxide solution from a microburet. The reaction was carried out in a multinecked flask similar to that used in the potentiometric titrations described previously, except that an extra delivery tube was provided for the Sarin solution. The reaction vessel and titrator head were mounted in a hood fitted with a high capacity blower, the flask being immersed in a constant temperature bath which was maintained at 0.3, 25.0 or 42.5°.

In a typical run an aliquot of copper chelate solution was introduced into the titration cell and the volume was adjusted to 150 ml. with potassium nitrate solution and distilled water so that the final ionic strength was approximately 0.10. Presaturated nitrogen was bubbled through the solution to exclude carbon dioxide and the hydrogen ion concentration was adjusted as desired by means of the automatic titrator unit. An anticipation setting of 9 was used in all of the experiments. An aliquot of Sarin (200 micromoles) was then added by means of an automatic buret. Time measurements were begun at the point at which half of the Sarin solution had been added. Readings of time *vs.* corresponding standard base delivered were recorded over the course of the titration. A plot of log $a/(a-x)$ *vs.* time (where a is the amount of base required for complete hydrolysis and x is the amount of base added at time t) gave a straight line in nearly all cases studied.

A small amount of free acid was present in the stock Sarin solution, probably as a result of the very slow reaction



Titration showed the amount of acid thus formed to be present in a concentration of 1.5×10^{-3} *M*. Corrections for free acidity were made by adding an equivalent amount of base to the reaction mixture before introduction of the Sarin.

Catalytic hydrolysis of Sarin in the presence of the copper (II) chelates of HEN, 2-HEN, DMEN, TMEN, DIPY and PHEN was carried out at $-\log\,[H^+]$ values of 6.90, 7.40, 7.90, 8.40 and 8.90 with several concentrations of catalyst at 25.0°. Several experiments were also carried out at 0.3° and 42.5° with each of the chelates mentioned above. The kinetics of the reaction of Sarin with hydroxyl ion was determined at each of the three temperatures, and the catalytic effect of small amounts of $Cu(NO_3)_2$ was investigated in the $-\log[H^+]$ range 5.4–7.9 at 25.0°.

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[1] This investigation was supported by a research grant from the National Institute of Neurological Diseases and Blindness, Public Health Service.

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

[3] T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens and R. Proper, *ibid.*, **77**, 922 (1955).

[4] F. M. Fowkes, G. S. Ronay and L. B. Ryland, *J. Phys. Chem.*, **62**, 867 (1958).

Mathematical Treatment of Data.—Solution Equilibria.—The distribution of chelate species as a function of *p*H and total concentration was calculated as described in previous publications.[5,6] Values of the acid dissociation constants of the various ligands as well as values of the chelate formation constants have not been reported at 0.3° and $\mu = 0.10$. For the copper chelates of DMEN and TMEN such data are available at temperatures of 0° and 25° and $\mu = 0.50$.[7-9] Values of the various constants were estimated by assuming that the relative values of the equilibrium constants at ionic strength 0.1 are proportional to those reported at $\mu = 0.5$. Values for the HEN, 2-HEN, DIPY and PHEN systems were approximated in a similar way using for the constants at $\mu = 0.50$ the average values obtained for a large number of substituted diamine systems as studied by Basolo, *et al.*[7-10] It should be noted that precise values of chelate stability constants and dissociation constants of the ligands are not required, since the constants are merely used to correct the metal chelate concentrations for dissociation to the free metal ion. These corrections were small in most cases.

Kinetic Measurements.—First order kinetics were observed since the copper chelate and hydroxyl ion concentrations were maintained at constant values during the course of each hydrolysis experiment. First order rate constants, $k_{\text{obsd.}}$, were calculated according to the equation, $k_{\text{obsd.}} = 0.693/t_{1/2}$, where $t_{1/2}$ is the experimental half time.

Since hydroxyl ion also reacts with Sarin, experiments were carried out in the absence of a metal chelate catalyst. The measured rate of hydrolysis may be summarized by the relationship

$$k_{\text{obsd.}} = k_{\text{OH}}[\text{OH}^-] + c \qquad (1)$$

where k_{OH} is the rate constant assigned to the hydroxyl ion species, and c is a constant which corresponds to the spontaneous hydrolysis of Sarin in the solvent employed. According to this rate expression, the plot of $k_{\text{obsd.}}$ *vs.* $[\text{OH}^-]$ should give a straight line of slope k_{OH} and intercept c.

The possible catalytic metal species are: 1, the diaquo chelate, CuL^{2+}; 2, the monohydroxo chelate, Cu[OH]L^+; 3, the dihydroxo chelate, $\text{Cu[OH]}_2\text{L}$; 4, a binuclear diolated species, $(\text{Cu[OH]L})_2^{2+}$; and 5, the unbound or aquo copper (II) ion, Cu^{2+}. Since in the dimer, the copper(II) ions are shielded by two ligand molecules, it was reasoned that the dimer should have very low (*i.e.*, negligible) catalytic activity. On this basis the total observed rate would be written as

$$\begin{aligned} k_{\text{obsd.}} = {} & k_{\text{ML}}[\text{CuL}^{2+}][\text{OH}^-] + k_{\text{M[OH]L}}[\text{Cu[OH]L}^+] + \\ & + k'_{\text{M[OH]L}}[\text{Cu[OH]L}^+][\text{OH}^-] + \\ & k_{\text{M[OH]}_2\text{L}}[\text{Cu[OH]}_2\text{L}] + k_{\text{M}}[\text{Cu}^{2+}][\text{OH}^-] + \\ & k_{\text{OH}}[\text{OH}^-] + c \qquad (2)^{11} \end{aligned}$$

