Kraus, Nelson and Moore.[9] The values of the ordinates for the distribution data are purely relative for each of the functions plotted; the shapes of the curves are the feature of consequence. Although all the evidence relating to the extraction by ethers indicates that the extracted species contains two chlorines, the fact that the extraction curves do not correspond to the spectral data is not surprising; the distribution depends on many factors other than the equilibrium in the aqueous phase, and this equilibrium itself is shifted due to the presence of ether in the aqueous phase. For example, a decrease in the distribution ratio for isopropyl ether would be expected at the highest acidities even if there were no decrease in the amount of the extractable species in the aqueous phase.[10] The rapid rise of all curves for acidities up to 4 *M* indicates that the equilibrium in the aqueous phase is the most important factor in determining the distributions at these conditions.

The anion resin data corresponds sufficiently well with the spectral data to suggest that the species containing two chlorines is the form bound by the anion exchanger.

The most glaring failure of correspondence is the apparent leveling off in the amount of the two-chlorine species in 1–2 *M* HCl. The most likely explanation is that these solutions contain another species of Mo(VI) that also has an absorption maximum in the 260–270 mμ region, and that the amount of the two-chlorine species actually follows the dashed line indicated on the figure. Examination of the spectrum of Mo(VI) in $HClO_4$ solutions indicates that species with such absorption characteristics are present at such acidities.

The trends displayed in the spectra of these chloro complexes of Mo(VI) are consistent with the trends displayed by other elements. The resolved peaks with maxima at 264 and 302 mμ are those associated with the Mo–Cl bond, and the complex with the larger number of chlorines has the absorption at the longer wave length. It is also of interest that the absorptions at the maxima of the two resolved curves differ by only 3% (well within the errors inherent in the method). This relationship has been observed previously with the chlorocomplexes of Sb(V),[11] but there are not sufficient data from other elements to decide whether this is a general type of behavior.

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[9] K. A. Kraus, F. Nelson and G. E. Moore, THIS JOURNAL, **77**, 3972 (1955).

[10] D. E. Campbell, A. H. Laurene and H. M. Clark, *ibid.*, **74**, 6193 (1952).

[11] H. M. Neumann, *ibid.*, **76**, 2611 (1954).

EVANSTON, ILLINOIS

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY]

Metal Chelate Compounds as Catalysts in the Hydrolysis of Isopropyl Methylphosphonofluoridate and Diisopropylphosphorofluoridate[1]

BY R. C. COURTNEY, R. L. GUSTAFSON, S. J. WESTERBACK, H. HYYTIAINEN, S. C. CHABEREK, JR., AND A. E. MARTELL

RECEIVED SEPTEMBER 7, 1956

The rates of hydrolysis of Sarin and DFP have been studied in the presence of a wide variety of metal chelate compounds as catalysts. The metal ion which yielded the largest number of catalytic metal chelates was found to be Cu(II), while a number of metal chelates of UO_2(VI), ZrO(IV), Th(IV) and MoO_2(VI) were also found to have considerable activity. Although the Cu(II) catalysts were apparently in a class by themselves, the following characteristics were found to be required in these hydrolytic catalysts: 1, incomplete coördination of the metal ion by the ligand; or 2, presence of oxy groups (or hydrated oxy groups) attached to the metal in certain cases where coördination was apparently complete. The wide variety of active metal complexes of Cu which were investigated made it possible to observe the following factors which favor maximum catalytic activity: 1, the presence of two aquo groups on the metal; 2, low stability of the metal chelate compound; and 3, the presence of maximum positive charge on the metal chelate. The importance of steric factors is indicated by the high activity of Cu(II) chelates of highly substituted diamines.

The purpose of this investigation was to study the catalytic effects of various metal chelate compounds in the hydrolysis of the cholinesterase inhibitors known as Sarin (isopropyl methylphosphonofluoridate $(C_3H_7O)(CH_3)POF$ and DFP (diisopropyl phosphorofluoridate, $(C_3H_7O)_2POF$). Wagner-Jauregg, *et al.*,[2] have recently reported that Cu(II) chelates active as catalysts in the hydrolysis of DFP contain a 1:1 molar ratio of the Cu(II) ion to a number of ligands, which include various α-amino acids and diamines. More recently Ryland, *et al.*,[3] have described a detailed study of the catalytic activity of the Cu(II) chelates of ethylenediamine, dipyridyl and *o*-phenanthroline, and have proposed a mechanism to explain the observed rates as a function of the metal chelate species present under their experimental conditions. The only other study of metal ion catalysis of hydrolysis of cholinesterase inhibitors is a report by Augustinsson and Heimbürger[4] which describes the effectiveness of Cu(II), Ni(II), Co(II), Ag(I), Au(III) and Pd(II) salts in accelerating the hydrolysis of Tabun (N,N-dimethyl - ethylphosphoroamidocyanidate). No previous reports on the catalysis of Sarin hydrolysis by metal chelate compounds have appeared in the literature.

Experimental

The liberation of acid during hydrolysis of Sarin was measured as a function of time with a Beckman automatic titrator, which was operated so as to automatically maintain the experimental solution at constant *p*H by addition of

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[1] This paper reports work done under contract with the Chemical Corps, U. S. Army, Washington 25, D. C.

