Ligand Effects on the Rate of Metal-Ion-Catalyzed Decarboxylation of Dimethyloxaloacetic Acid

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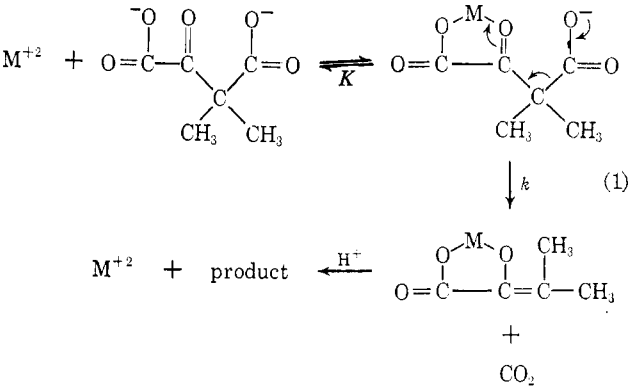
Abstract: The rate of decarboxylation of dimethyloxaloacetic acid catalyzed by metal ions is shown to be sensitive to the ligands attached to the metal. The $Mn(phen)^{2+}$ complex (phen = 1,10-phenanthroline) is a more effective catalyst than aqueous manganese, and $Mn(phen)_2^{2+}$ is still more active. Catalysis by zinc and magnesium ions is unaffected by coordinated phenanthroline. Substitution of the hydrogens on the phenanthroline with various groups affects the rates of catalysis of both manganese and zinc. Some substituents appear to cause a change in which step of the reaction is rate determining. The authors suggest that conjugation between the phenanthroline and the acid through the metal occurs, and that there is also another influence on the rate.

Many reactions are known during the course of which the reacting molecules are coordinated to metal ions.[1] The effect of the other ligands associated with the metal on the reaction has also been studied.[2,3] This is particularly interesting in the case of metallo enzymes. Enzyme proteins are often said to be activated by metal ions. In some simple cases, at least, the converse seems to be true: metal ions by themselves can carry out a reaction, but the addition of enzyme protein considerably speeds it up. One ligand (the protein) is acting upon the reaction rate of another (the substrate) while both are coordinated to a common metal ion. More elaborate effects, such as substrate discrimination by the enzyme and influence on the steric path of the reaction, are also known, but these will not be considered here. Even for simple protein-induced increases in rate, a number of mechanisms can be envisioned by which the substrate–protein interactions may result. (1) The protein by coordination may change the electron distribution or density of the metal in such a way as to modify the electronic environment of the substrate. (2) The large protein molecule may create a local disruption of the solvent structure and decrease the solvent-rearrangement contribution to the activation energy. (3) The protein may have a functional group which is situated near the site of coordination and assists in the reaction. (4) The metal may change the configuration of the protein in such a way as to unfold an active catalytic site from the interior.

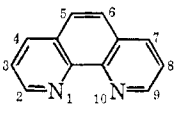
This paper reports an attempt to discover whether electronic influences can be transferred by one ligand to another through a metal ion. The investigation was carried out on an enzyme-like model system. The reaction studied was the decarboxylation of the β-keto acid, dimethyloxaloacetic acid. Oxaloacetic acid is decarboxylated enzymatically in certain biological systems,[4] and the two methyl groups simplify the kinetics by preventing enolization. The metals studied were manganese, zinc, and magnesium. 1,10-Phenanthroline derivatives were used in place of the enzyme protein. It had been shown[5] that when these molecules were coordinated to a +2 metal ion, they acted in a fashion somewhat similar to real enzymes. The course of the reaction for a hydrated metal ion in aqueous solution is[6]



(1)

The metal acts as a positive center which attracts electrons and facilitates the rupture of the bond between the carboxyl group and the rest of the molecule. The same mechanism occurs with the metal–phenanthroline complex. In the enzyme, there is evidence that an amine group is involved at some point in the reaction,[7] but the same sequence of substrate association, decarboxylation, and dissociation undoubtedly occurs.

In order to test the transference of electronic effects from one ligand to another through the metal, a number of derivatives of 1,10-phenanthroline were prepared, most substituted in the 4 and 7 positions. Groups in



1,10-phenanthroline

these positions influence the electron density of the nitrogens *para* to them. Not only are the metal–nitrogen σ bonds affected, but it has been shown by nmr that there is significant mixing between the orbitals of the paramagnetic metal ion and the π system of the phenanthroline.[8] Withdrawal of electron density from

(1) For example, see "Reactions of Coordinated Ligands," Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963.
(2) W. F. Little and R. Eisenthal, *J. Org. Chem.*, **26**, 3609 (1961).
(3) W. F. Little and R. Eisenthal, *J. Am. Chem. Soc.*, **83**, 4936 (1961).
(4) B. Vennesland, M. G. Gollub, and J. F. Speck, *J. Biol. Chem.*, **178**, 301 (1949).
(5) J. V. Rund and R. A. Plane, *J. Am. Chem. Soc.*, **86**, 367 (1964).
(6) R. Steinberger and F. H. Westheimer, *ibid.*, **73**, 429 (1951).
(7) I. Fridovich and F. H. Westheimer, *ibid.*, **84**, 3208 (1962).
(8) M. W. Dietrich and A. C. Wahl, *J. Chem. Phys.*, **27**, 1591 (1963).

the metal should increase k and K (see eq 1), while electron donation should decrease them; π interactions among the ligands must be transferred through the d orbitals of the metal. In zinc and magnesium these are of too high an energy to play a significant role. σ-Bond effects may occur with any of the metals, possibly through the rehybridization mechanism suggested to explain the *trans* effect in transition metal complexes.[9]

Experimental Section

Chemicals. Metal catalysts were made up from reagent grade salts and their concentrations determined by standard volumetric and gravimetric techniques. Water was distilled before use in kinetic runs. The following phenanthroline compounds were purchased from the G. Frederick Smith Chemical Co. and used without further purification: the 4,7-dimethyl, 2,9-dimethyl, 4,7-diphenyl, and 4,7-diphenyl sodium sulfonate derivatives. Others were prepared by published procedures listed below.