Since the concentration of the monohydroxo species is proportional to that of the diaquo chelate according to the equilibrium

$$\text{CuL}^{2+} \rightleftharpoons \text{Cu[OH]L}^+ + [\text{H}];\ K_{\text{M[OH]L}} = \frac{[\text{Cu[OH]L}^+][\text{H}^+]}{[\text{CuL}^{2+}]}$$

it is impossible to distinguish between the quantities $k_{\text{ML}}[\text{CuL}^{2+}][\text{OH}^-]$ and $k_{\text{M[OH]L}}[\text{Cu[OH]L}^+]$, where the former expression represents equilibrium combination of the diaquo chelate and substrate, followed by the rate determining reaction with the hydroxyl ion, and the latter represents hydrolysis caused by direct reaction of the monohydroxo chelate with a Sarin molecule. The first two terms on the right hand side of equation 2 may be combined to give the quantity

$$[\text{CuL}^{2+}][\text{OH}^-]\left(k_{\text{ML}} + \frac{k_{\text{M[OH]L}}K_{\text{M[OH]L}}}{K_{\text{w}}}\right)$$

or

$$[\text{CuL}^{2+}][\text{OH}^-]k_{\text{L}}$$

Here k_{L} is a rate constant which represents catalysis by the diaquo chelate and/or the monohydroxo compound. Similarly it is impossible to distinguish between the quantities $k'_{\text{M[OH]L}}[\text{Cu[OH]L}^+][\text{OH}^-]$ and $k_{\text{M[OH]}_2\text{L}}$ $[\text{Cu[OH]}_2\text{L}]$, and the third and fourth terms on the right side of the equation 2 may be combined to give

$$[\text{Cu[OH]}_2\text{L}\left(\frac{K_{\text{w}}k'_{\text{M[OH]L}}}{K_{\text{M[OH]}_2\text{L}}}\right) + k_{\text{M[OH]}_2\text{L}}$$

or

$$[\text{Cu[OH]}_2\text{L}]k_{\text{B}}$$

Equation 2 may thus be modified to give

$$\begin{aligned} k_{\text{obsd.}} = {} & k_{\text{L}}[\text{CuL}^{2+}][\text{OH}^-] + k_{\text{B}}[\text{Cu[OH]}_2\text{L}] + \\ & k_{\text{M}}[\text{Cu}^{2+}][\text{OH}^-] + k_{\text{OH}}[\text{OH}^-] + c \qquad (3) \end{aligned}$$

The "rate constant" k_{M} for the unchelated copper(II) species may be calculated in either of two ways: by separate measurements of the rate of Sarin hydrolysis in the presence of cupric nitrate or by the mathematical treatment of the data obtained in the copper chelate catalyzed reactions. At constant *p*H, the concentration of the dihydroxo chelate is directly proportional to the amount of diaquo species present, while the concentration of unbound cupric ion varies as the square root of the diaquo chelate concentration. Equation 3 may be written in the form

$$\begin{aligned} k_{\text{obsd.}}{}^* = {} & k_{\text{L}}\ [\text{CuL}^{2+}][\text{OH}^-] + k_{\text{B}}[\text{Cu[OH]}_2\text{L}] + \\ & k_{\text{M}}[\text{Cu}^{2+}][\text{OH}^-] \qquad (4) \end{aligned}$$

where $k_{\text{obsd.}}{}^* = k_{\text{obsd.}} - k_{\text{OH}}[\text{OH}^-] - c$.

However, since

$$[\text{Cu[OH]}_2\text{L} = \frac{K_{\text{M[OH]}_2\text{L}}[\text{CuL}^{2+}]}{[\text{H}^+]^2}$$

equation 4 may be written as

$$\frac{k_{\text{obsd.}}{}^*}{[\text{OH}^-]} = [\text{CuL}^{2+}\left(k_{\text{L}} + \frac{k_{\text{B}}K_{\text{M[OH]}_2\text{L}}}{[\text{H}^+]K_{\text{w}}}\right) + k_{\text{M}}[\text{Cu}^{2+}] \qquad (5\text{a})$$

where K_{w} is the ionization constant of water, or

$$\frac{k_{\text{obsd.}}{}^*}{[\text{CuL}^{2+}][\text{OH}^-]} = k' + k_{\text{M}}\frac{[\text{Cu}^{2+}]}{[\text{CuL}^{2+}]}\ (\text{at constant } p\text{H}) \qquad (5\text{b})$$

Hence a plot of $k_{\text{obsd.}}{}^*/[\text{CuL}^{2+}][\text{OH}^-]$ as ordinate *vs.* $[\text{Cu}^{2+}]/[\text{CuL}^{2+}]$ as abscissa with data obtained at constant *p*H, should give a straight line of slope k_{M}, provided that the relative concentrations of $\text{Cu(H}_2\text{O)}_4{}^{2+}$, $\text{Cu[OH](H}_2\text{O)}_3{}^{1+}$ and $(\text{Cu[OH](H}_2\text{O)}_2)_2{}^{2+}$ remain approximately constant. In the concentration range employed, a ten-fold change in the total concentration of metal chelate resulted in only a two to three fold change in the concentration of unchelated cupric ion, and linear plots corresponding to equation 5b were obtained in nearly all cases. In cases where the contribution of $k_{\text{B}}[\text{Cu[OH]}_2\text{A}]$ is small; *i.e.*, less than the experimental error of approximately 5%, equation 4 may be modified to give

$$\frac{k_{\text{obsd.}}{}^*}{[\text{Cu}^{2+}][\text{OH}^-]} = k_{\text{L}}\frac{[\text{CuL}^{2+}]}{[\text{Cu}^{2+}]} + k_{\text{M}} \qquad (6)$$

Equation 6 makes it possible to calculate k_{L} and k_{M} from data collected under varying *p*H conditions. Once the rate constant for the unchelated copper species has been determined, k_{L} and k_{B} may be calculated by a plot of the experimental data in accordance with the following modification of equation 4

$$\frac{k_{\text{obsd.}}{}^{**}}{[\text{CuL}^{2+}][\text{OH}^-]} = k_{\text{L}} + k_{\text{B}}\frac{K_{\text{M[OH]}_2\text{L}}}{[\text{H}^+]K_{\text{w}}} \qquad (7)$$

where $k_{\text{obsd.}}{}^{**} = k_{\text{obsd.}}{}^* - k_{\text{M}}[\text{Cu}^{2+}][\text{OH}^-] \qquad (7\text{a})$

The enthalpies of activation may be calculated according to the equation

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(5) R. C. Courtney, R. L. Gustafson, S. Chaberek, Jr., and A. E. Martell, *J. Am. Chem. Soc.*, **81**, 519 (1958).

(6) R. L. Gustafson and A. E. Martell, *ibid.*, **81**, 525 (1959).

(7) F. Basolo and R. K. Murmann, *ibid.*, **76**, 211 (1954).

