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Retrograde Aldol Reaction of 3-(1-Hydroxy-2,2,2-trichloroethyl)-2,4-pentanedione Catalyzed by the Bivalent Metal Complexes of 2,4-Pentanedione[1]

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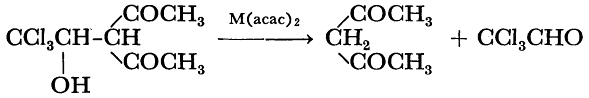
The bivalent metal complexes of 2,4-pentanedione($M(acac)_2$) catalyzes the conversion of 3-(1-hydroxy-2,2,2-trichloroethyl)-2,4-pentanedione(A) into chloral and acetylacetone(Hacac) in a chloroform solution. The order of activity of $M(acac)_2$ as the catalyst is: Mg(II), Mn(II)>Co(II)>Ni(II)>Cu(II)<Zn(II). It was found that the catalyzed reaction proceeds through saturation-type kinetics. The Lineweaver-Burk-type plots show linear relationships and are consistent with a mechanism in which a preequilibrium complex formation between $M(acac)_2$ and a substrate is followed by the rate-determining decomposition to give the products. Acetylacetone acts as a competitive inhibitor for the $Cu(acac)_2$-catalyzed reaction. The third stability constant for the Cu-Hacac chelate system can be evaluated from the inhibitor constant as $\log K_3=4.3$. The retrograde aldol reactions of 3-(1-hydroxy-2,2,2-trichloroethyl)-5-methyl-2,4-hexanedione and 3-(1-hydroxy-2,2,2-trichloroethyl)-4-phenyl-2,4-butanedione were studied in the same manner as 3-(1-hydroxy-2,2,2-trichloroethyl)-2,4-pentanedione. A possible mechanism for the catalysis is proposed.

A number of studies have been carried out on the catalysis of metal ions or chelates for the clarification of the role of metal ions in metalloenzymes. Sigman and Jorgensen[2] reported the zinc(II)-catalyzed transesterification of *N*-(2-hydroxyethyl)ethylenediamine by *p*-nitrophenyl picolinate which involved a reactive ternary complex analogous to metalloenzyme–substrate complexes. Breslow *et al.*[3] found that the mechanism of metal-catalyzed hydration of 2-cyano-1,10-phenanthroline is related to the "rack mechanism" proposed for some enzymatic processes.

These metal-catalyzed processes represent models for the catalytic role of metals in the active site and not for overall enzymatic processes, since catalysis of metal ions or chelates differs essentially from that of enzymes. However, the rate of the metal-catalyzed reaction can be described by saturation-type kinetics if the substrate(S) coordinates to a vacant site of metal ion or chelate(M) to give the complex(SM) which is decomposed to products(P) and M; $S+M \rightleftarrows SM \rightarrow P+M$. Tsuchida *et al.*[4] found that the oxidative polymerization of 2,6-xylenol with a copper–amine complex proceeds *via* a mechanism similar to that of a Michaelis-Menten-type reaction.

In the present paper it is shown that the rates of $M(acac)_2$-catalyzed retrograde aldol reaction (1) can be explained in terms of saturation-type kinetics, and that the third stability constant for the Cu–Hacac chelate system can be obtained from the kinetic parameters of the inhibitory action of acetylacetone on the $Cu(acac)_2$-catalyzed reaction as shown below.



$$\mathrm{CCl_3CH(OH)\text{-}CH(COCH_3)_2} \xrightarrow{\mathrm{M(acac)_2}} \mathrm{CH_2(COCH_3)_2} + \mathrm{CCl_3CHO}$$

(A) H(acac)

(1)