1,10-Phenanthroline[10] had mp 118°, lit. 117°; 5-nitro-1,10-phenanthroline,[11] mp 200°, lit. 199°; 3,8-dicarbethoxy-4,7-dihydroxy-1,10-phenanthroline, 3,8-dicarboxy-4,7-dihydroxy-1,10-phenanthroline, and 4,7-dihydroxy-1,10-phenanthroline[12] are not readily purified to give analytical samples. 4,7-Dichloro-1,10-phenanthroline[12] had mp 248°, lit. 249–250°; subsequent recrystallizations raised the melting point to 262°. 4,7-Dibromo-1,10-phenanthroline[13] had mp 233°, lit. 236°. A reported method[14] for 4,7-dimethoxy-1,10-phenanthroline involving a sealed tube reaction with a copper catalyst did not give satisfactory results. Instead, 2.0 g of 4,7-dichloro-1,10-phenanthroline and 65 ml of methanol were warmed on a steam bath; 35 ml of 10% sodium methoxide in methanol was added, and the solution refluxed for about 20 hr. The precipitated sodium chloride was filtered off, and the solvent was evaporated. The residue was recrystallized from aqueous ethanol, then benzene, and then 20% aqueous methanol with decolorizing charcoal. The final product is white and melts at 205°. *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.66. Found: C, 70.23; H, 4.99; N, 11.67.

All kinetic measurements were made on reactions in glutarate buffer. Matheson Coleman and Bell glutaric acid was recrystallized from chloroform to give a material melting at 98–99°. A weighed amount of acid was mixed with a measured volume of standardized sodium hydroxide and diluted to an appropriate volume. The measured pH was 5.3.

The preparation of dimethyloxaloacetic acid has already been described.[6]

Kinetic Runs. The rate of evolution of carbon dioxide was measured by a simple manometer under conditions of partial vacuum in a vessel resembling a Warburg flask.[5] Five or six runs were made for each set of concentrations, and four to eight different concentrations of catalyst were used for each phenanthroline.

The reactions generally gave good pseudo-first-order plots in CO_2 pressure. Some deviations occurred at the beginning of the reactions, but the pressures began to fall on a straight line within a small fraction of a half-life. First-order kinetics was observed over three or four half-lives in a number of cases, but routine runs were normally carried out for only one or two. A precipitate was observed in some of the reactions, particularly near completion. No change in kinetics seemed to accompany precipitation, and the reactions were not otherwise anomalous.

Calculations. The association constant between the catalyst and substrate and the rate constant for decarboxylation of this complex (K and k in reaction 1) were calculated using an IBM 7072 computer. A program written by one of the authors calculated the concentrations of all the species present and then corrected the observed rate constant for effects of substrate autodecarboxylation and catalysis due to metal ions not coordinated to phenanthroline. The best straight line fitting the corrected data was determined by a weighted-least-squares method. Weighting factors were calculated from the standard deviation of rates of several identical runs. The values of K and k were calculated from the resulting straight line.

Treatment of Kinetic Data. The method of calculating the intrinsic rate constant, k, and the intrinsic equilibrium constant, K, may be most easily explained by illustrating the calculation for the hydrated-metal-ion catalyst. The reactions of consequence are

$$HS^+ \overset{K_a}{\rightleftharpoons} H^+ + S \quad (2)$$

$$M + S \overset{K}{\rightleftharpoons} MS \quad (3)$$

$$MS \overset{k}{\longrightarrow} MP + CO_2 \quad (4)$$

$$MP \rightleftharpoons M + P \quad (5)$$

S is the dianion of the substrate dimethyloxaloacetic acid, M is the metal ion, and P is the decarboxylated acid. For a rate-determining decarboxylation step, the mechanism requires that

$$\frac{d[CO_2]}{dt} = k[MS] \quad (6)$$

Experimentally, the observed rate constant is defined by

$$\frac{d[CO_2]}{dt} = k_c S_t \quad (7)$$

where S_t is the total amount of substrate present, and where the rate has been corrected for a small amount of autodecarboxylation of the substrate. Combining these equations, one obtains

$$\frac{1}{k_c} = \frac{S_t}{k[MS]} \quad (8)$$

Expanding S_t gives

$$\frac{1}{k_c} = \frac{[S] + [HS^+] + [MS]}{k[MS]} = \frac{[S]}{k[MS]} + \frac{[HS^+]}{k[MS]} + \frac{1}{k} \quad (9)$$

Substituting $[H^+][S]/K_a$ for $[HS^+]$

$$\frac{1}{k_c} = \frac{[S]}{k[MS]} + \frac{[H^+][S]}{k[MS]K_a} + \frac{1}{k} \quad (10)$$

$1/K[M]$ is substituted for $[S]/[MS]$ and terms are combined to give

$$\frac{1}{k_c} = \frac{1 + [H^+]/K_a}{kK[M]} + \frac{1}{k} \quad (11)$$

At very high metal-ion concentrations (where all the substrate is in the form of the MS complex), the observed rate will approach as a limit the rate of the decarboxylation step, and the observed and intrinsic rate constants will become equal. Equation 11 shows that a plot of $1/k_c$ against $1/[M]$ will be a straight line. The limit is best found by extrapolating the plot back to $1/[M] = 0$ to find the intrinsic rate constant, k. Plots of this kind are shown in Figure 4.

The calculation is more complicated, however, since [M] may not be found until K is known. It is possible to change the variable into known total metal concentration. Consider two points, $(1/[M]_1, 1/k_1)$ and $(1/[M]_2, 1/k_2)$, on the straight line which fits the plot of $1/[M]$ against $1/k_c$. Equation 11 indicates that

$$\frac{1}{k} = \frac{1}{k_2} - \frac{1}{[M]_2}\left(\frac{1/k_1 - 1/k_2}{1/[M]_1 - 1/[M]_2}\right) \quad (12)$$

that is, the extrapolation of $1/k_c$ to $1/[M] = 0$ gives $1/k$. The equilibrium metal concentration may be expressed as

$$[M] = M_t - [MS] \quad (13)$$

where M_t is the total metal concentration. Using relation 8 for [MS], one obtains

$$[M] = M_t - \frac{k_c}{k} S_t \quad (14)$$

(9) See F. Basolo and R. G. Pearson, *Progr. Inorg. Chem.*, **4**, 381 (1962), and references contained therein.
(10) K. Madeja, *J. Prakt. Chem.*, **17**, 104 (1962).
(11) G. F. Smith and F. W. Cagle, *J. Org. Chem.*, **12**, 781 (1947).
(12) H. R. Snyder and H. E. Freier, *J. Am. Chem. Soc.*, **68**, 1320 (1946).
(13) F. H. Case, *J. Org. Chem.*, **16**, 941 (1951).
(14) D. E. Zacharias and F. H. Case, *ibid.*, **27**, 3878 (1962).

