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Catalysis of Metal(II) Acetate-2,2′-Bipyridine Complexes in the Aldol Condensations

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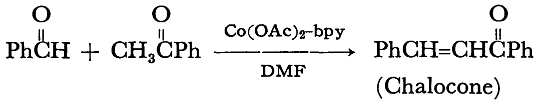
The rate of the condensation of benzaldehyde with excess acetophenone catalyzed by Co(II) acetate–2,2′-bipyridine complex was obtained by GLC analysis. The rate increased in proportion as the amount of the complex catalyst. 2,2′-Bipyridine ligand in the Co(II) complex enhanced the catalytic activity remarkably, though the ligand itself had no activity. When the molar ratio of Co(II): bpy was 1 : 1 or 1 : 2, the highest activity was observed. The activation energy of the complex (1 : 1) catalyzed reaction was calculated as 13.7 kcal/mol. The catalysis of the complex behaved like a base catalyst. Briefly, the relation of the complex catalyzed aldol condensations with the enzymatic reaction of Class II aldolase is also described.

The aldol condensation reactions are generally catalyzed by strong acids or bases. In preceding paper, we have reported that many kinds of the condensation are catalyzed by metal(II) complexes under neutral conditions and afford only cross condensation products, α,β-unsaturated ketones, in satisfactory yields.[1,2] The potent catalysts are complexes of 2,2′-bipyridine(bpy) and the first-row transition metal acetates, particularly Co(II), Ni(II), Cu(II), and Zn(II), and DMF is an excellent solvent.

In this paper, we describe the kinetics of the condensation of the benzaldehyde with acetophenone in DMF containing $\mathrm{Co(OAc)_2}$–bpy complex and features of M(II)acetate–bpy complex. As this study might be connection with the catalysis of Class II aldolase governing the aldol condensation in microorganism, some considerations are also described briefly.

Results and Discussion

Catalytic Behavior of the Metal(II) Complexes. In order to examine the catalytic behavior of the metal complexes in the reaction, the condensations of benzaldehyde with acetophenone(excess) in the presence of $\mathrm{Co(OAc)_2}$–bpy complex were carried out. In the case of this reaction system, dehydration of the addition product occurred immediately to give 1,3-diphenyl-2-propen-1-one(chalcone) without any by-product. The yields of chalcone were determined by GLC analysis.



$$\mathrm{Ph\overset{O}{\overset{\|}{C}}H + CH_3\overset{O}{\overset{\|}{C}}Ph \xrightarrow[\text{DMF}]{\mathrm{Co(OAc)_2\text{-}bpy}} PhCH{=}CH\overset{O}{\overset{\|}{C}}Ph}$$

(Chalocone)

The correlation of the yield(%) with reaction time was observed as a curve line shown in left hand of Fig. 1 which is a typical example. The ln plot of $(a-x)$ (a: initial concentration of the aldehyde, x: concentration of the chalcone produced) *versus* reaction time was shown as a straight line (right hand in Fig. 1). This meant the first order reaction for the concentration of the aldehyde used. The observed rate constant (k'_{obsd}) was calculated from the slope. Thus similar reaction profile was observed in other examples as mentioned below, and therefore, these rate constants were compared to elucidate the catalytic activity.

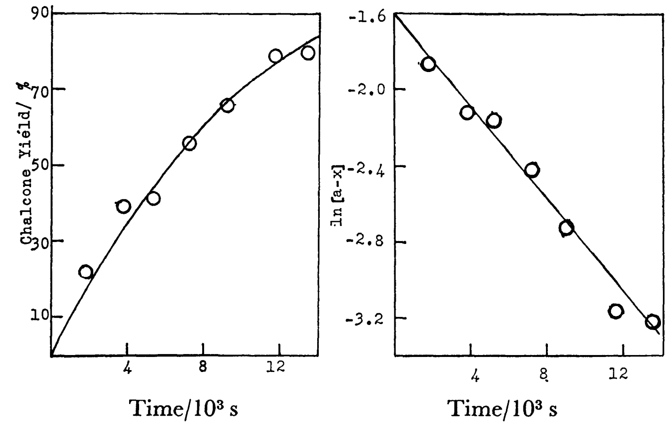


Fig. 1. Reaction profile of the aldol condensation catalyzed by $\mathrm{Co(OAc)_2}$–bpy(1: 1)complex in DMF at 82 °C. [catalyst]=0.008 mol/dm^3, [benzaldehyde]=0.2 mol/dm^3, [acetophenone]=4 mol/dm^3.
a: Initial concentration of the aldehyde, x: concentration of the chalcone produced.