Experimental

Materials. 3-(1-Hydroxy-2,2,2-trichloroethyl)-2,4-pentanedione(A) was prepared according to the method described in the preceding paper.[5] Similarly, 3-(1-hydroxy-2,2,2-trichloroethyl)-5-methyl-2,4-hexanedione(B) was prepared from a mixture of 5.9 g (0.046 mol) of isobutyrylacetone,[6] 6.8 g (0.046 mol) of chloral and a few drops of piperidine in a yield of 20% (2.54 g). Mp 59 °C. Found: C, 39.19; H, 4.70%. Calcd for $C_9H_{13}O_3Cl_3$: C, 39.23; H, 4.76%. IR(KBr disk): 3380(s), 2920(m), 1720(s), 1690(s), 1460(s), 1350(s), 1290(m), 1150(m), 1100(m), 990(w), 810(s), and 710 cm^{-1} (s). UV($CHCl_3$): λ_{max} 290 nm(ε_{max} 137). 3-(1-Hydroxy-2,2,2-trichloroethyl)-4-phenyl-2,4-butanedione (C) was synthesized from 3.1 g (0.019 mol) of benzoylacetone and 2.8 g (0.019 mol) of chloral in the presence of piperidine (yield, 3.4 g(59%)). Mp 91 °C. Found: C, 46.14; H, 3.52%. Calcd for $C_{12}H_{12}O_3Cl_3$: C, 46.41; H, 3.89%. IR(KBr disk): 3370(s), 1705(s), 1680(s), 1450(m), 1360(s), 1290(s), 1180(s), 1100(s), 1050(w), 980(m), 840(m), 805(m), 790(s), 760(s), and 700 cm^{-1}(m). UV($CHCl_3$): λ_{max} 252 nm(ε_{max} 317). $M(acac)_n$ of GR grade reagents(Dojindo Co. Ltd., Research Laboratories, Kumamoto) were used without further purification. Copper(II) chelates of isobutyrylacetone and benzoylacetone were prepared by the method of Adams *et al.*[6] Commercial acetylacetone and chloroform were distilled before use.

Spectral Measurements. The IR spectra were measured with a Hitachi Model 215 grating spectrophotometer, the UV spectra with a Shimadzu UV-200 spectrophotometer, and the NMR spectra with a Hitachi Model R-20 spectrometer. Tetramethylsilane was used as an internal standard, deuteriochloroform being used as the solvent. Elemental analyses were carried out with a Yanagimoto Model MT-2 CHN analyzer.

Kinetic Measurements. Kinetic measurements were carried out spectrophotometrically by monitoring the spectral changes in the 250—350 nm region. The absorbance of a mixed solution of A(or either B or C) and $M(acac)_2$ increased with time, the spectrum being similar to that of acetylacetone (or the corresponding β-diketones) even at a very low conversion(below 2%) since absorbance of A and chloral is regarded as negligible as compared with that of acetylacetone. The chloroform solution containing only $M(acac)_2$ showed no observable spectral change during the course of measurement. An example of the time-dependent UV spectra of a reaction mixture is shown in Fig. 1. The initial rate of the retrograde aldol reaction can be followed conveniently by the measurement of UV absorption. The amount of produced acetylacetone, or consumed A, can be calculated as follows: where Abs(t) and $c_{\mathrm{Hacac}}(t)$ denote absorbance and concentration, respectively, of acetylacetone at time t, c_{A}^{0} and c_{M}^{0} the initial concentrations of A and $M(acac)_2$, respectively, and ε_{A}, ε_{M}, $\varepsilon_{\mathrm{Hacac}}$, and $\varepsilon_{\mathrm{chloral}}$ the molar extinction coefficients of A, $M(acac)_2$, Hacac, and chloral,

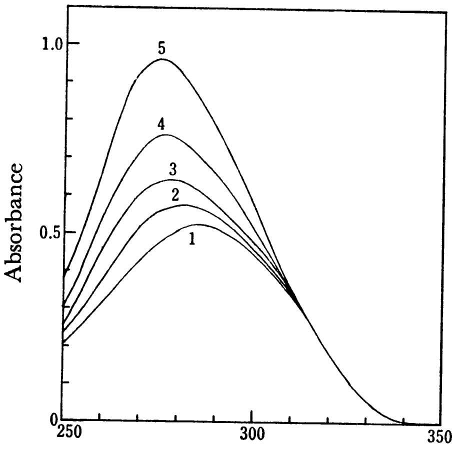


Fig. 1. Time-dependent UV spectra of a mixture of A and $Cu(acac)_2$ at 26 °C in chloroform after mixing. $[A]=3.53\times10^{-3}$ M, $[Cu(acac)_2]=5.83\times10^{-6}$ M, 1 : $t=2$ min, 2 : $t=11$ min, 3 : $t=21$ min, 4 : $t=37$ min, 5 : $t=63$ min (conversion=1.77%).