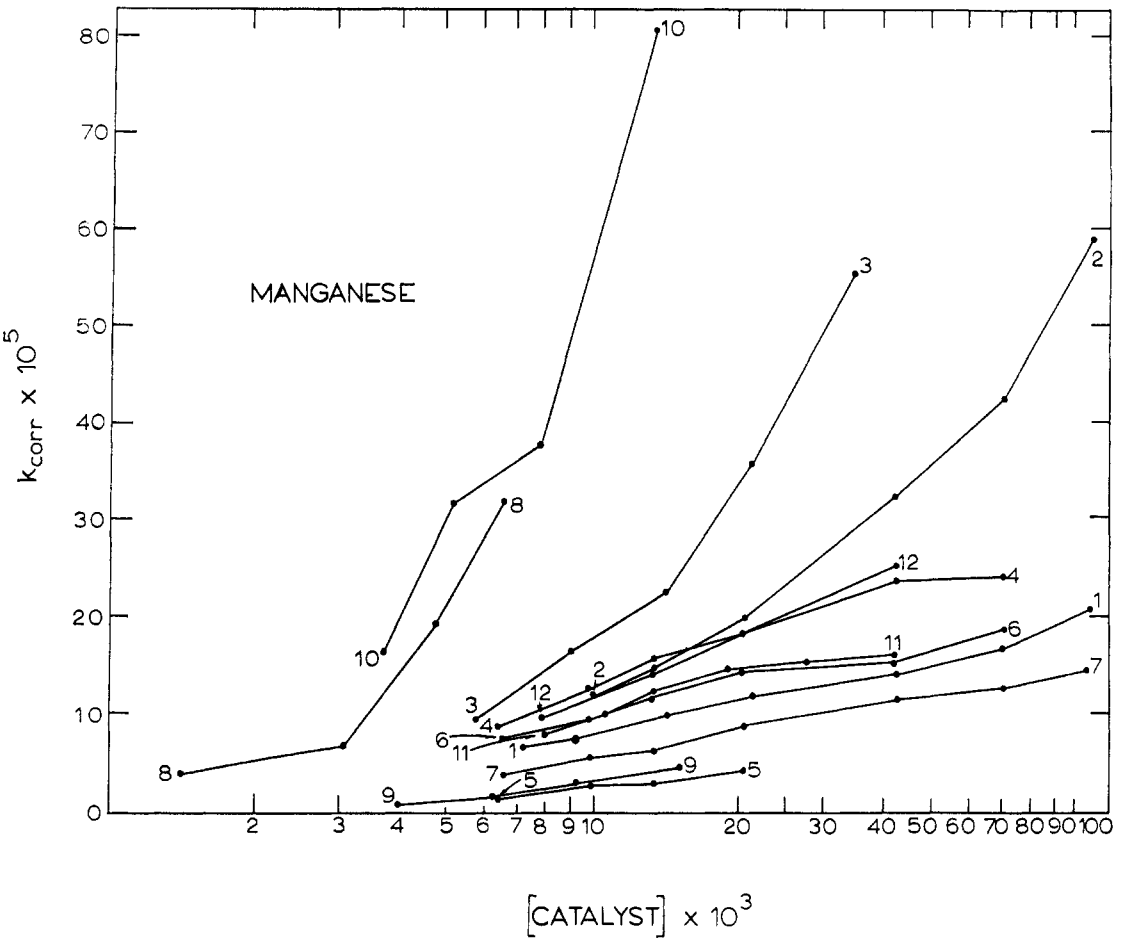


Figure 1. Corrected rate constants as a function of catalyst concentration for manganese catalysts. Numbers refer to Table I.

Substitution of (14) into (12) gives

$$\frac{1}{k} = \frac{1}{k_2} - \left(\frac{1}{M_2 - \frac{k_2}{k} S_t}\right)\left(\frac{1/k_1 - 1/k_2}{1\Big/\left(M_1 - \frac{k_1}{k} S_t\right) - 1\Big/\left(M_2 - \frac{k_2}{k} S_t\right)}\right) \quad (15)$$

where M_1 and M_2 are total metal concentrations corresponding to $[M]_1$ and $[M]_2$. Rearrangement of this equation gives a quadratic in k

$$k^2[(M_1k_2/k_1) - M_2] + k[k_2(M_2 - M_1)] + [(k_2k_1 - k_2^2)S_t] = 0 \quad (16)$$

The value of k which is calculated from this equation is inserted into eq 11 to calculate K.

When the catalyst is a metal–phenanthroline complex, additional corrections must be made as a result of the incomplete association between the metal and the ligand. Relatively few association constants between metals and substituted phenanthrolines have been measured. The constants which are known are not very different from that of 1,10-phenanthroline itself. Since the corrections involving these constants are minor, the value of the association constant for a metal with 1,10-phenanthroline is used for the value of the association constant for the same metal with substituted phenanthrolines. An exception is made in the case of 2,9-dimethyl-1,10-phenanthroline, where some association data are available. We are led to assume the relatively small value of 300 for its association constant with manganese.

The range in the values for constants K and k was estimated by moving the line best fitting $1/k_c$ *vs.* 1/[catalyst] within the confines of the standard deviations of k_c. It is important to test the results in this way, since the intercepts of the lines are often near zero on the reciprocal plot, and even small deviations can cause large fluctuations in the values of the constants.

Results and Discussion

Table I presents the data and calculated results. M_t in the first column is the total concentration of metal ion in the reaction, [cat] is the calculated concentration of metal–phenanthroline catalyst, k_o is the observed rate constant, σ is its standard deviation, k_c is the rate constant from which the contributions from other reactions have been subtracted, and K and k are the intrinsic reaction constants of eq 1. Figures 1 and 2 show the corrected rate constants, k_c, as functions of the catalyst concentrations for manganese and zinc. For clarity the rate constants are plotted without indicating the standard deviations, and the concentrations are placed on a logarithmic scale. Generally speaking, when the data are plotted with their standard deviations on a linear scale, they can be fit by a smooth, monotonic curve. At high concentrations of catalyst, the curve will level off as the corrected rate constant approaches the intrinsic rate constant of decarboxylation, k. It has been pointed out above that k can also be determined by extrapolation of the linear plot of $1/k_c$ against 1/[M], and this method is considerably more accurate.