(8) F. Basolo, R. K. Murmann and Y. T. Chen, *ibid.*, **75**, 1478 (1953).

(9) F. Basolo, R. K. Murmann and Y. T. Chen, *ibid.*, **76**, 956 (1959).

(10) F. Basolo and R. K. Murmann, *ibid.*, **74**, 5243 (1952).

(11) In equation 2, the first term on the right represents catalysis of hydroxide ion attack by the metal chelate (analogous to catalysis by the metal ion), while the second term represents a supposedly alternative mechanism for the same process. The third and fourth terms represent alternative processes for the additional catalytic effect found to occur at high *p*H, under conditions where the effects expressed by the remaining terms are not sufficient to account for the observed rates. Various combinations of these terms (with the exception of the third) have been described in previous papers.[2-4,13]

$$\Delta H^{\ddagger} = \frac{2.303\ RT_1T_2 \log (k_2T_1/k_1T_2)}{T_2 - T_1} \quad (8)$$

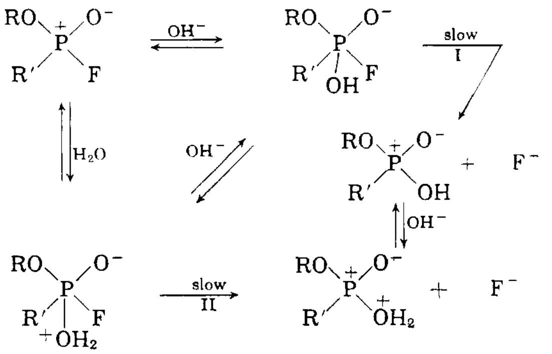
whereas the entropies of activation may be calculated by the relationship

$$\Delta S^{\ddagger} = 2.303\ R \log (kNh/RT) + \Delta H^{\ddagger}/T \quad (9)$$

In equation 8 k_1 and k_2 are the rate constants (k_L, k_B or k_{OH}) calculated at temperatures T_1 and T_2, respectively. The other terms have their usual meaning.

Results and Discussion

Interaction of Sarin with Hydroxyl Ion.—Before rate constants for the chelate catalyzed reaction may be calculated, it is necessary to know the contribution of hydroxyl ion to the total observed rate of the hydrolysis reaction. The experimental data obtained from hydrolysis experiments which were carried out at temperatures of 0.3°, 25.0° and 42.5° in the absence of copper(II) compounds are given in Table I. From the linear portion of each curve it was possible to calculate the rate constant k_{OH} and the solvent constant c at the various temperatures employed. The values thus obtained are shown in Table II. By the use of equation 8, a value for $\Delta H^{\ddagger}$ of 10.0 kcal./mole was obtained while $\Delta S^{\ddagger}$ has a value of −18.6 cal./mole deg. at 25.0° for the reaction of Sarin with hydroxyl ion. The scheme shown is consistent with our experimental results:



Reaction of a Sarin molecule with solvent or hydroxyl ion would result in the easier elimination of the fluoride ion. The saturation effect observed in the variation of rate constant with hydroxyl ion concentration is compatible with increasing importance of path I for the reaction in the absence of metal ions and metal complexes, as the pH is increased.

Catalytic Hydrolysis of Sarin with Cupric Nitrate.—The results of experiments in which low concentrations of cupric nitrate were allowed to react with Sarin in a 0.10 molar potassium nitrate solution at 25° are shown in Table III. It may be noticed that for any series of experiments at constant pH, there is a decrease in the ratio of $k_{\text{obsd.}}$* to $T_M[OH^-]$ with a corresponding increase in total copper species concentration, T_M. This is typical of the effect observed when polymeric metal species are formed, since the extent of polymerization increases with increasing total concentration. Berecki-Biedermann[12] has shown that the equilibrium constants for the hydrolysis reactions

$$Cu^{2+} + H_2O \rightleftarrows CuOH^+ + H^+$$

$$2Cu^{2+} + 2H_2O \rightleftarrows Cu[OH]_2Cu^{2+} + 2H^+$$

correspond to pK values of 8.0 and 10.6, respectively. An attempt was made to assign rate con-

TABLE I

RATES OF REACTION OF SARIN WITH HYDROXYL ION

$-\log [OH^-]$	$t_{1/2}$ (sec.)	$k_{\text{obsd.}}$ (sec.$^{-1}$)
$t = 0.3°$ $K_w = 1.88 \times 10^{-15}$		
5.03	13,300	5.20×10^{-5}
4.83	6,960	9.96×10^{-5}
4.63	5,640	1.23×10^{-4}
4.43	3,720	1.86×10^{-4}
4.23	2,580	2.69×10^{-4}
4.03	1,860	3.73×10^{-4}
3.68	1,020	6.79×10^{-4}
$t = 25.0°$ $K_w = 1.61 \times 10^{-14}$		
5.69	7,920	8.75×10^{-5}
5.49	5,940	1.17×10^{-4}
5.29	3,990	1.74×10^{-4}
5.09	2,960	2.34×10^{-4}
4.89	1,910	3.62×10^{-4}
4.69	1,370	5.07×10^{-4}
4.49	940	7.40×10^{-4}
4.29	800	8.68×10^{-4}
4.09	590	1.17×10^{-3}
3.89	330	2.10×10^{-3}
$t = 42.5°$ $K_w = 5.61 \times 10^{-14}$		
5.95	6,360	1.09×10^{-4}
5.75	4,140	1.67×10^{-4}
5.55	2,760	2.51×10^{-4}
5.35	2,010	3.45×10^{-4}
5.15	1,450	4.79×10^{-4}
4.95	750	9.24×10^{-4}

TABLE II

RATE CONSTANTS ASSIGNED TO THE REACTION OF HYDROXYL ION WITH SARIN

$\Delta H^{\ddagger}$ = 10.0 kcal./mole, $\Delta S^{\ddagger}$ = −18.6 cal./mole deg. at 25° and $\Delta F^{\ddagger}$ = 15.5 kcal./mole at 25°.