$$A + M(acac)_2 \rightarrow Hacac + chloral + M(acac)_2 \tag{2}$$

$$Abs(t) = \varepsilon_A c_A^0(1-x) + \varepsilon_M c_M^0 + \varepsilon_{Hacac} x c_A^0 + \varepsilon_{chloral} x c_A^0 \tag{3}$$

$$c_{Hacac}(t) = x c_A^0 = \frac{Abs(t) - \varepsilon_A c_A^0 - \varepsilon_M c_M^0}{\varepsilon_{Hacac} + \varepsilon_{chloral} - \varepsilon_A} \tag{4}$$

respectively. The initial rate of reaction can be calculated from the initial slope obtained from a time-conversion curve. For example, at 280 nm,

$$Rate = \frac{Abs(\Delta t) - Abs(0)}{\Delta t \times 2.598\times10^7} \quad (M\,s^{-1}) \tag{5}$$

At low conversions below 2%, time-conversion curves gave straight lines passing through the origin, suggesting that the ligand exchange reaction beween A and $M(acac)_2$ can be neglected.

Spectrometric Determination of Equilibrium Constant. The reaction (1) is reversible.[7] The formation of A was followed by means of NMR in a deuteriochloroform solution of chloral, acetylacetone, and $M(acac)_2$. 0.0013 g of $M(acac)_2$ was added to a 2 ml deuteriochloroform solution of chloral and acetylacetone($[CCl_3CHO]=[Hacac]=1.02$ M). The NMR spectrum of this solution was measured after it had been left to stand at room temperature for a few hours. Similarly, the NMR spectrum of a deuteriochloroform solution containing A ($[A]=1.02$ M) and 0.0013 g of $Mg(acac)_2$ was also measured after being left to stand for several hours. The two spectra agreed with each other. The equilibrium constant K of Eq. 6 was obtained to be 1.22 M^{-1} from the NMR data.

$$Chloral + Hacac \overset{K}{\rightleftharpoons} A \tag{6}$$

Results and Discussion

Rate Equation of Retrograde Aldol Reaction. Though the reaction took place without catalyst, the reaction rate in chloroform solution was low at room temperature. The rate of catalyzed reaction was found to be of pseudo-first order with respect to $M(acac)_2$ at constant initial concentration of A. Thus, the rate of disappearance of A is described as

$$Rate = k_{cat}[M(acac)_2] + E \tag{7}$$

TABLE 1. PSEUDO-FIRST-ORDER RATE CONSTANTS CATALYZED BY $M(acac)_n$, SECOND STABILITY CONSTANTS FOR METAL COMPLEXES WITH ACETYLACETONE, AND FORCE CONSTANTS OF $M(acac)_2$

$[A]=3.35\times10^{-3}$ M, at 26 °C in chloroform

$M(acac)_n$	$k_{cat}\times10^2\ s^{-1}$	$\log K_2$[8]	$K(M\text{-}O)$[12] $N\ cm^{-1}$
$Mg(acac)_2$	14.0	6.27	
$Mn(acac)_2$	14.0	7.35	
$Co(acac)_2$	6.5	9.54	1.50
$Ni(acac)_2$	1.8	10.77	2.05
$Zn(acac)_2$	1.2	8.81	1.50
$Cu(acac)_2$	0.08	16.34	2.20
$Co(acac)_3$	0		2.40
$Cr(acac)_3$	0		2.30

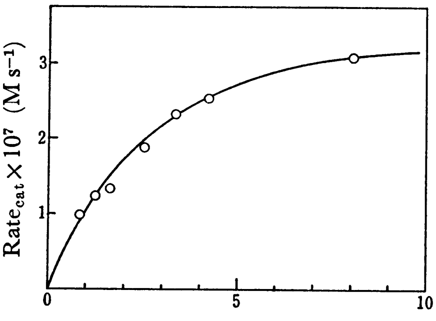


Fig. 2. Plot of initial rate of retrograde aldol reaction, catalyzed by $Co(acac)_2$ *vs.* concentration of A at 26 °C in chloroform. $[Co(acac)_2]=5.66\times10^{-6}$ M.