Electronic Effects. The activation of aqueous manganese by one and two coordinated molecules of phenanthroline can be seen in Figure 1 (data numbered 2 and 3, respectively). That there is no activation of zinc

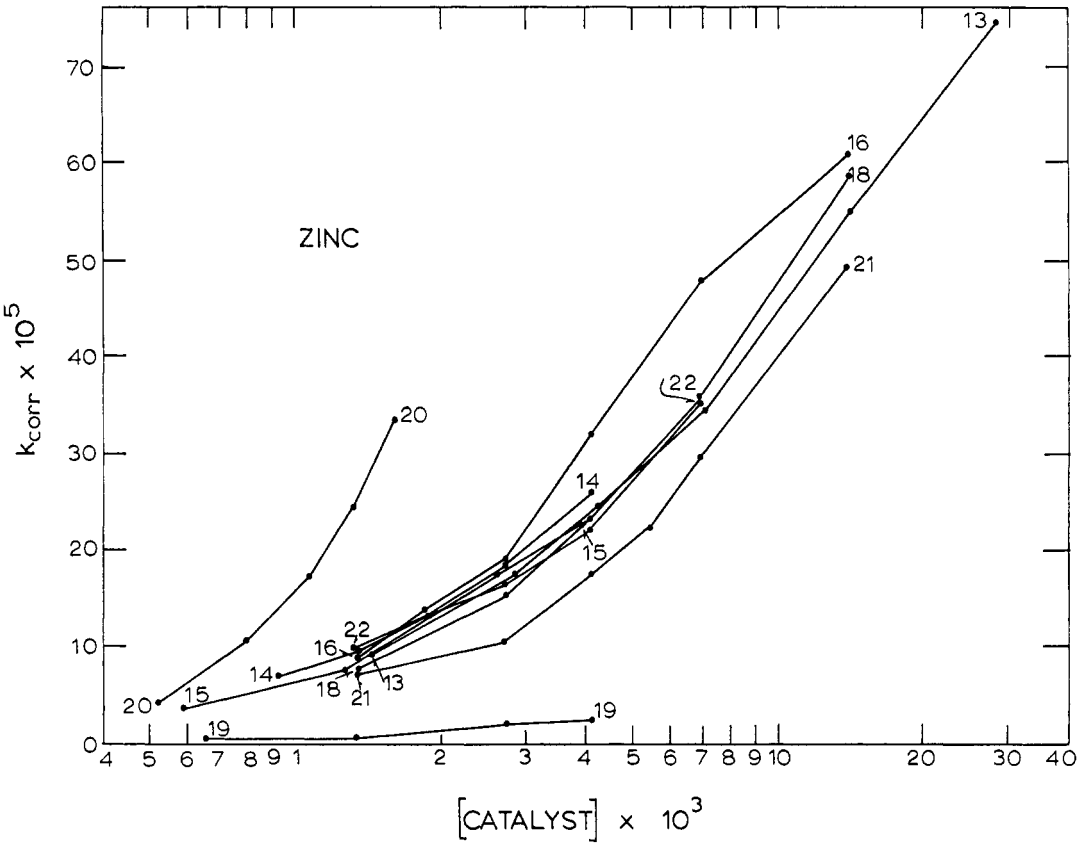


Figure 2. Corrected rate constants as a function of catalyst concentration for zinc catalysts. Numbers refer to Table I.

by phenanthroline is shown in Figure 2, in which the three catalysts, $Zn(aq)^{2+}$, $Zn(phen)^{2+}$, and $Zn(phen)_2^{2+}$ have nearly the same catalytic activity. This result is consistent with the explanation that the function of the metal is to accept electron density from the substrate, and that coordination to a phenanthroline molecule increases the metal's ability to act in this way by an interaction with its d orbitals to delocalize the substrate electron density over a greater volume of space. Manganese(II) interacts readily, but the d orbitals of zinc(II) are of too high an energy to mix extensively with the substrate or phenanthroline π orbitals. To use the terminology developed in physical organic chemistry, the substrate and the phenanthroline are conjugated through the manganese, but not through zinc because of the absence of an appropriate π orbital. If this were the only influence operating on the decarboxylation rate, one would expect that upon substitution of the phenanthrolines at the 4 and 7 positions additional changes in rate would occur for the manganese catalyst but not for the zinc, as a result of the resonance effect. Many of the zinc catalysts in fact have quite similar rates, but at least the dichloro and dimethoxy derivatives show marked differences. Some other influence must also be operating on the substrate as a result of the substitution of remote positions on the phenanthroline. It should be noted that the resonance effect can be made to correlate a considerable amount of the data. Ligands may be picked out which seem to be affected to the same extent by whatever influence is operative beyond the resonance effect. These are the aqueous catalyst, the phenanthroline complex, the bis(phenanthroline) complex, and the complexes of 4,7-dihydroxy and 4,7-dibromo derivatives, which all have the same rates for zinc, where resonance does not operate. Examining the rates of the corresponding manganese complexes, one finds them in an order consistent with resonance activation. The aqueous catalyst is slow, $Mn(phen)^{2+}$ is faster, and $Mn(phen)_2^{2+}$ is still faster. The bromo derivative seems a little slower and the dihydroxy derivative much slower than the unsubstituted phenanthroline.

Some other cause must be invoked to help account for the results. The inductive effect, which could operate in both the zinc and manganese catalysts, seems to be a logical complement to the resonance effect. The methoxy group attracts electrons inductively, and this might be responsible for its activation of the catalyst. The apparently contradictory inhibiting effect of hydroxide substitution may be due to partial ionization of the protons on the hydroxide, which would lower the positive charge on the catalyst.