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

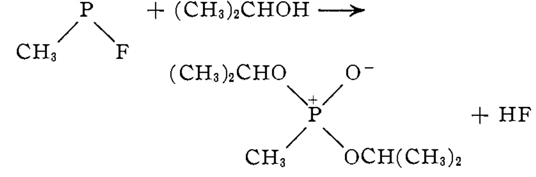
[3] L. B. Ryland, F. M. Fowkes and G. S. Ronay, Paper No. 108, Division of Physical and Inorganic Chemistry, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., September 11–16, 1955.

[4] K. B. Augustinsson and G. Heimbürger, *Acta Chem. Scand.*, **9** 383 (1955).

standard base from a micro-buret. The reaction was carried out in a multinecked glass flask fitted with a mercury-seal stirrer, nitrogen-inlet and outlet tubes, delivery tips for Sarin and potassium hydroxide solutions, and glass and calomel electrodes. The reaction vessel and the titrator head unit were mounted in a high-speed hood, the flask being immersed in a constant temperature bath which was maintained at 25.3 ± 0.05°.

In operation, an aliquot of metal chelate solution was introduced into the titration cell, presaturated nitrogen was bubbled through the solution to exclude CO_2, and the *p*H was adjusted as desired by means of the automatic titrator unit. An anticipation setting of 5 was used in most of the experiments. An aliquot of Sarin (approximately 150 μ moles) was now added by means of an automatic microburet. Time measurements were begun at the point at which half of the Sarin solution had been added. Readings of time *vs.* corresponding KOH consumption were recorded over the course of the titration. A plot of t *vs.* $\log a/(a - x)$ (where a is the amount of base required for complete hydrolysis and x is the amount of base consumed at the corresponding time t) gave a straight line in all cases studied. The half-time, that is the time required for the hydrolysis of one-half of the Sarin, is the time corresponding to a $\log a/(a - x)$ value of 0.301. Two moles of acid per mole of Sarin are liberated upon hydrolysis.

The Sarin was used as a 0.05 *M* stock solution in anhydrous isopropyl alcohol. A small amount of free acid was present in this solution as the result of the very slow reaction



Corrections for free acidity were made by adding a corresponding amount of base to the reaction mixture before the introduction of the Sarin. The total volume of the solution at the start of a titration was 150 ml.

The electrode system was calibrated at *p*H 4, 7 and 9 by means of suitable buffers which were checked against an acetate buffer as the primary standard.

Reagent grade nitrates of all metals were used except for ZrO(IV) and Sn(IV) which were used in the form of chlorides, and VO(IV), which was obtained as the sulfate. Standardization of the metal solutions consisted for the most part of evaporation and subsequent ignition to the corresponding oxides. Copper was standardized by titration with standard Na_2EDTA reagent with murexide as an indicator in ammoniacal solution.[5] Thorium was standardized by means of Na_2H_2EDTA with alizarin red indicator,[6] while manganese was determined by titration with the salt of nitrilotriacetic acid, brom thymol blue being used as an indicator.[6] The vanadyl solution was standardized by titration with standard NaOH in the presence of excess Na_2H_2EDTA according to the method of Schwarzenbach.[7]

Samples of ethylenediaminetetraacetic acid, N-hydroxyethylethylenediaminetriacetic acid, N,N'-dihydroxyethylethylenediaminediacetic acid, N-hydroxyethyliminodiacetic acid, nitrilotriacetic acid, aspartic acid, N-hydroxyethylaspartic acid and N-aminoethylaspartic acid were obtained through the courtesy of Versenes, Inc., Framingham, Massachusetts. Samples of N-hydroxyethylethylenediamine, N,-N'-dihydroxyethylenediamine, diethylenetriamine and triethylenetetramine were obtained from Carbide and Carbon Chemical Co., purified by fractional distillation, and converted to the corresponding hydrochlorides. Ethylenediamine, 5-sulfosalicylic acid and 1,8-dihydroxynaphthalene-3,6-disodium sulfonate were purchased from Eastman Kodak Co. The ethylenediamine was dried over solid potassium hydroxide, redistilled and isolated as the dihydrochloride. Pyrocatechol-3,5-disodium sulfonate was purchased from LaMotte Chemical Products Corp., Baltimore, Maryland. The 1,3-diaminopropane was obtained from the Sharples Chemical Company while the dipicolinic acid (pyridine-2,6-dicarboxylic acid) was donated by Dr. Stanley Chaberek, of the Dow Chemical Co., Framingham, Massachusetts. Samples of the dihydrochlorides of N,N'-dimethylethylenediamine and N,N,N',N'-tetramethylethylenediamine were prepared and recrystallized by conventional methods. Standardization of the aqueous solutions of the above chelating agents was effected by means of potentiometric titration with either standard carbonate-free potassium hydroxide or hydrochloric acid.

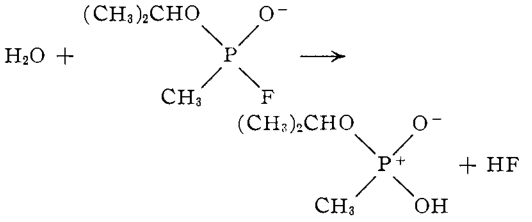
The Sarin was obtained through the courtesy of the Army Chemical Center. Standardization was effected using the automatic titrimeter in two ways: 1, neutralization of the hydrogen ions produced when an aliquot of Sarin was introduced into a 0.1 *M* nitrate solution at *p*H 10.0; and 2, neutralization of the acid produced upon catalytic hydrolysis by copper dipyridyl at *p*H 7.0. In the former case, hydrolysis was complete after approximately 40 minutes, while in the latter case, no further uptake of base was recorded after 60 minutes using approximately a five to one molar ratio of Sarin to copper dipyridyl.