where E is the rate for the spontaneous reaction in the absence of $M(acac)_2$. The values of k_{cat} for various $M(acac)_2$ are given in Table 1. The trivalent metal complexes of 2,4-pentanedione such as $Co(acac)_3$ and $Cr(acac)_3$ were inactive as a catalyst. It was found that the order of activity of $M(acac)_2$ as the catalyst is: Mg(II), Mn(II) > Co(II) > Ni(II) > Cu(II) < Zn(II). $M(acac)_2$ having a stable O–M bond is unfavorable for a high catalytic activity. Thus, it is suggested that the present catalysis also proceeds *via* the dissociation of the O–M bond as shown for the metal-ion-catalyzed alcoholysis of β-diketones.[9]

Figure 2 shows a typical example of the plots of observed initial rates *vs.* concentrations of A. The observed saturation phenomenon can be analyzed in terms of saturation-type kinetics. The kinetics is based on the assumption that substrate A coordinates reversibly to a vacant site of $M(acac)_2$ to form a complex which is then decomposed, giving back the free $M(acac)_2$ and products(acetylacetone and chloral). The kinetic expression for the present reaction can be written as

$$A + M \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} AM \xrightarrow{k_2} M + P \tag{8}$$

where M stands for $M(acac)_2$, A is 3-(1-hydroxy-2,2,2-trichloroethyl)-2,4-pentanedione, and P is acetylacetone and chloral.

If the aldol reaction ($P \xrightarrow{M} A$) is neglected when the concentration of P is sufficiently small, the catalyzed reaction rate ($\mathrm{Rate_{cat}}$) is expressed as follows from the steady state of the intermediate AM.

$$\mathrm{Rate_{cat}} = \frac{V[\mathrm{A}]}{K_\mathrm{m}+[\mathrm{A}]} \tag{9}$$

where $V=k_2[\mathrm{M}]^0$, $K_\mathrm{m}=(k_{-1}+k_2)/k_{+1}$. This is of the same form as the Michaelis-Menten mechanism and explains the fact that the rate of the catalyzed reaction is proportional to the initial concentration of $\mathrm{M(acac)_2}$ at a given concentration of A and that the initial rate *vs.* [A] curve shows a pronounced saturation. Equation 9 can be rearranged to give Eq. 10. If $1/\mathrm{Rate_{cat}}$ is plotted against $1/[\mathrm{A}]$ (Lineweaver-Burk plot),[10] the values of the maximum rate V and the constant K_m can be obtained from the intercepts of vertical and horizontal axis, respectively.

$$\frac{1}{\mathrm{Rate_{cat}}} = \frac{1}{V} + \frac{K_\mathrm{m}}{V}\frac{1}{[\mathrm{A}]} \tag{10}$$

As shown in Fig. 3, the Lineweaver-Burk plot (Fig. 2) gives a straight line with intercepts of vertical axis of $1/V$ and of horizontal axis of $-1/K_\mathrm{m}$, supporting the above hypothesis that the present reaction can be written by Eq. 8 and the aldol reaction is neglected presumably because of very low concentration of P in the initial stage of the reaction. The rate constant k_2 is evaluated from the maximum rate V, which is defined as $k_2[\mathrm{M}]^0$. The values of K_m, k_2 and k_2/K_m obtained from Lineweaver-Burk plots for the various $\mathrm{M(acac)_2}$-catalyzed reactions are given in Table 2. If $k_{-1} \gg k_2$, K_m can be defined as k_{-1}/k_{+1} (dissociation constant of complex AM), and if $k_{-1} \ll k_2$, $K_\mathrm{m}=k_2/k_{+1}$. An approximate parallelism is observed between K_m and k_2 within a series of $\mathrm{M(acac)_2}$-catalyzed retrograde aldol reactions of A(Table 2).