Another possible cause of activation is the disruption of the solvent structure in the region of the metal ion. Reorientation of the water molecules during decarboxylation may contribute to the activation energy of the reaction, and the exclusion of water by phenanthrolines may lower the activation energy. Large substituents on the phenanthrolines should increase water exclusion. The two most effective zinc catalysts do in fact contain the largest substituents, methoxy and phenyl groups. Neither of these arguments, however, will explain the results of methyl substitution at the 4 and 7 positions, which increases the catalytic activity of the manganese complex and decreases that of the zinc complex. It may be that the 4,7-dimethyl-

Table I. Decarboxylation Rates and Rate Constants for Various Catalysts[a]

$M_t \times 10^3$	[cat] $\times 10^3$	$k_o \times 10^5$ sec^{-1}	$\sigma \times 10^5$ sec^{-1}	$k_c \times 10^5$ sec^{-1}	$k \times 10^5$ sec^{-1}	K
1. Aqueous Manganese						
7.25	7.25	8.0	0.39	6.5	19	116
9.48	9.48	8.6	0.38	7.5	±1	±13
14.5	14.5	10.3	0.97	9.6		
21.7	21.7	12.1	1.00	11.7		
43.4	43.4	14.2	1.12	14.0		
72.5	72.5	16.7	0.23	16.6		
108.6	108.6	18.8	0.76	18.7		
2. Manganese–1,10-Phenanthroline						
11.3	10.1	14.0	0.62	11.5	84	18
15.0	13.7	16.9	0.84	14.6	±8	±3
22.5	20.9	22.3	1.19	19.9		
45.0	42.7	34.9	1.44	32.1		
75.1	72.0	45.9	2.78	42.5		
112.6	108.8	62.8	2.30	58.8		
3. Manganese–2(1,10-Phenanthroline)						
7.90	5.88	13.5	0.85	9.3	1650[b]	
11.8	9.31	20.6	0.32	16.4		
17.8	14.6	26.9	0.89	22.4		
25.7	21.8	40.9	1.74	35.8		
39.5	34.6	62.5	2.07	56.4		
4. Manganese–4,7-Diphenyl-1,10-phenanthroline						
7.50	6.57	11.8	1.00	8.8	30	107
11.3	10.1	14.6	0.69	12.2	±4	±40
15.0	13.7	17.7	1.41	15.4		
22.5	20.8	20.5	3.03	18.1		
45.0	42.7	26.5	3.42	23.7		
75.1	72.0	27.6	3.60	24.2		
5. Manganese–3,8-Dicarboxy-4,7-dihydroxy-1,10-phenanthroline						
7.50	6.57	14.36	0.09	1.45	23	12
11.3	10.1	14.94	0.16	2.49	+22	+7
15.0	13.7	5.22	0.37	2.93	−8	
22.5	20.8	6.18	0.14	4.16		
6. Manganese–5-Nitro-1,10-phenanthroline						
7.50	6.57	10.8	0.75	7.5	27	82
11.3	10.1	12.3	0.35	9.5	±2	±19
15.0	13.7	14.2	0.57	11.7		
22.5	20.9	16.8	0.91	14.4		
45.0	42.7	23.1	0.97	20.2		
75.1	72.0	27.0	1.60	23.6		
7. Manganese–4,7-Dihydroxy-1,10-phenanthroline						
7.50	6.57	6.6	0.19	3.7	16	67
11.3	10.1	7.8	0.22	5.4	±1	±10
15.0	13.7	8.5	0.16	6.2		
22.5	20.8	10.7	0.45	8.4		
45.0	42.7	14.0	0.51	11.2		
75.0	72.0	16.0	0.92	12.6		
112.6	108.8	18.3	0.65	14.3		
8. Manganese–4,7-Dimethyl-1,10-phenanthroline						
1.88	1.44	7.9	0.03	3.6		
2.81	2.26	9.6	0.71	5.6		
3.75	3.11	10.3	2.21	6.5	*c*	
5.63	4.83	22.5	3.15	19.2		
7.50	6.57	34.8	5.07	31.8		
9. Manganese–2,9-Dimethyl-1,10-phenanthroline						
7.50	3.89	6.0	0.51	0.3	280[b]	
10.5	6.28	7.3	0.22	1.6		
15.0	9.40	8.9	0.31	2.7		
22.5	15.3	11.1	0.15	4.4		
10. Manganese–4,7-Dimethoxy-1,10-phenanthroline						
4.50	3.79	21.0	1.00	16.5		
6.00	5.17	35.5	3.17	31.6		
9.01	7.98	40.7	2.10	37.6	*c*	
12.0	10.8	62.9	7.84	60.2		
15.0	13.7	83.0	8.45	80.5		
11. Manganese–4,7-Dichloro-1,10-phenanthroline						
9.01	7.98	11.1	0.44	8.0	21	153
12.0	10.8	12.7	0.65	9.9	±1	±25
15.0	13.7	14.8	0.21	12.2		
21.0	19.4	16.5	0.08	14.1		
30.0	28.1	17.6	0.37	15.1		
45.0	42.7	18.9	0.51	16.0		
12. Manganese–4,7-Dibromo-1,10-phenanthroline						
9.01	7.98	12.3	0.56	9.21	44	45
15.0	13.7	16.8	0.73	14.3	±13	±27
22.5	20.8	20.5	2.52	18.1		−17
45.0	42.7	29.2	6.27	26.3		
13. Aqueous Zinc						
0.431		6.3	0.14		111	103
0.718		8.0	0.19		±10	±15
1.44	1.44	12.6	0.20	9.2		
2.87	2.87	20.3	0.98	17.6		
4.31	4.31	26.7	0.90	24.6		
7.18	7.18	35.8	1.84	34.7		
14.4	14.4	55.3	2.95	55.0		
28.7	28.7	74.7	4.52	74.6		
14. Zinc–1,10-Phenanthroline						
0.718		9.7	0.33			
1.01	0.94	11.6	0.20	7.2	119	112
1.44	1.36	14.0	0.18	9.7	±30	±40
2.01	1.92	17.6	0.29	13.5		
2.87	2.76	22.8	0.46	19.0		
4.31	4.18	29.9	1.20	26.6		
15. Zinc–2(1,10-Phenanthroline)						
0.718	0.601	8.8	0.20	3.8	350	22
1.44	1.27	12.8	1.34	7.7		
2.87	2.63	22.1	1.40	17.2		
4.31	4.00	27.9	0.91	23.1		
16. Zinc–4,7-Diphenyl-1,10-phenanthroline						
1.44	1.36	13.4	0.31	9.1	164	66
2.87	2.76	22.9	0.83	19.1	±18	±10
4.31	4.18	35.3	4.25	32.0		
7.18	7.01	50.5	5.10	48.0		
14.4	14.1	63.0	11.67	61.0		
17. Zinc–4,7-Diphenyl-1,10-phenanthroline, Sulfonated, Sodium Salt						
1.44	1.36	12.61	1.33	8.3		
2.01	1.92	15.31	1.69	11.2		
2.87	2.76	14.21	0.96	10.4		
3.44	3.33	15.18	0.17	11.6	*d*	
4.31	4.18	16.13	1.68	12.8		
5.74	5.59	18.81	2.68	16.0		
18. Zinc–4,7-Dihydroxy-1,10-phenanthroline						
1.44	1.36	12.2	0.74	7.9	250	31
2.87	2.76	19.1	0.41	15.3	+325	+30
4.31	4.17	26.8	0.64	23.5	−100	−20
7.18	7.01	38.3	2.09	35.9		
14.35	14.1	60.8	10.25	58.8		
19. Zinc–4,7-Dimethyl-1,10-phenanthroline						
0.718	0.665	5.9	0.31	0.1		
1.44	1.36	6.1	0.23	0.7	*d*	
2.87	2.76	6.8	1.18	2.1		
4.31	4.18	6.7	1.28	2.7		
20. Zinc–4,7-Dimethoxy-1,10-phenanthroline						
0.574	0.528	10.0	0.78	4.3		
0.861	0.804	16.3	1.56	10.7		
1.15	1.08	22.8	0.28	17.3	*c*	
1.44	1.36	30.8	4.92	25.4		
1.72	1.64	39.0	5.36	33.8		