In addition to the Sarin experiments, several metal chelate systems were studied to determine their effect as hydrolysis catalysts upon diisopropyl phosphorofluoridate (DFP). The DFP was obtained from the Colgate-Palmolive Company and had the following physical properties: b.p. 60-61° (8.2 mm.); density 1.055 at 25°; refractive index 1.3792 at 25°. A solution in anhydrous isopropyl alcohol was standardized by titration of acid liberated during catalytic hydrolysis by the copper chelate of N,N,N',N'-tetramethylethylenediamine at *p*H 9.0. Hydrolysis was complete in approximately 40 minutes when a molar ratio of ten to seven (copper chelate to DFP) was used. Attempts at standardization of DFP solutions by direct reaction with hydroxyl ion at a *p*H of 11.5 or greater required more than the theoretical two moles of base per mole of DFP. The exact nature of this phenomenon has not been determined but it is possible at such a high *p*H that alkyl groups also split off with consequent uptake of additional hydroxyl ions.

In order to check the accuracy of the instrument, several check runs were made using manual addition of base while recording the *p*H using a Beckman model G *p*H meter. Hydrolysis rates as determined by the manual method were approximately 10-16% greater than those observed using the automatic system. This increase in rate is probably due to the fact that in the former method the solution *p*H ranged from slightly below to slightly above the desired value, whereas due to a small lag in the instrument, the average *p*H in the automatic runs was probably lower than the desired value. For comparative purposes, the instrument seems to be quite suitable, since duplicate results agreeing within a few per cent. have been obtained in the great majority of cases.

Results

The metal chelate systems investigated for catalytic activity in the hydrolysis of Sarin are listed in Table I. The concentrations of metal chelate, Sarin and the solution *p*H are given in all cases. The metal chelates listed refer to the 1:1 chelates, unless otherwise noted. The stabilities of the metal chelate compounds investigated are sufficiently high ($\log k \geqq 10$) that they are not appreciably dissociated at *p*H 7. The total activities of the metal chelate species in solution are expressed as first-order hydrolysis rate constants for the reaction



(2)

Corresponding half-times of reaction also are listed.

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(5) G. Schwarzenbach, "Die Komplexometrische Titrationen," Ferdinand Enke Verlag, Stuttgart, 1955, p. 68.

(6) J. J. Gritz and J. J. Ford, *Anal. Chem.*, **25**, 1640 (1953).

(7) G. Schwarzenbach and W. Biedermann, *Helv. Chim. Acta*, **31**, 331 (1948).