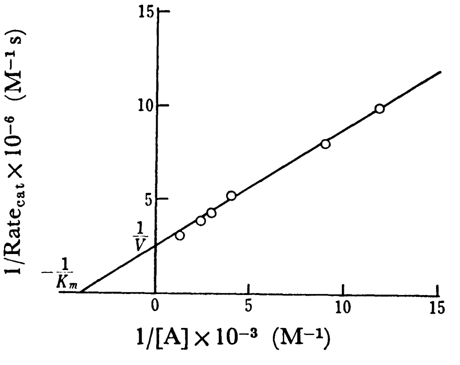


Fig. 3. Lineweaver-Burk-type plot of the data of Fig. 2.

Table 2. Kinetic parameters for the retrograde aldol reaction of A catalyzed by various $\mathrm{M(acac)_2}$ at 26 °C in chloroform

$\mathrm{M(acac)_2}$	$K_\mathrm{m}\times10^4$ M	$k_2\times10^2\ \mathrm{s^{-1}}$	k_2/K_m $\mathrm{M^{-1}\,s^{-1}}$
$\mathrm{Mg(acac)_2}$	37.0	14.0	38
$\mathrm{Co(acac)_2}$	2.6	7.1	270
$\mathrm{Ni(acac)_2}$	7.2	2.2	30
$\mathrm{Zn(acac)_2}$	9.1	1.4	15
$\mathrm{Cu(acac)_2}$	0.34	0.076	22

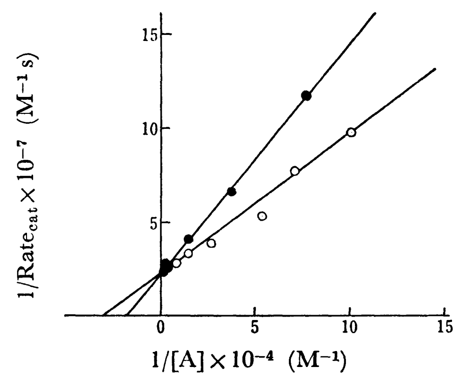


Fig. 4. Inhibitory action of acetylacetone on the $\mathrm{Cu(acac)_2}$-catalyzed retrograde aldol reaction of A at 26 °C in chloroform. $[\mathrm{Cu(acac)_2}]=5.92\times10^{-5}$ M.
—○—: In the absence of Hacac,
—●—: in the presence of Hacac ($[\mathrm{Hacac}]=3.11\times10^{-5}$ M).

Inhibitory Action of Acetylacetone on the $\mathit{Cu(acac)_2}$*-Catalyzed Reaction.* It is highly probable that the catalytic action of $\mathrm{M(acac)_2}$ will be suppressed in the presence of a compound which can coordinate to $\mathrm{M(acac)_2}$. Conversely, observation of the inhibitory action should emphasize the validity of the proposed mechanism. Acetylacetone which is one of the reaction products is an effective ligand for the metal ions and should act as a competitive inhibitor. In the presence of acetylacetone, the initial rate of the $\mathrm{Cu(acac)_2}$-catalyzed retrograde aldol reaction of A in chloroform was measured as a function of the concentration of A. Figure 4 shows the relationship between initial rate and substrate concentration [A] in the absence and presence of acetylacetone. Compared with the initial rate in the absence of the inhibitor, the initial rate in the presence of acetylacetone was somewhat reduced without alteration of the maximum rate. This suggests that acetylacetone behaves as a typical competitive inhibitor, *i.e.*, acetylacetone competes with A for occupation of the coordination site of $\mathrm{Cu(acac)_2}$ to form a five-coordinated copper(II) complex. The whole reaction containing the inhibition of acetylacetone can be represented as follows.

$$\mathrm{A} + \mathrm{M} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} \mathrm{AM} \xrightarrow{k_2} \mathrm{Hacac} + \mathrm{CCl_3CHO} + \mathrm{M} \tag{11}$$

$$\mathrm{Hacac} + \mathrm{M} \xrightarrow[k_{-1}]{k_{+1}} \mathrm{Hacac{\cdot}M} \tag{12}$$