Temp., °C.	k_{OH} (l. mole^{-1} sec.$^{-1}$)	c (sec.$^{-1}$)
0.3	4.67	1.7×10^{-5}
25.0	2.37×10^{1}	5×10^{-5}
42.5	6.37×10^{1}	5×10^{-5}

TABLE III

CATALYTIC HYDROLYSIS OF SARIN BY COPPER(II) NITRATE

$t = 25.0°$ $\mu = 0.10$ (KNO_3)

$[OH^-]$, M	T_M, M	$k_{\text{obsd.}}$* $\times 10^4$ (sec.$^{-1}$)	$\frac{k_{\text{obsd.}}*}{T_M[OH^-]} \times 10^7$
4.04×10^{-9}	6.87×10^{-4}	1.60	5.8
4.04×10^{-9}	1.72×10^{-3}	3.98	5.7
4.04×10^{-9}	5.17×10^{-3}	10.0	4.8
1.28×10^{-8}	1.72×10^{-4}	1.32	6.0
1.28×10^{-8}	5.17×10^{-4}	3.46	5.2
1.28×10^{-8}	1.03×10^{-3}	6.6	5.0
4.04×10^{-8}	3.45×10^{-5}	0.68	4.9
4.04×10^{-8}	1.03×10^{-4}	2.27	5.5
4.04×10^{-8}	3.45×10^{-4}	7.2	5.2
1.28×10^{-7}	1.03×10^{-5}	0.57	4.3
1.28×10^{-7}	3.45×10^{-5}	2.16	4.9
1.28×10^{-7}	1.03×10^{-4}	5.0	3.8
1.28×10^{-7}	3.45×10^{-4}	10.5	2.4
4.04×10^{-7}	3.45×10^{-6}	0.45	3.2
4.04×10^{-7}	1.03×10^{-5}	1.36	3.3
4.04×10^{-7}	3.45×10^{-5}	3.55	2.6

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[12] C. Berecki-Biedermann, *Arkiv. Kemi*, **9**, 175 (1956).

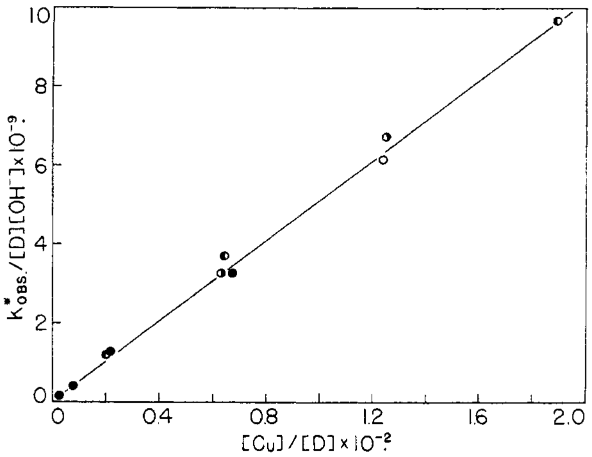


Fig. 1.—Graphical demonstration of relative catalytic activities of aquo Cu(II) ion and binuclear dihydroxo Cu(II) species in the catalysis of the hydrolysis of Sarin at 25° in 0.1 M KNO$_3$. Values of $-\log[H^+]$: ○, 5.40; ◑, 5.90; ◐, 6.40; ●, 6.90.

stants to the diaquo and dimeric copper(II) species on the basis of the kinetic data obtained at $-\log[H^+]$ values of 5.40–6.90. If it is assumed that the strength of $Cu[OH]^{1+}$ as a Lewis acid is negligible compared to that of Cu^{2+}, we may neglect the catalytic activity of the former species, and the rate equation for the hydrolysis of Sarin in the presence of cupric nitrate may be written as

$$k_{\mathrm{obsd.}}{}^* = k_M{}'\,[Cu^{2+}][OH^-] + k_{M[OH]}[Cu[OH]^+] + k_D[D][OH^-]$$

or

$$k_{\mathrm{obsd.}}{}^* = k_M[Cu^{2+}][OH^-] + k_D[D][OH^-]$$

where [D] represents the concentration of the dimeric species. Therefore, a plot of $k_{\mathrm{obsd.}}{}^*/[D][OH^-]$ as ordinate *vs.* [Cu]/[D] as abscissa should give a straight line with a slope equal to k_M and with an intercept equal to k_D. As may be seen in Fig. 1, an intercept of zero was obtained, indicating negligible catalytic activity of the dimer relative to that of the tetraaquo (and/or monohydroxo) copper(II) species. The value of $k_M = 5.1 \times 10^7$ sec.$^{-1}$ was used to determine the rate contribution of the unchelated copper species for the Cu(II)-HEN and Cu(II)-2-HEN systems at 25°. Values of k_M as determined from equations 5b or 6 for the DMEN, DIPY and PHEN systems were found to agree within 10–15% of the above value throughout the 6.9–8.9 pH range. Since the unchelated copper species usually account for about 10% of the total rate, such an error in the value of k_M introduces an error of less than 1–2% in the value of $k_{\mathrm{obsd.}}{}^{**}$.

Catalytic Hydrolysis of Sarin by Copper(II) Chelates.—The experimental results obtained on the catalytic hydrolysis of Sarin in the presence of copper(II) chelates are presented in Tables IV-VI, in which the experimental half times are given as a function of $-\log[H^+]$ and T_M. The relative overall catalytic activities of the various copper(II) chelates were found to be: TMEN > DMEN > DIPY > PHEN > HEN > 2-HEN. In general, it appears that the least stable chelates are the most active catalysts. If this were strictly true, the copper chelate of dipyridyl would possess the highest catalytic activity.

TABLE IV

CATALYTIC HYDROLYSIS OF SARIN WITH Cu(II) CHELATES

Sarin Concentration = 1.30×10^{-3} M; t = 25.0°; μ = 0.10(KNO$_3$)

Half times in seconds for various metal chelate concentrations

Ligand DMEN

$-\log[H^+]$	137 μ M/l.	54.7 μ M/l.	27.4 μ M/l.	13.7 μ M/l.
6.90	1160	2640	4500	7140
7.40	490	1010	1850	3000
7.90	270	470	850	1470
8.40	..	..	490	820
8.90	160	250	350	530

Ligand TMEN

$-\log[H^+]$	59.8 μ M/l.	20.3 μ M/l.	5.98 μ M/l.	2.99 μ M/l.
6.90	660	1060	4920	11040
7.40	310	680	2700	...
7.90	180	440	1500	2820
8.40	..	..	980	...
8.90	110	250	700	...