TABLE I

Metal	Ligand	*p*H	Concn., μmoles/l. Metal	Concn., μmoles/l. Ligand	Concn., μmoles/l. Sarin	$t_{1/2}$ (min.)	k_1 (min.$^{-1}$)
Cu(II)	2-HxG	7.0	1020	1020	1005	25.0	2.8×10^{-2}
Cu(II)	HIMDa	7.0	995	995	955	57.0	1.2×10^{-2}
Cu(II)	HEDDA	7.0	1005	1005	960	32.0	2.2×10^{-2}
Cu(II)	HEDDA	7.0	9725	9725	960	19.0	3.6×10^{-2}
Cu(II)	HEDTA	7.0	1035	1035	945	29.0	2.4×10^{-2}
Cu(II)	HEDTA	7.0	10230	10230	975	25.0	2.8×10^{-2}
Cu(II)	HEN	7.0	10030	10030	970	4.6	1.5×10^{-1}
Cu(II)	2-HEN	7.0	10740	10740	955	4.1	1.7×10^{-1}
Cu(II)	HASPA	7.0	950	950	975	45.0	1.5×10^{-2}
Cu(II)	PDS	7.45	6286	6286	1593	10.0	6.9×10^{-2}
Cu(II)	PDS	7.45	653	653	1645	55.0	1.3×10^{-2}
Cu(II)	DNS	7.0	1313	1313	729	27.0	2.6×10^{-2}
Cu(II)	EN	7.20	980	980	1075	8.0	8.7×10^{-2}
Cu(II)	CU	7.20	995	995	1090	11.0	6.3×10^{-2}
Cu(II)	TU	7.20	995	995	980	8.5	8.2×10^{-2}
Cu(II)	CS	7.25	990	990	1070	8.5	8.2×10^{-2}
Cu(II)	TS	7.25	1000	1000	1015	10.5	6.6×10^{-2}
Cu(II)	2-HEN	6.10	1250	1250	1050	57.0	1.2×10^{-2}
Cu(II)	2-HEN	7.15	1135	1135	950	12.2	5.7×10^{-2}
Cu(II)	2-HEN	8.00	1050	1050	1050	11.0	6.3×10^{-2}
Cu(II)	2-HEN	8.00	1050	1050	1030	11.0	6.3×10^{-2}
Cu(II)	HEN	6.15	1020	1020	1080	71.0	9.8×10^{-3}
Cu(II)	HEN	7.00	1020	1020	990	15.5	4.5×10^{-2}
Cu(II)	HEN	8.00	1010	1010	1100	10.0	6.9×10^{-2}
Cu(II)	$Na_4P_2O_7$	7.00	1035	1035	995	75.0	9.2×10^{-3}
Cu(II)	$Na_5P_3O_{10}$	7.00	995	995	1000	$\gg$100	....
Cu(II)	DIEN	7.10	1055	1055	995	25.0	2.8×10^{-2}
Cu(II)	DIEN	7.00	1555	1035	960	7.0	9.9×10^{-2}
Cu(II)	TRIEN	7.00	990	990	985	65.0	1.1×10^{-2}
Cu(II)	DPA	6.20	990	990	955	45.0	1.5×10^{-2}
Cu(II)	DAP	7.50	510	510	975	2.1	3.3×10^{-1}
Cu(II)	DAP	7.50	5340	5340	515	1.3	5.3×10^{-1}
Cu(II)	DIPY	7.40	436	436	850	7.1	9.8×10^{-2}
Cu(II)	DIPY	7.40	2236	2236	872	3.0	2.3×10^{-1}
Cu(II)	DMEN	7.00	1025	1025	1005	3.5	2.0×10^{-1}
Cu(II)	DMEN	7.00	5010	5010	1035	1.7	4.1×10^{-1}
Cu(II)	TMEN	7.00	970	970	925	1.0	6.9×10^{-1}
Cu(II)	TMEN	7.00	2425	2425	490	0.5	1.4
Cu(II)	PYR	7.00	785	1570	489	64.0	1.1×10^{-2}
Cu(II)	TEEN	7.00	398	1590	497	6.0	11.5×10^{-2}
Cu(II)	AE-ASPA	7.00	3270	3270	478	6.0	11.5×10^{-2}
Cu(II)	DAB	7.00	589	4710	504	9.0	7.7×10^{-2}
Cu(II)	GG	7.00	1400	1400	492	35.0	2.0×10^{-2}
Cu(II)	GGG	7.00	1190	1190	492	17.0	2.0×10^{-2}
UO_2(II)	2-HxG	7.2	515	1030	975	55.0	1.3×10^{-2}
UO_2(II)	HEDTA	7.0	1025	1025	955	33.0	2.1×10^{-2}
UO_2(II)	PDS	6.8	1027	1027	1471	>100	....
UO_2(II)	DNS	7.0	411	822	1304	4.4	1.6×10^{-1}
UO_2(II)	DNS	7.0	819	1638	1317	3.2	2.2×10^{-1}
UO_2(II)	DNS	7.0	5521	11042	675	2.2	3.2×10^{-1}
La(III)	2-HxG	7.0	1000	1000	950	>100	....
La(III)	HIMDA	7.0	1000	1000	955	>100	....
La(III)	HEDDA	7.0	1005	1005	1000	>100	....
La(III)	HEDTA	7.0	1040	1040	980	>100	....
La(III)	5-SSA	7.0	525	1050	960	63.0	1.1×10^{-2}
La(III)	DNS	7.0	811	811	1285	52.0	1.3×10^{-2}
La(III)	PDS	7.0	5416	5416	1580	45.0	1.5×10^{-2}
La(III)	PDS	7.5	943	943	1498	56.0	1.2×10^{-2}
VO(II)	2-HxG	7.0	510	1020	975	63.0	1.1×10^{-2}
VO(II)	HIMDA	7.0	1000	1000	960	$\gg$100	....
VO(II)	HEDDA	7.0	1010	1010	960	$\gg$100	....
VO(II)	HEDTA	7.0	1045	1045	980	$\gg$100	....
VO(II)	PDS	6.8	1000	1000	1348	>100	....
VO(II)	DNS	7.0	1285	1285	1285	>100	....

TABLE I (*continued*)