$M_t \times 10^3$	[cat] $\times 10^3$	$k_o \times 10^5$ sec^{-1}	$\sigma \times 10^5$ sec^{-1}	$k_c \times 10^5$ sec^{-1}	$k \times 10^5$ sec^{-1}	K
21. Zinc–4,7-Dichloro-1,10-phenanthroline						
1.44	1.36	12.0	0.73	7.7	112	71
2.87	2.76	14.7	0.79	10.9	±21	±22
4.31	4.18	21.0	0.73	17.7		
5.74	5.59	25.6	1.18	22.7		
7.18	7.01	31.8	1.47	29.3		
14.4	14.1	51.9	1.46	49.8		
22. Zinc–4,7-Dibromo-1,10-phenanthroline						
1.44	1.36	14.2	0.42	9.9	80	196
2.87	2.76	20.6	0.71	16.8	±7	±35
4.31	4.18	25.8	1.08	22.5		
7.18	7.01	37.7	0.71	35.3		
23. Aqueous Magnesium						
10.0	10.0	5.1	0.12	3.1	8.5	93
15.0	15.0	5.7	0.27	4.2	±0.3	±10
22.5	22.5	6.3	0.24	5.2		
45.0	45.0	6.8	0.20	6.2		
75.0	75.0	7.6	0.28	7.3		
150.0	150.0	8.6	0.25	8.4		
24. Magnesium–1,10-Phenanthroline						
45.0		6.7	0.16			
75.0		7.8	0.29	*e*		

[a] The initial concentration of dimethyloxaloacetic acid was 7.81 × 10^{-3} *M* in every case. Metals were introduced as solutions of chloride salts. [b] Calculated on the assumption of an association-limited mechanism. [c] Mechanism is dissociation limited. [d] Results are too erratic for a meaningful calculation. [e] Compare with aqueous magnesium rates at the same catalyst concentrations.

1,10-phenanthroline–zinc catalyst is a very effective decarboxylating agent, but that its affinity for the decarboxylated product is large enough to prevent a rapid or extensive regeneration of the catalyst. The corresponding manganese catalyst would be more easily regenerated because of the larger size of the metal ion. A more compelling conclusion will have to await determination of the rate-determining step by the mass-spectrometric method.

The Rate-Determining Step. In the cycle of decarboxylation catalysis, any of three steps may limit the rate: the association of the substrate and the catalyst, the decarboxylation of the complex, or the dissociation of the catalyst and the decarboxylated substrate. In the system under study, the rate-determining reaction can usually be distinguished. A rate-limiting association will be first order in catalyst concentration and a graph of k_c *vs.* [catalyst] (or of $1/k_c$ *vs.* 1/[catalyst]) will

$$\mathrm{LM} + \mathrm{S} \underset{k}{\overset{\text{slow}}{\longrightarrow}} \mathrm{LMS} \overset{\text{fast}}{\longrightarrow} \mathrm{LMP} + \mathrm{CO_2} \qquad (17)$$

$$\text{rate} = k[\mathrm{LM}][\mathrm{S}] = k_{\mathrm{obsd}}[\mathrm{S}] \qquad (18)$$

$$k_{\mathrm{obsd}} = k[\mathrm{LM}] \qquad (19)$$

be a straight line going through the origin. This would occur when association was for some reason very unfavorable, for example, due to steric effects.

When decarboxylation is rate-determining, the graph of k_c *vs.* [catalyst] will be curved. This is indicated by (22), which results from [LM] being a function of [S],

$$\mathrm{LM} + \mathrm{S} \underset{K}{\overset{\text{fast}}{\rightleftharpoons}} \mathrm{LMS} \underset{k}{\overset{\text{slow}}{\longrightarrow}} \mathrm{LMP} + \mathrm{CO_2} \qquad (20)$$

$$\text{rate} = k[\mathrm{LMS}] = kK[\mathrm{LM}][\mathrm{S}] \qquad (21)$$

$$k_{\mathrm{obsd}} \neq kK[\mathrm{LM}] \qquad (22)$$

and prevents eq 21 from being integrated as a first-order equation in [S]. The graph of $1/k_c$ *vs.* 1/[catalyst] will be a straight line with a nonzero intercept. Derivation of the proper equation has already been dealt with.

If the dissociation step, which regenerates the catalyst, should become rate determining, a rapid initial decarboxylation will occur until the catalyst is saturated with decarboxylated substrate. The rate will then decrease as it becomes limited by catalyst regeneration. This initial fast rate would be expected to be visible when the catalyst is at a concentration which is smaller, but not a great deal smaller, than the substrate.

$$\mathrm{LM} + \mathrm{S} \underset{K}{\overset{\text{fast}}{\rightleftharpoons}} \mathrm{LMS} \overset{\text{fast}}{\longrightarrow} \mathrm{LMP} + \mathrm{CO_2} \overset{\text{slow}}{\longrightarrow} \mathrm{LM} + \mathrm{P} + \mathrm{CO_2} \qquad (23)$$

Caution must be exercised in the interpretation of the rate-determining step. In particular, a fast rate-determining decarboxylation will have a very small intercept on the plot of $1/k_c$ *vs.* 1/[catalyst], and may thus be confused with a rate-determining association. Generally speaking, the latter should be slow and the former fast, if an appropriate standard of "normal" speed can be found.