Ligand HEN

$-\log[H^+]$	762 μ M/l.	306 μ M/l.	153 μ M/l.	76.6 μ M/l.
6.90	1070	2240	4020	6420
7.40	590	1190	2010	3120
7.90	450	820	1340	2100
8.40	..	680	1090	1390
8.90	360	550	790	1000

Ligand 2-HEN

$-\log[H^+]$	1390 μ M/l.	700 μ M/l.	281 μ M/l.	140 μ M/l.
6.90	1090	1820	4080	6660
7.40	680	1070	2460	3780
7.90	530	830	1680	2700
8.40	..	730	1380	1920
8.90	410	630	970	1320

Ligand DIPY

$-\log[H^+]$	273 μ M/l.	136 μ M/l.	68.3 μ M/l.	27.3 μ M/l.
5.90	4440	..	..	..
6.40	..	2960	..	..
6.60	..	..	3540	..
6.90	822	1400	2280	4440
7.40	550	820	1240	2460
7.90	450	640	920	1560
8.40	400	530	750	1210
8.90	370	480	630	920
9.90	..	..	..	320

Ligand PHEN

$-\log[H^+]$	267 μ M/l.	107 μ M/l.	53.6 μ M/l.	26.8 μ M/l.
6.90	1460	2880	4020	7440
7.40	970	1600	2400	3960
7.90	790	1220	1750	2460
8.40	700	1026	1340	1750
8.90	550	800	970	1070

An examination of the data for the various chelate systems studied shows that for a given change in concentration, there is not a corresponding change in the reaction rate, even in pH regions where, to a first approximation, only a single catalytic species exists. This effect is due mainly to the presence of a greater proportion of catalytically-inactive dimer in the more concentrated copper chelate solutions. An equation which describes the rate of hydrolysis of Sarin in the pH region 6.9–

TABLE V

CATALYTIC HYDROLYSIS OF SARIN WITH COPPER(II) CHELATES

$t = 0.3°$; $\mu = 0.10(\text{KNO}_3)$

Ligand	$-\log [\text{H}^+]$	Catalyst concentration (μ moles/liter)	$t_{1/2}$ (sec.)
DMEN	7.40	137	5760
	7.90	137	2520
	8.90	137	900
TMEN	6.90	59.7	7380
	7.40	59.7	2580
	7.90	59.7	1200
HEN	7.40	765	5880
	7.90	763	3000
	8.90	760	2520
2-HEN	7.40	1393	6060
	7.90	1389	3780
	8.90	1382	2700
DIPY	7.40	273	4620
	7.90	273	3120
	8.90	273	2520
PHEN	7.90	267	6060
	8.40	267	5460
	8.90	267	4860

TABLE VI

CATALYTIC HYDROLYSIS OF SARIN WITH COPPER(II) CHELATES

$t = 42.5°$; $\mu = 0.10(\text{KNO}_3)$

Ligand	$-\log [\text{H}^+]$	Catalyst concentration (μ moles/liter)	$t_{1/2}$ (sec.)
DMEN	6.90	13.7	1620
	7.40	13.7	730
	7.90	13.7	390
TMEN	6.90	5.98	1920
	7.40	5.98	780
	7.90	5.98	440
HEN	6.90	76.9	1750
	7.40	76.6	940
	7.90	76.6	570
2-HEN	6.90	140	1740
	7.40	140	1090
	7.90	140	750
DIPY	6.40	27.3	2520
	6.90	27.3	1120
	7.40	27.3	610
PHEN	6.90	26.8	1680
	7.40	26.8	930
	7.90	26.8	630

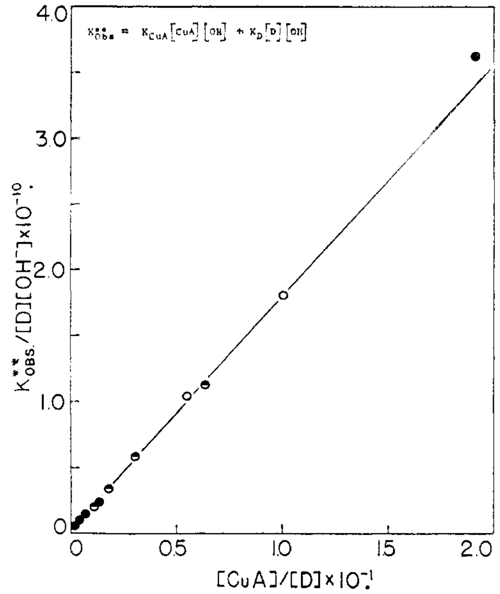


Fig. 2.—Graphical demonstration of catalytic inactivity of the binuclear, diolated Cu(II)-dipyridyl chelate in the catalysis of the hydrolysis of Sarin at 25° in 0.1 *M* KNO_3. Values of $-\log [\text{H}^+]$: ○, 6.90; ◒, 7.40; ●, 7.90.

7.9 may be written as

$$k_{\text{obsd.}}^{**} = k_L[\text{CuL}^{2+}][\text{OH}^-] + k_D[(\text{Cu}[\text{OH}]\text{L})_2{}^{2+}][\text{OH}^-] \qquad (10)$$

where k_L and k_D are specific rate constants assigned to diaquo and dimeric chelates, respectively. A plot of $k_{\text{obsd.}}^{**}[(\text{Cu}[\text{OH}]\text{L})_2{}^{2+}][\text{OH}^-]$ as ordinate *vs.* $[\text{CuL}^{2+}]/[(\text{Cu}[\text{OH}]\text{L})_2{}^{2+}]$ as abscissa should give a straight line of slope k_L and intercept k_D. As may be seen in Fig. 2, a straight line with an intercept equal to zero is obtained from data on the hydrolysis of Sarin in the presence of the Cu(II)-dipyridyl catalyst. Thus, the original assumption that the dimer has a negligible catalytic activity is experimentally verified. In the foregoing treatment, although both the diaquo and monohydroxo chelates are present in appreciable quantities, the relative contributions of each cannot be determined, as has been pointed out above.