Metal	Ligand	pH	Concn., μmoles/l. Metal	Ligand	Sarin	$t_{1/2}$ (min.)	k_1 (min.$^{-1}$)
Fe(III)	2-HxG	7.0	1035	1035	960	$\gg 100$	....
Fe(III)	HIMDA	7.0	1005	1005	965	$\gg 100$	....
Fe(III)	HEDDA	7.0	985	985	960	$\gg 100$	....
Fe(III)	HEDTA	7.0	1020	1020	965	$\gg 100$	....
Fe(III)	PDS	7.0	1010	1010	935	>100	....
Fe(III)	DNS	7.0	950	950	855	>100	....
MoO_2(VI)	...	7.00	1000	1000	1000	75	....
MoO_2(VI)	HEN	7.00	1000	1000	1000	70	....
MoO_2(VI)	EDTA	7.00	1000	1000	1000	105	....
MoO_2(VI)	HEDTA	7.00	950	950	890	~ 95	....
MoO_2(VI)	HEDDA	6.95	960	960	900	~ 75	....
MoO_2(VI)	2-HxG	7.00	980	980	940	~ 75	....
MoO_2(VI)	HIMDA	7.00	960	960	900	~ 100	....
MoO_2(VI)	NTA	7.00	970	970	900	~ 60	....
MoO_2(VI)	PDS	7.10	965	965	910	7.5	9.2×10^{-2}
MoO_2(VI)	PDS	7.00	4950	4950	975	1.5	4.6×10^{-1}
MoO_2(VI)	PDS	5.20	4950	4950	960	5.0	1.4×10^{-1}
MoO_2(VI)	5-SSA	6.90	990	990	890	~ 75	....
MoO_2(VI)	DNS	7.10	890	890	940	~ 90	....
MoO_2(VI)	CIT	7.00	890	890	890	~ 85	....
MoO_2(VI)	ASPA	7.20	945	945	900	~ 75	....
MoO_2(VI)	DPA	7.00	970	970	910	~ 70	....
MoO_2(VI)	EN	7.15	950	950	900	~ 60	....
MoO_2(VI)	TU	7.00	920	920	900	~ 85	....
ZrO(II)	HEDDA	7.00	1000	1000	845	110	....
ZrO(II)	PDS	7.00	995	995	850	78	....
ZrO(II)	2-HxG	7.55	1013	1013	850	7.0	....
ZrO(II)	HIMDA	7.45	988	988	838	7.0	....
ZrO(II)	CIT	7.50	919	919	846	7.0	....
ZrO(II)	EDTA	6.40	515	515	865	5.0	1.4×10^{-1}
ZrO(II)	EDTA	7.40	515	515	890	2.5	2.8×10^{-1}
ZrO(II)	EDTA	7.00	1005	1005	850	2.2	3.2×10^{-1}
ZrO(II)	EDTA	8.40	510	510	870	2.3	3.0×10^{-1}
ZrO(II)	HEDTA	6.00	990	990	840	21	3.3×10^{-2}
ZrO(II)	HEDTA	7.00	990	990	840	64	1.1×10^{-2}
ZrO(II)	HEDTA	7.05	990	990	850	65	1.1×10^{-2}
Cr(III)	2-HxG	7.0	900	900	915	Inactive	....
Ti(IV)	PDS	7.0	2970	5940	503	100	....
Sn(IV)	PDS	7.0	1510	3020	504	Very large	....
Sn(IV)	DNS	7.0	Sat'd	3100	497	Very large	....
Sn(IV)	5-SSA	7.0	Sat'd	3160	504	Very large	....

The definitions of the abbreviations used to identify the various ligands employed are given in Table II. The corresponding catalytic activities of a number of Cu(II) chelates in the hydrolysis of DFP are listed in Table III.

Discussion

Effect of Ligand on Activity of Cu(II) Chelate Compounds.—The 29 catalytically active Cu(II) chelates listed in Table I may be classified into the following groups on the basis of the type of ligand involved: amino acids (7), phosphates (2), *o*-diphenols (2), peptides (2), diamines (12), hydroxyethylsubstituted diamines (2), and polyamines containing more than two basic nitrogen atoms (2). Of these, the diamines form the most active Cu(II) chelates, and have been explored to the greatest extent. The chelates of amino acids, peptides and phenolic ligands have somewhat less activity. The least active compounds listed in Table I are the Cu(II) chelates of the polyphosphates and of ligands with more than two donor groups per molecule. Not listed in Table I is a wide variety of chelate compounds which were not of sufficiently high activity to be interesting. These compounds

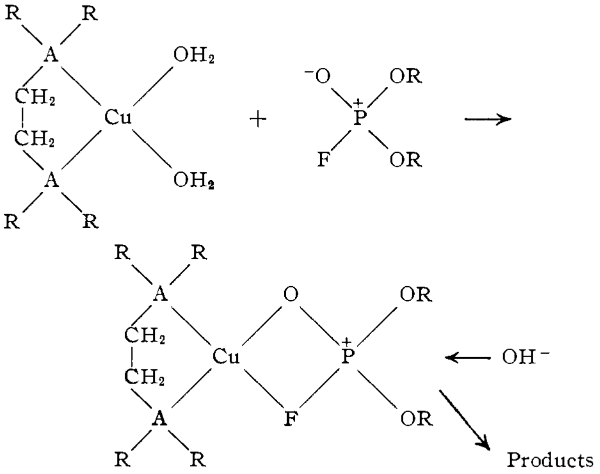


TABLE II

KEY TO LIGAND ABBREVIATIONS

AE-ASPA	N-aminoethylaspartic acid
ASPA	aspartic acid
CIT	citric acid
CS	*cis*-1,2-diaminocyclohexane
CU	*cis*-Δ^4-1,2-diaminocyclohexene
DAB	1,4-diaminobutane
DAP	1,3-diaminopropane
DIEN	diethylenetriamine
DIPY	dipyridyl
DMEN	N,N′-dimethylethylenediamine
DNS	1,8-dihydroxynaphthalene-3,6-disodium sulfonate
DPA	pyridine-2,6-dicarboxylic acid
EDTA	ethylenediaminetetraacetic acid
EN	ethylenediamine
GG	glycylglycine
GGG	glycylglycylglycine
HASPA	N-hydroxyethylaspartic acid
HEDDA	N,N′-dihydroxyethylethylenediamine-diacetic acid
HEDTA	N-hydroxyethylethylenediaminetriacetic acid
HEN	N-hydroxyethylethylenediamine
2-HEN	N,N′-dihydroxyethylethylenediamine
HIMDA	N-hydroxyethyliminodiacetic acid
2-HxG	N,N-dihydroxyethylglycine
NTA	nitrilotriacetic acid
PDS	pyrocatechol-3,5-disodium sulfonate
PYR	pyridoxamine
5-SSA	5-sulfosalicylic acid
TEEN	N,N,N′,N′-tetraethylethylenediamine
TMEN	N,N,N′,N′-tetramethylethylenediamine
TRIEN	triethylenetetramine
TS	*trans*-1,2-diaminocyclohexane
TU	*trans*-Δ^4-1,2-diaminocyclohexene