By applying the steady-state treatment to AM, we obtain the rate equation

$$\mathrm{Rate_{cat}} = \frac{V[\mathrm{A}]}{K_\mathrm{m}(1+i/K_\mathrm{I})+[\mathrm{A}]} = \frac{V[\mathrm{A}]}{K_\mathrm{p}+[\mathrm{A}]} \tag{13}$$

where i is concentration of acetylacetone, and K_I is dissociation constant of Hacac·M, *viz.*, $K_\mathrm{I}=k_{-1}/k_{+1}$. K_I is also called the inhibitor constant. The value of $K_\mathrm{p}(=K_\mathrm{m}(1+i/K_\mathrm{I}))$ was found to be 5.6×10^{-5} M at $i=3.11\times10^{-5}$ M from Fig. 4, and the K_I value to be 4.8×10^{-5} M from K_p and K_m values.

Since the reciprocal of K_I should be the stability constant of Hacac·M, the value of log $(1/K_\mathrm{I})$, 4.3, corresponds to the third stability constant for the Cu–

Hacac chelate system. The first and second stability constants have been reported to be 8.22 and 6.73, respectively.[11)]

Kinetics for Compounds B and C. The kinetics was studied for the retrograde aldol reactions of 3-(1-hydroxy-2,2,2-trichloroethyl)-5-methyl-2,4-hexanedione(B) and 3-(1-hydroxy-2,2,2-trichloroethyl)-4-phenyl-2,4-butanedione(C) in the same manner as for compound A. Copper(II) chelate of isobutyrylacetone and benzoylacetone were employed as catalyst for the reaction of B and C, respectively. The initial rate of the copper(II)-catalyzed reaction was found to be proportional to the initial concentration of copper(II) chelate at a given concentration of B or C. The saturation-type kinetics was again observed in the plots of initial rates *vs.* concentrations of B or C. The corresponding Lineweaver-Burk-type plots were found to be linear. Kinetic parameters for the reaction of A, B, and C are summarized in Table 3.

TABLE 3. KINETIC PARAMETERS FOR THE REACTION OF A, B, AND C AT 26 °C IN CHLOROFORM

Substrate	$K_m \times 10^4$ M	$k_2 \times 10^3$ s^{-1}	k_2/K_m M^{-1} s^{-1}
A	0.34	0.76	22
B	0.46	6.2	135
C	13	34	26

The k_2 values increase in the order A<B<C. This arises from replacement of the methyl group of acetylacetone by the isopropyl or phenyl group. The substituent effect can be attributed to an increased steric hindrance of intermediate. There is a tendency for the value of K_m to increase with increase in k_2. When the metal ion of $M(acac)_2$ changes as Cu→Ni→Mg, a similar variation in K_m and k_2 values (Cu<Ni<Mg) was observed. This parallelism in K_m and k_2 may be characteristic of the present retrograde aldol reaction, but it is impossible to understand its meaning.

Reaction Mechanism. On the basis of the results, a possible mechanism for the $M(acac)_2$-catalyzed retrograde aldol reaction of A may be proposed as follows. Compound A coordinates to a vacant site of $M(acac)_2$ to give the intermediate AM. The hydroxyl group of the complex is then deprotonated to give acetylacetone with the concomitant rearrangement of electrons in the intermediate leading to chloral elimination and regeneration of $M(acac)_2$.

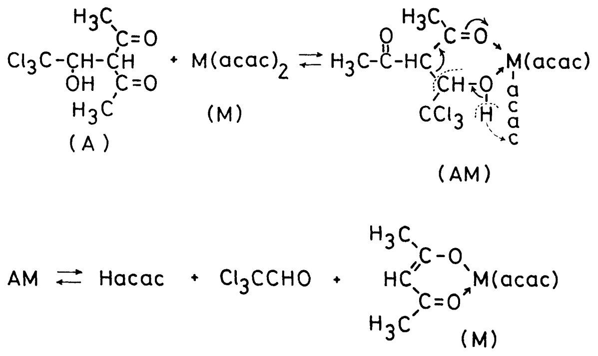


Fig. 5. Reaction scheme.

The present reaction is reversible, the equilibrium constant for the overall reaction being 1.22 M^{-1}. Reaction of acetylacetone with chloral by $M(acac)_2$ will occur with the opposite route of the retrograde aldol reaction to give an equilibrium mixture.

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