By the use of the rate constants for hydroxyl ion outlined in Table II and the values of k_M determined from equation 5b, it is possible to describe the total rate in terms of only two unknown quantities, k_L and k_B, as indicated by equation 7. Solution of equation 7 with kinetic data obtained in the *p*H range 6.9–8.9 at 25.0°, resulted in the rate constants listed in Table VII. In the higher *p*H ranges there were usually appreciable contributions to the observed rate from both the diaquo and dihydroxo chelate species. In general, however, the constants assigned to the diaquo species may be considered to be more accurate than those assigned to the dihydroxo species, since the calculation of k_B involves the difference of two quantities of similar magnitude.

TABLE VII

RATE CONSTANTS ASSIGNED TO CATALYTIC COPPER CHELATE SPECIES

Ligand	k_L (25.0°) ($\text{l.}^2\ \text{mole}^{-2}\ \text{sec.}^{-1}$)	k_B (25.0°) ($\text{l. mole}^{-1}\ \text{sec.}^{-1}$)	k_L (0.3°) ($\text{l.}^2\ \text{mole}^{-2}\ \text{sec.}^{-1}$)	k_B (0.3°) ($\text{l. mole}^{-1}\ \text{sec.}^{-1}$)
TMEN	1.0×10^8	....	7.8×10^7	....
DMEN	3.2×10^7	2.2×10^2	1.77×10^7	....
DIPY	3.10×10^7	....	1.97×10^7	....
PHEN	1.93×10^7	....	8.8×10^6	....
HEN	9.3×10^6	5.5	4.3×10^6	....
2-HEN	5.2×10^6	9.0×10^{-1}	2.3×10^6	3.0×10^{-1}

Calculation of rate constants at 42.5° was not possible because in the dilute solutions employed the amount of unbound copper species was relatively large. Since estimated values of k_M as well as the formation constant, K_{ML}, were employed, the errors encountered in the arbitrary assignment

TABLE VIII

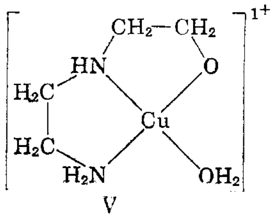
ENTHALPIES, ENTROPIES AND FREE ENERGIES OF ACTIVATION FOR THE COPPER(II) CHELATE CATALYZED THIRD-ORDER HYDROLYSIS OF SARIN

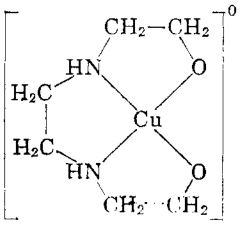
Ligand	$\Delta H^\ddagger$ (kcal./mole)	$\Delta S_{25°}^\ddagger$ (cal./mole deg.)	$\Delta F_{25°}^\ddagger$ (kcal./mole)
TMEN	0.9	−18.9	6.5
DMEN	3.3	−13.1	7.2
DIPY	2.4	−16.2	7.2
PHEN	4.6	− 9.8	7.5
HEN	4.5	−11.6	8.0
2-HEN	4.8	−11.8	8.3

of rates to free copper(II) species were considerable at the highest temperature. Conditions for calculation of rate constants at 0.3° were more favorable since a relatively large error in the assignment of rate constants to unbound copper(II) species represented a small contribution in terms of the over-all rate. On the basis of rate constants obtained at 0.3° and 25.0°, enthalpies and entropies of activation for the catalytic reactions were calculated and are listed in Table VIII.

Comparison of the values of k_L obtained for Cu(II)-DMEN and Cu(II)-DIPY shows that the diaquo or monohydroxo chelates of DIPY are actually as active as catalysts as those of DMEN, although the total observed rate of the latter compound is greater in terms of the total amount of metal chelate present in solution. The explanation of this effect is that the DIPY chelate dimerizes to a much greater extent than that of DMEN, with the result that a lower concentration of catalytic species is present in the dipyridyl system. With respect to the correlation of catalytic rate constants and the relative activities of the copper(II) chelates as Lewis acids, it is difficult to see why the copper chelates of dipyridyl and *o*-phenanthroline are not the most active of all the systems investigated. On the basis of the inverse order of chelate stability, it might be expected that the order of activity of the more efficient catalysts might be Cu(II)-DIPY > Cu(II)-PHEN > Cu(II)-TMEN > Cu(II)-DMEN. If, on the other hand the complexes of aromatic ligands and of aliphatic ligands are compared separately, it seems that the correlation with chelate stability holds quite well. This behavior may be due to the effectiveness of the metal ion as a Lewis acid, which is in turn better measured by the enthalpy of coördination, rather than the free energy of reaction. Although these enthalpies are not available, it is apparent that they would follow the stability order closely when the charges and structures are relatively similar, since the entropies of coördination of the compounds studied in this research would be either relatively constant or would vary slightly because of differences in the size and shape of the ligand molecules.

The relatively low values of k_L and k_B of Cu(II)-HEN and of Cu(II)-2-HEN, relative to the equally stable Cu(II)-DMEN, suggest the possibility of additional coördination of the copper ion by the hydroxyethyl groups to form chelates of the types indicated by V and VI. Such a compound as VI would be expected to be a relatively poor catalyst because of complete coördination of the copper(II) ion. Alternatively the low catalytic rates of Cu(II)-HEN and Cu(II)-2-HEN may be attributed to steric repulsions caused by the hydroxyethyl substituents.


V


VI

It has been suggested that the monohydroxo chelate is the most important catalytic species. On this basis the chelate would act as a Lewis acid in polarizing the phosphonyl group while at the same time performing the basic function of donating a hydroxyl group. Such a push-pull mechanism for Sarin hydrolysis has been suggested by Epstein[13] and by Courtney, *et al.*[5] If this type of reaction is assumed to predominate, the rate equation in the *p*H regions where dihydroxo chelate species may be neglected takes the form

$$k_{\text{obsd.}}^{**} = k_C[\text{Cu[OH]L}]$$

From values of k_C for the various systems investigated, given in Table IX, it may be seen that for the three most active catalysts the values of k_C are in excess of the values of k_{OH}(2.37×10^1 sec.$^{-1}$ at 25° and 4.67 sec.$^{-1}$ at 0.3°) obtained for the hydroxyl ion, which is undoubtedly more basic than Cu(OH)L^{1+}. Evidence of this type has led previous workers to support the view that a mechanism involving the monohydroxo chelate species is inherently quite different in nature from the type indicated for the third order reaction described above as well as for the simple reaction with a base such as the OH^- ion. Because of this difference, it is not necessary that the rates be logically comparable. Indeed the higher rate constant for the push-pull mechanism was more or less expected because of the special nature of the catalyst.