TABLE III

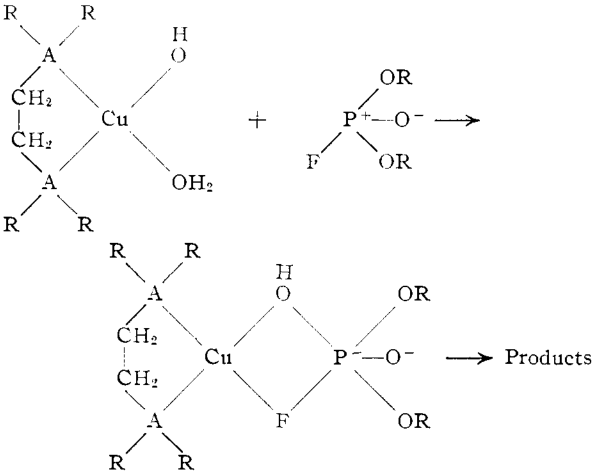
CATALYTIC EFFECTS OF Cu(II) CHELATES ON DFP HYDROLYSIS

DFP = 4.14×10^{-3} *M*; *p*H 7.00; $\mu = 0.1$; $T = 25.3°$

Catalyst	Concn., μmoles/l.	$t_{1/2}$ (min.)
TMEN	2070	15
DIPY	2070	23
EN	2070	60
HEN	2070	96
2-HEN	2290	250
DIEN	2070	3000

include the Cu(II) chelates of ligands which are quite negative, or form very stable chelates, or both, such as the Cu(II) chelates of EDTA, NTA, citrate and tartrate.

Influence of Charge.—The qualitative observation mentioned above indicates that the charge of the complex may have a great deal to do with the activity of a copper chelate as a hydrolytic catalyst. There are two general mechanisms by which a Cu(II) chelate compound may act as a catalyst in the hydrolysis of Sarin and DFP. The first involves the combination of the metal chelate compound with the substance being hydrolyzed, followed by attack of this complex with the hydroxide ion. Thus the nucleophilic attack of the phosphorus atom by the hydroxide ion is greatly increased by the interaction of the metal ion with the groups attached to the phosphorus atom. It is apparent that the more electropositive the Cu(II) atom is, the greater will be its effect on the acceptor activity of the phosphorus atom. Therefore, one would expect that an electron donor which carries considerable negative charge would tend to decrease the rate of the reaction outlined above. The alternate reaction mechanism may be considered analogous to the push–pull mechanism advanced by Swain[8] to explain the action of pyridone in the mutarotation of glucose. Thus the hydroxy form of the Cu(II) chelate may be considered to act as an amphoteric substance in the catalytic reaction, which may be formulated as



The copper chelate would therefore have two functions: 1, the acidic function of accepting the fluoride ion: and 2, the basic function of donating the hydroxide ion. It is seen that the metal ion must be as electropositive as possible for maximum catalytic activity. The more positive the metal ion in the normal 1:1 chelate, the greater will be its tendency to hydrolyze to give the monohydroxy chelate compound illustrated above. Also, the more positive the metal, the greater will be its residual affinity for attracting the fluoride ion from the phosphate group.

The results listed in Table I indicate that the reaction rate decreases with increasing negative charge of the Cu(II) chelate. The following ligands are arranged in the order of decreasing catalytic activities of their Cu(II) chelates in the hydrolysis of Sarin: HEN > HxG > HIMDA > ASPA > EDTA. A similar series may be taken from the data of Wagner-Jauregg, *et al.*,[2] for the catalysis of DFP hydrolysis by Cu(II) chelates: *o*-PHEN, EN > glycine, alanine >> EDTA. Further examples are the greater activity of the Cu(II) pyrophosphate chelate over that of the corresponding tripolyphosphate compound, and the higher activity of the Cu(II) HEDDA chelate over that of HEDTA.

Influence of Number of Donors in Ligand.—Inspection of the catalytic activities of Cu(II) chelates of various ligands listed in Table I indicates that the highest activity is obtained with bidentate donors, and that additional donor groups per mole of ligand reduce the effectiveness of the

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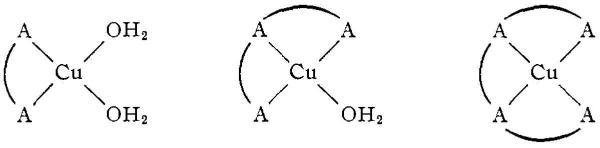
(8) C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, **74**, 2534 (1952).

metal chelate as a catalyst. Thus the hydrolysis of Sarin in the presence of the 1:1 Cu(II)–ethylenediamine chelate is three times faster than it is in the presence of the corresponding chelate of diethylenetriamine. It is, of course, difficult to separate the simple structural or steric effect of the number of positions of the Cu(II) ion which are coördinated (see below), from allied effects such as the enhanced stability which results from the increased number of donor positions on the ligand. In the series of Cu(II) chelates of EN, HEN and 2-HEN, there is no additional stability resulting from the relatively weak coördination of the auxiliary hydroxyl groups, in contrast to analogous series EN, DIEN and TRIEN. (The steric factors resulting from the substitution of alkyl groups on the basic nitrogen atoms are nearly compensated for by coordination of the hydroxyl groups so that the stabilities in the former series do not differ significantly.)