Rate-Determining Association. One catalyst seems to have its activity limited by the rate at which the substrate can coordinate to the metal ion: the 2,9-dimethyl-1,10-phenanthroline–manganese complex. Its rate is plotted in Figure 3 and may be seen to fit the expected pattern fairly well. The rate is slowed by steric hindrance. The methyl groups project out beyond the metal and must considerably impede the approach of the substrate to the metal. The reaction is kinetically well behaved. Steric and neighboring-group effects will be treated in a later paper. The intrinsic constant for this catalyst is 0.00280 sec^{-1}. This number refers to k in eq 15. It can be compared to the product kK for a reaction with a rate-determining decarboxylation step and is seen to be much smaller than the rates of other mono(phen) derivatives. Another catalyst which may be in this category is the $Mn(phen)_2^{2+}$ complex (see Figure 3). Its reaction rate is also first order in catalyst. Its reactions are fast, however, and its intrinsic rate constant, assuming this mechanism, is 0.0165 sec^{-1}. It is possible that this is a case of rate-determining decarboxylation which is fast enough that the intercept of the reciprocal plot is not distinguishable from zero. These two alternatives can be decided between using the kinetic isotope approach employed by Westheimer.[15]

Rate-Determining Decarboxylation. The aqueous metal ions and catalysts 2, 4–6, 7, 11, 12, 14–16, 18, 21, and 22 have rate-determining decarboxylation steps. Some reciprocal plots are illustrated in Figure 4. Coordination of the enzyme protein to a metal ion causes this step to become so much faster that it is no longer rate determining.[15] Thus the factors which influence the rate of this step are of particular interest in under-

(15) S. Seltzer, G. A. Hamilton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **81**, 4018 (1959).

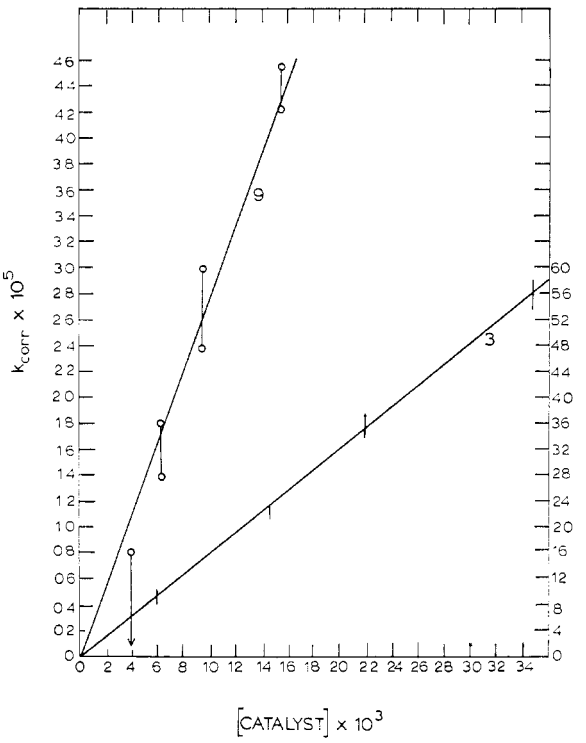


Figure 3. Catalysts conforming to the expected pattern for rate-determining association. Numbers refer to Table I. Units on the left ordinate refer to catalyst 9, and those on the right to 3.

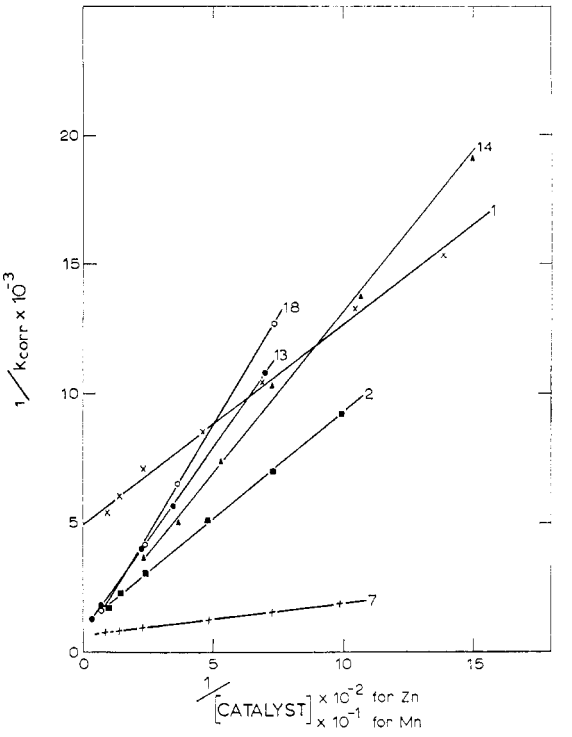


Figure 4. Some representative plots for catalysts with rate-determining decarboxylation steps. Numbers refer to Table I.

standing the function of the protein. The intrinsic reaction constants are a disappointment in this regard because of their great sensitivity both to the exact fit of the line to the reciprocal plot and to the value chosen for the rate of the autodecarboxylation. The rate of autodecarboxylation was influenced by the addition of ligand, even when no metal ion was present. The error in this correction cannot have been large, but, in an unfavorable case, it might have made a considerable error in the intrinsic rate constants, larger than that indicated in Table I.

In examining the intrinsic rate constants for manganese, it may be seen that the $Mn(phen)^{2+}$ catalyst has the largest k. Even the groups on the phenanthroline which are expected to be electron withdrawing, Br and Cl, seem to be slower than H. This may perhaps be explained on the basis of the high charge on the metal ion, which might polarize these groups more than it can the hydrogen and cause them to be relatively electron donating. The range for most of the constants is so great for zinc that no general statement about those catalysts is possible. The results are not readily explained.

The intrinsic equilibrium constants are smaller than the ones reported between these metals and similar β-keto acids.[16] It has already been pointed out[5] that this is a result of the difference in what is being measured. The kinetic method used here measured only coordination of the acid in the manner favorable for decarboxylation (see reaction 1), while the potentiometric method measured coordination through any atoms. The difference in the two equilibrium constants, which is about an order of magnitude, suggests that the substrate spends most of its time on the metal

(16) E. Gelles and R. W. Hay, *J. Chem. Soc.*, 3673 (1958).