TABLE IX

VALUES OF k_C BASED ON THE SECOND ORDER REACTION BETWEEN Cu[OH]L AND SARIN

Ligand	k_C(25.0°) (l. mole^{-1} sec.$^{-1}$)	k_C(0.3°) (l. mole^{-1} sec.$^{-1}$)
TMEN	1.58×10^2	3.2×10^1
DMEN	6.3×10^1	1.15×10^1
CIPY	4.0×10^1	7.3
PHEN	2.0×10^1	3.3
HEN	3.0	4.0×10^{-1}
2-HEN	1.2	1.8×10^{-1}

The enthalpies, entropies and free energies of activation for the second order reaction (Table X) are approximately equal to the values calculated for the hydroxyl ion reaction (Table II). If the monohydroxo chelate were the predominant catalytic species, a substantial lowering of the free energy of activation relative to that of interaction of Sarin with hydroxyl ion would be expected, Examination of data for the third order reaction

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[13] J. Epstein and D. H. Rosenblatt, *J. Am. Chem. Soc.*, **80**, 3596 (1958).

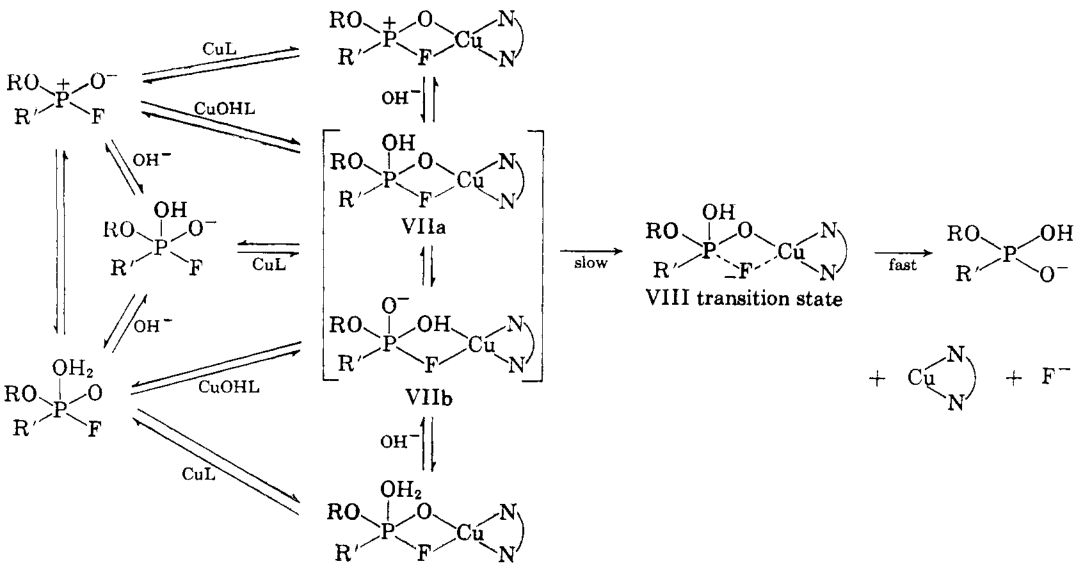

PLATE I

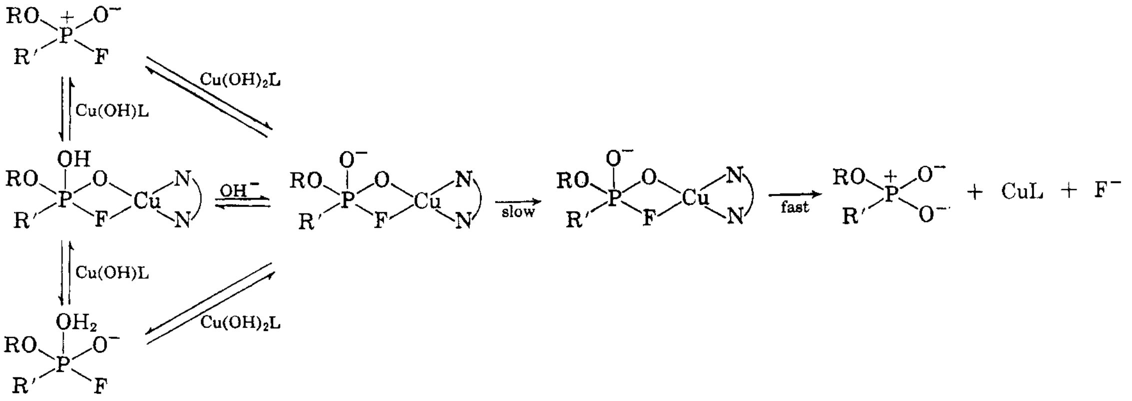

PLATE II

(Table VIII) shows a marked decrease in $\Delta H^{\ddagger}$ and hence $\Delta F^{\ddagger}$ values relative to values obtained for the uncatalyzed reaction. Thus it appears that the third order reaction is favored over a second order process for the catalytic reactions.

TABLE X

ENTHALPIES, ENTROPIES AND FREE ENERGIES OF ACTIVATION FOR THE REACTION

$$\mathrm{Cu(OH)L} + \text{Sarin} \longrightarrow \text{Products} + \mathrm{CuL}$$

Ligand	$\Delta H^{\ddagger}$, (kcal./mole)	$\Delta S^{\ddagger}$, 25° (cal./mole deg.)	$\Delta F^{\ddagger}$, 25° (kcal./mole)
TMEN	10.0	−14.9	14.4
DMEN	10.6	−14.8	15.0
DIPY	10.6	−15.7	15.3
PHEN	11.2	−15.0	15.7
HEN	12.7	−13.8	16.8
2-HEN	11.6	−19.3	17.4

On the basis of the experimental data available, it is not possible to make a choice between the second order and third order routes for the metal chelate-catalyzed reaction, since they differ only in the nature of the preequilibria involved, only one of which can be determined. The apparently lower activation energy of the third order reaction is compensated by the less favorable entropy of dilution of the reacting species, a factor which corresponds to making the reaction less probable.