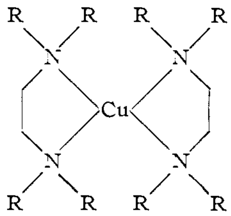


Bidentate Terdentate Quadridentate

Cu(II) chelates formed with bi-, ter-, and quadridentate ligands

Since the catalytic activities of the HEN and 2-HEN chelates are about half of that of EN, it is seen that a bidentate chelate compound containing two water molecules bound directly to the metal ion is apparently the most favorable structure for producing catalytic activity in Cu(II) chelate compounds. There remains the possibility of catalysis on systems containing monodentate ligands. For the systems investigated, however, 1:1 Cu(II) complexes with monodentate reagents were not sufficiently stable to prevent precipitation at *p*H 7.

Steric Factors.—It has been shown previously[9] that the stability of a 1:1 Cu(II) chelate compound frequently is controlled by the tendency to disproportionate to the 2:1 chelate and copper hydroxide, as well as by its own intrinsic stability constant. Thus a 1:1 chelate with a high stability constant may be unstable in solution if the 2:1 chelate is also very stable. Since Cu(II) chelates are square planar, the substitution of alkyl groups in place of the amino hydrogen atoms would help to prevent this disproportionation reaction by steric repulsion between the substituents on two different moles of ligand, as is indicated by the formula shown below. This effect has been observed in the case of the N-substituted ethylenediamines such as TMEN, DMEN, DIPY and *o*-PHEN. It is notable that all of these substances form soluble 1:1 Cu(II) chelates which do not disproportionate in aqueous solution at *p*H 7 and above, whereas the 1:1 Cu(II) chelate of ethylenediamine is not stable and is quickly converted to the 2:1 chelate with the precipitation of copper hydroxide. It is seen, therefore, that N-substitution of a 1,2-diamine is helpful in obtaining a stable aqueous catalytic chelate of Cu(II).



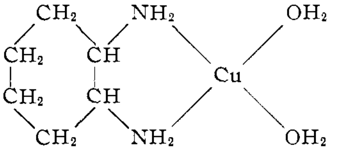
The influence of N-substitution on the specific catalytic activity of Cu(II)–ethylenediamine chelates cannot be determined unambiguously from the examples available since changes of structure also affect the stability of the metal chelate compound. The influence of stability on catalytic activity is discussed below.

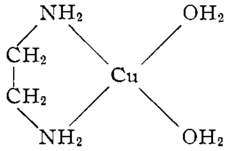
Influence of Stability.—Although Wagner–Jauregg, *et al.*,[2] stated that stability of a Cu(II) chelate is not a significant factor in determining its catalytic activity, the evidence obtained in this research seems to indicate otherwise. While it is certain that many factors affect the catalytic activity of chelate compounds, the evidence in Table I seems to indicate that catalytic activity generally decreases with increasing stability of the metal chelate compound. This generalization is supported by a number of comparisons taken from the results of Table I.

1. In the series of 1:1 Cu(II) chelates formed by N-substituted ethylenediamines, the chelate stability constants decrease in the order: EN > DMEN > TMEN. The order of catalytic activity is seen to be exactly the reverse.

2. Although chelate stability constants are not available for monobipyridyl-Cu(II) and for mono-*o*-phenanthroline-Cu(II), the order of decreasing stability of these compounds and of the corresponding EN chelate may be deduced from the published stabilities of the chelates of other metal ions with these ligands to be: EN > *o*-PHEN > DIPY. It is seen that the order of increasing activity is the same: EN < *o*-PHEN[10] < DIPY.

3. Comparison of the Cu(II) chelates of the four diaminocyclohexenes and cyclohexanes with that of ethylenediamine shows no appreciable difference in catalytic activity, although it is known that the stability of the EN-Cu(II) chelate is 2 to 3 log *K* units lower than those formed from the cyclic diamines. A possible explanation of this anomaly is based on the fact that the two types of structures indicated below have equivalent electronic interaction (binding energy) between the Cu(II) ion and the basic nitrogen donor groups





The observed difference in stability, therefore, would be merely an entropy effect which depends on the initial and final states of the ligands in the formation of the metal chelate. Hence, the environment, or electronic condition of the Cu(II) ion, would be

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[9] A. E. Martell, R. Gustafson and S. Chaberek, Jr., paper no. 34, International Congress on Catalysis, Philadelphia, Pa., Sept. 10–14, 1956 (to be printed in a special volume of "Advances in Catalysis," Academic Press, Inc., New York).

[10] *o*-Phenanthroline data observed from ref. 3.

the same in both cases, and the similarity of catalytic activity is not surprising.

In view of these correlations with stability, one would look for the least stable metal chelate compound in order to obtain maximum catalytic activity. There is a definite limit beyond which this concept cannot be pushed, however, which is defined by the stability necessary to keep the metal ion in solution. Thus the most active catalyst would be the aquo ion itself. Since the aquo ion cannot be obtained in sufficient concentration at a *p*H where the hydroxide ion concentration is also sufficient to carry out the reaction at a reasonable rate, it seems that an important function of the metal chelate compound is to maintain the metal ion at a reasonably high concentration (and activity) in aqueous solution.