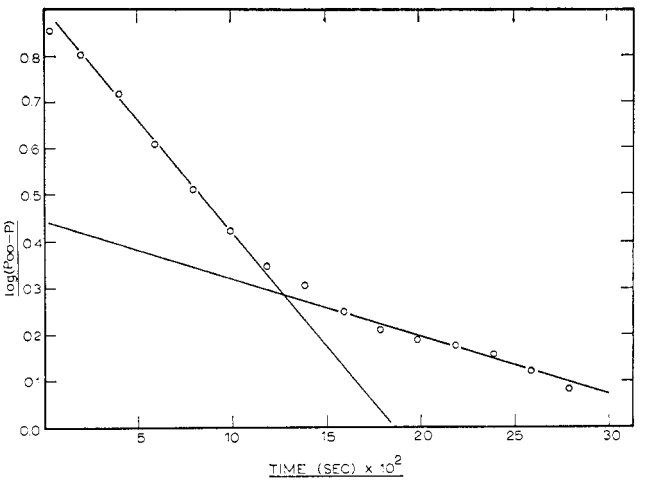


Figure 5. A kinetic run for manganese–4,7-dimethoxy-1,10-phenanthroline catalyst at a concentration of 0.00657 *M*. This illustrates the predicted pattern for a rate-determining dissociation step.

in a position in which it cannot be decarboxylated. If an enzyme protein were capable of causing the substrate to approach the metal only in a disposition favorable to reaction, the rate would be greatly enhanced.

Rate-Determining Dissociation. There are three mono(phen) catalysts which are much more active than any of the others. These are the 4,7-dimethoxyphenanthroline complexes of manganese and zinc and the 4,7-dimethyl complex of manganese. None of these fits either of the previous patterns of variation in rate as a function of catalyst concentration. An initial large rate, slowing as the catalyst becomes saturated

with decarboxylated substrate, was observed for a number of the reactions. The effect was most pronounced where the catalyst was present to the extent of about 60–80% of the substrate. Figure 5 illustrates a reaction where this is occurring. Both manganese catalysts exhibited this behavior, but it was not observed for zinc, where the highest concentration of catalyst was only 20% of the substrate. It may be that the initial fast reaction was over before any measurements were made. Certainly when the manganese catalysts were at this concentration, the fast initial rate was difficult to see. The values given in Table I are for the slower part of the reaction. Initial rates were as much as five times this fast.

These complexes are the most like the enzyme, inasmuch as they are the most efficient catalysts and appear to have the same rate-determining step. The methoxy complexes at least do not derive their activation from the resonance effect, which does not occur for zinc and would be expected to deactivate the complex for manganese.

Other Catalysts. At low concentrations, some of the complexes showed deviations from the expected patterns of behavior. The corrections for these were large relative to the rate constant itself. Their observed rates are reported in Table I, but the corrected constants are omitted. These data were not used to compute intrinsic constants. The sodium salt of the sulfonated 4,7-diphenyl-1,10-phenanthroline complexes gave such erratic results that computations based on them are not meaningful.

Conclusions

It has been shown that when two ligands are coordinated to a single metal ion, changes in one can affect the reaction rate of the other, even when the changes in the first are remote from the second. Coordination of a manganese ion with a phenanthroline molecule greatly increases its ability to catalyze the decarboxylation of a β-keto acid. Catalysis by zinc, however, is unaffected by coordination with phenanthroline. Substitution of the phenanthroline at the 4 and 7 positions is also shown to change the rate. The resonance effect, which allows electron density from the acid to be delocalized into the system of the metal–phenanthroline complex, is suggested as a contributing influence. A second influence, the nature of which has not yet been determined, also affects the catalytic behavior of these compounds. The inductive effect is not usefully invoked to do this. Some very effective catalysts for decarboxylation have been found, and these are activated by the second influence. The data strongly suggest that they have the same rate-determining step as the decarboxylase enzyme. The enzyme protein does not activate the metal ion in the same way as phenanthroline itself does, but the second and unidentified influence, exerted for example by the methoxy phenanthrolines, may be a contributor to the activation by the enzyme.

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Preparation and Characterization of New Fluoroxy Compounds. Bis(fluoroxy)perfluoroalkanes[1,2]

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Abstract: The synthesis and characterization of $CF_3CF(OF)_2$ and $(CF_3)_2C(OF)_2$, representing the new class of geminal bisfluoroxy compounds, are reported. Their formation from $(CF_3)_2C(OH)ONa$ illustrates the unique behavior of salts in direct fluorination.

We have reported[3] the preparation and reactions of the monofluoroxy compounds: CF_3CF_2OF, $CF_3CF_2CF_2OF$, $(CF_3)_2CFOF$, $(CF_3)_3COF$, $NO_2CF_2CF_2OF$, $ClCF_2CF_2OF$, Cl_2CFCF_2OF, and Cl_3CCF_2OF, as well as[4] $FC(O)CF_2CF_2OF$ and $FOCF_2CF_2CF_2OF$. Cady and co-workers previously described the synthesis of CF_3OF[5] and several unstable acyl OF compounds.[6] In this paper the preparation of two members of a new class of compounds, the bis(fluoroxy)perfluoroalkanes, is reported. The characterization and certain reactions of these compounds, $CF_3CF(OF)_2$ and $(CF_3)_2C(OF)_2$, are also presented. In addition, an improved synthesis of C_2F_5OF[3] is reported.

Discussion

The direct fluorination of perfluoroacetone hydrate, $(CF_3)_2C(OH)_2$, yields $(CF_3)_2CFOF$.[3] We now report

(1) (a) Some of the material in this paper was included in the review paper "Oxygen Fluorides and Hypofluorites" by P. G. Thompson at the Fluorine Symposium of the Inorganic Division of the American Chemical Society, Ann Arbor, Mich., June 27, 1966. (b) In accordance with the recommendations of the American Chemical Society Committee on Nomenclature of Highly Fluorinated Molecules, the term fluoroxy is used for the OF group.

(2) This research was supported by the Advanced Research Projects Agency under Contract NOrd 18688 and was monitored by the Bureau of Naval Weapons.

(3) J. H. Prager and P. G. Thompson, *J. Am. Chem. Soc.*, **87**, 230 (1965).

(4) J. H. Prager, *J. Org. Chem.*, **31**, 392 (1966).

(5) K. B. Kellogg and G. H. Cady, *J. Am. Chem. Soc.*, **70**, 3986 (1948).

(6) (a) G. H. Cady and K. B. Kellogg, *ibid.*, **75**, 2501 (1953); (b) A. Menefee and G. H. Cady, *ibid.*, **76**, 2020 (1954).