In view of the above considerations favoring the third order reaction, it now seems necessary to propose a new reaction mechanism for the metal-catalyzed reaction which takes these factors into account. This proposed mechanism represents the only possible way in which the metal may act as a catalyst in the hydrolysis of Sarin. In order that the rate of dissociation of the fluoride ion be increased, it is necessary that the metal ion lower the energy of the transition state by coördination of the partially-ionized fluorine atom. An alternate method of binding Sarin by the metal ion or metal chelate would be the coördination of two adjacent oxygen atoms attached to phosphorus, which would increase the strength of the phosphorus-oxygen bond and thus could not be involved in the observed catalytic effect.

The scheme in Plate I assumes fast transfer of protons between various interacting species in a complex pre-equilibrium, with a rate determining dissociation of the fluoride ion. From the nature of the equilibria between protonated forms of Sarin, the metal chelate and the association complex formed, it is seen that the two alternative mechanisms proposed by previous investigators are essentially one and the same. The association complex between Sarin and the metal chelate has two tautomeric forms, which are no doubt in rapid equilibrium. It is apparent that it makes no difference which of these forms is produced initially or which is present in the higher concentration.

The reason for the previous suggestions of two alternative mechanisms was due to the fact that the relative concentrations of two of the metal chelate precursors of VIIa and VIIb, CuL^{2+} and $Cu[OH]L^{+}$, can be determined in these and many other similar systems, coupled with the assumption that the rate determining step was considered to be the nucleophilic attack of the hydroxyl ion in the phosphorus atom, with simultaneous displacement of the fluoride ion. The concept of unimolecular dissociation of fluoride, with or without help from the metal ion or chelate, however, resolves the supposed dichotomy in the mechanism of this reaction.

A similar interpretation may be given to the catalytic effect of the dihydroxo chelate, as is illustrated in Plate II.

Here again, it is seen that, if the dissociation of fluoride ion is rate-determining, it is impossible to distinguish between related pre-equilibrium species which differ only in the positions of hydroxyl groups. In this case, the precursor of the activated complex does not exist in more than one tautomeric form, since it does not contain bound hydrogen ions.

The mechanisms proposed above are also in agreement with other factors known to influence the activity of the Cu(II) chelate as a catalyst. Notable among these are the requirements that the charge of the complex be as positive as possible and that a maximum of two coordination sites of the copper(II) ion be occupied by the ligand. Both of the requirements would act so as to increase the binding of the fluoride ion by the metal of the metal chelate compound, in the formation of the transition state.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY, NASHVILLE 5, TENNESSEE]

The Effect of Coördination on the Reactivity of Aromatic Ligands. III. Halogenation of Some 8-Hydroxyquinoline Chelates

BY KEITH D. MAGUIRE AND MARK M. JONES[1]

RECEIVED OCTOBER 27, 1961

Halogenation of 8-hydroxyquinoline chelates of Cr(III), Co(III), Fe(III), Cu(II) and Al(III) results in the same products as are obtained in the halogenation of the free ligand; though the relative amounts of the various haloderivatives may vary somewhat. Under no circumstance has any change in orientation of the entering substituent been observed. A survey of the results available on the reactions of coördinated aromatic ligands shows that the coördination act *per se*, in isolation from other complicating factors, has only a very slight effect on the gross pattern of aromatic reactivity exhibited in the free ligand.

In earlier studies in this series,[2,3] it was shown that the behavior of coördinated aromatic amines toward halogenation showed a surprising resemblance to that shown by the free ligand. The present study was undertaken to provide (1) information on the effect of the central metal ion on the reactivity and (2) data on a ligand capable of forming very stable chelates, 8-hydroxyquinoline. One of the reasons for selection of this ligand was the fact that its reactions have been studied in great detail and those of interest in the present study are well characterized.[4,5] It is important to emphasize that an added advantage of working with this ligand is the considerable stability of the metal chelates involved. This allows the isolation and characterization of the reaction products at each stage in the form of a metal complex. In some cases this stability was so great that isolation and characterization of the halogenated ligand was not possible. In these cases the reaction product was characterized by synthesis via an alternate sequence of reactions.

Experimental[6]

All infrared spectra were taken on a Perkin-Elmer model 137 recording spectrophotometer using a sodium chloride prism. All the spectra of the solid materials were obtained as pressed potassium bromide disks.

Preparation of 8-Hydroxyquinoline Chelates.—These chelates were prepared by the usual methods available in the literature[4] or by slight modifications of the analytical procedures employed for the gravimetric determination of these metal ions with 8-hydroxyquinoline.

The Cr(III) chelate was prepared on a large scale using a proceedure based upon an analytical method due to E. Taylor-Austin.[7]

The Co(III) chelate was prepared by reaction of a solution tris-(carbonato)-cobaltate(III) ion with 8-hydroxyquinoline. The cobalt intermediate was prepared using the procedure due to G. A. Barbieri[8a] and M. Mori, *et al.*[8b]

This compound is a green amorphous solid contrary to an earlier report which describes it as forming lustrous black crystals.[9]

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[1] To whom correspondence concerning this paper should be addressed.

[2] J. C. Taft and M. M. Jones, *J. Am. Chem. Soc.*, **82**, 4196 (1960).

[3] R. L. Jetton and M. M. Jones, *Inorg. Chem.*, in press.

[4] R. G. Hollingshead, "Oxine and its Derivatives," Butterworth's Scientific Pubs., London, 1956 four vols.

[5] J. P. Phillips, *Chem. Revs.*, **56**, 271 (1956).

[6] At the suggestion of the referees much of the experimental data has been summarized in tables. Complete details are available in the thesis of K. D. Maguire, Vanderbilt University, June 1962.

[7] E. Taylor-Austin, *Analyst*, **63**, 710 (1938).

[8] (a) G. A. Barbieri, *Atti Acc. Lincei Rend.* [6], **7**, 747 (1928). (b) M. Mori, M. Shibata, E. Kyuno and T. Adachi, *Bull. Chem. Soc. Japan*, **29**, 883, 887 (1957); M. Mori, M. Shibata, E. Kyuno and Y. O. Kuba, *ibid.*, **31**, 291, 940 (1958).