Influence of Metal Ion on Catalytic Activity.—Measurements of the catalytic activities of a number of stable aqueous metal chelates of the Fe(III), La(III), Cr(III), Ti(IV) and Sn(IV) ions are listed in Table I. Not listed are a number of additional measurements made on chelates of other common metal ions such as Zn(II), Cd(II), Co(II), Fe(II), Ni(II) and Pb(II). None of the metal chelates, listed and unlisted, showed interesting catalytic activity. The Zn(II) ion was unique in that it was the only third row metal for which no active chelates were found.

On the other hand, a number of metal chelate compounds of oxo- metal ions such as ZrO(IV), UO_2(VI) and MoO_2(VI) showed very high catalytic activity toward the hydrolysis of Sarin, the most active being the ethylenediaminetetraacetato-zirconyl ion ($t_{1/2}$ = 2.2 min.), the dioxomolybdenum(VI) chelate of 3,5-disulfopyrocatechol ($\sim$7.0 min.), and the dioxouranium(VI) chelate of 3,6-disulfo-1,8-dihydroxynaphthalene ($\sim$3.5 min.), the numbers corresponding to the approximate half times of hydrolysis in the presence of a 0.0010 molar solution of the catalyst. The lack of information on the stabilities of these chelate compounds and the small number of examples of very active chelates make correlation of activity with properties of the ligand impossible. It is noted, however, that all of the active catalysts contain one or more oxo groups bound to the metal ion. Although these chelates are in some instances formed with ligands containing many donor groups, it is possible to state in all cases that oxo- or hydroxy-groups are also present. It seems probable that these basic groups must be involved in the observed catalysis by a push–pull mechanism analogous to that already proposed for the Cu(II) chelates.

Although the uranyl 5-sulfosalicylate chelate has been reported by Ryland, *et al.*,[3] to be catalytically active, studies of systems containing this chelate indicate that it is unstable in aqueous solution at *p*H 7.

General Conclusions.—The catalytic activities of metal chelate compounds listed in Table I are seen to increase with increasing *p*H and increasing concentration of the chelate. The measured rate constants increase with an increase in hydroxide ion and metal chelate concentrations, in accordance with the mechanisms suggested above. The rate constants do not increase with the first power of the concentration of these substances, and possible side reactions or equilibrium with inactive species is indicated. The authors are now engaged in an extensive study of these effects and hope to report their findings in a subsequent publication.

The list of rate constants of DFP hydrolysis in the presence of various metal chelates in Table III is restricted to some of the more active catalysts with interesting structures. The results for these compounds, together with the results reported by Wagner-Jauregg, *et al.*, and by Ryland, *et al.*,[3] indicate that the generalizations made above for the hydrolysis of Sarin also apply to DFP, although the latter compound is more slowly hydrolyzed by all reagents investigated.

As a result of the correlation in this paper of the catalytic activity of metal chelates with structure and other properties of the ligand, the following generalizations may be made concerning the factors which tend to increase catalysis of hydrolysis by a metal chelate compound: 1, the presence of oxo, hydroxy or aquo groups bound directly to the metal; 2, bidentate ligands in the case of Cu(II) (does not hold for metals of higher valence); 3, minimum stability of the metal chelate compound which will still prevent dissociation to the metal ion; 4, high concentration (hence high solubility) of the metal chelate; 5, high *p*H.

The most active catalysts found in this investigation in the order of decreasing activity are

For Sarin: Cu(II)TMEN > Cu(II)DMEN > ZrO(II) EDTA > Cu(II) DAP > UO_2(II) $(DNS)_2$ > Cu(II) DIPY > MoO_2(VI) PDS > Cu(II) N > Cu(II) 2-HEN > Cu(II) HEN > Cu(II) DIEN

For DFP: Cu(II) TMEN > Cu(II) DIPY > Cu(II) EN > Cu(II) DAP > Cu(II) HEN > Cu(II) 2-HEN > Cu(II) 2-HEN >>> Cu(II) DIEN

The tetramethylethylenediamine-Cu(II) chelate is the most active catalyst found up to the present time.

Worcester, Mass.

[Contribution from the Chemical Laboratories, Clark University]

Hydrolytic Tendencies of Metal Chelate Compounds. I. Cu(II) Chelates[1]

By A. E. Martell, S. Chaberek, Jr., R. C. Courtney, S. Westerback and H. Hyytiainen

Received March 4, 1957

The hydrolysis of 1:1 chelates of copper with thirty ligands has been studied potentiometrically with a view to determining relative tendencies to form hydroxy complexes. Most of the bidentate chelate compounds investigated were found to undergo hydrolysis in a limited *p*H range, with *pK* values of 7.5 ± 0.3. The number of donor groups in the ligand was found to be more important than stability in determining hydrolytic tendencies. In certain cases the existence of a highly stable 2:1 chelate resulted in disproportionation of the 1:1 chelate with simultaneous precipitation of half of the metal in the form of its hydroxide.

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[1] This paper reports work done under contract with the Chemical Corps, U. S. Army, Washington 25, D. C.