Firstly, the dependence of k'_{obsd} on the concentration of the complex was examined. The reaction and the catalyst used were similar to that mentioned above, and the concentrations of the catalyst employed were 8 mmol/l, 4 mmol/l, and 2 mmol/l to that of the aldehyde 200 mmol/l. The $k'_{\mathrm{obsd}} \times 10^5$ (s^{-1}) were 12.3, 2.66, and 0.65, respectively, and the reaction rate was dependent apparently on the concentration of the complex catalyst. Thus, it has been shown that Co(II)–bpy complex has worked as true catalyst in this reaction.

Next, the effect of the molar ratio of bpy to the Co(II) on the catalytic activity was examined in the similar reaction as was shown in Table 1. According to the table, it was observed that the activities increased with

Table. 1 Effect of the molar ratio of bpy to Co (II) on the rate constants of the aldol condensation[a)]

cat=$\frac{(\mathrm{bpy})_n}{\mathrm{Co(II)}}$	$k'_{\mathrm{obsd}} \times 10^5$/s^{-1}
$n=0$	1.26
$n=0.5$	4.83
$n=1$	12.3
$n=2$	10.9
$n=3$	2.65

a) The reaction of benzaldehyde with acetophenone[b)] was carried out in DMF at 82 °C. b) [cat]=0.008 mol/dm^3, [aldehyde]=0.2 mol/dm^3, [ketone]=4 mol/dm^3.

an increase in the amount of bpy to a certain extent. When the molar ratio was $n=1$ or $n=2$, the highest activity was observed. However, when the molar ratio increased to $n=3$, the activity decreased remarkably. The suppressed reaction can be explained in terms of that the molar ratio of $n=3$ is enough amount to occupy the residual vacant coordination sites in Co(II) and that bpy as bidentate ligand can coordinate to Co(II) more easily than the substrates as monodentate ligand. Therefore, the assumption may be made that the reaction proceeds *via* a mixed ligand complex between the substrates and Co(II)–bpy$_n$ complexes.

Furthermore, the effect of the reaction temperature on the reaction was examined in the similar reaction mentioned above. As the result, the $k'_{\text{obsd}} \times 10^5$ (s^{-1}) were 1.27 at 62 °C, 2.53 at 72 °C and 12.3 at 82 °C, respectively. Thus, the correlation of the log k'_{obsd} and three different reaction temperatures was shown as a straight line in Fig. 2 and the activation energy was calculated as 13.7 kcal/mol.

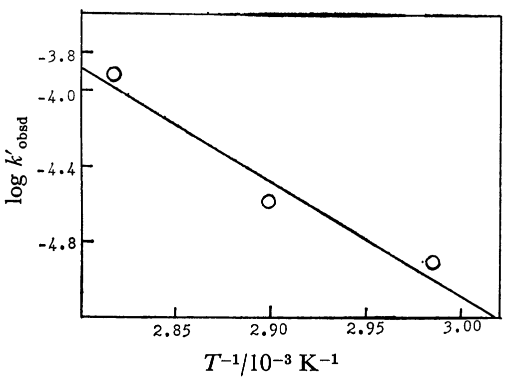


Fig. 2. Arrhenius plot for the aldol condensation of benzaldehyde with acetophenone catalyzed by Co(OAc)$_2$–bpy(1: 1) complex.
[cat.] = 0.008 mol/dm^3, [aldehyde] = 0.2 mol/dm^3, [ketone] = 4 mol/dm^3 in DMF.

Effects of Kind of the Ligand. The complex catalyzed aldol condensations are largely affected by the kind of ligand in the complex, and such ligand as bpy or 1,10-phenanthroline is fairly effective to give the reaction products in high yield.[2] Therefore, the effects of ligands on the catalytic activity of the Co(II) complexes were examined in detail at 82 °C in the similar reaction system mentioned above. The k'_{obsd} of the reactions catalyzed by Co(II)–L(bpy, en, 4-dm-bpy, and 6-dm-bpy) complexes and by Co(OAc)$_2$ itself are shown in Table 2.

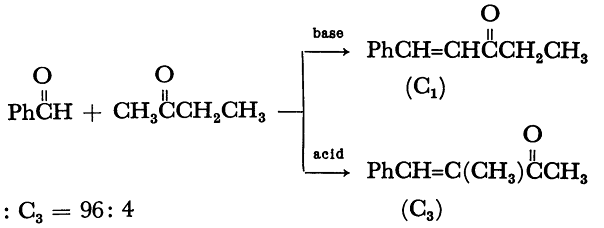
Table 2. Ligand effect on the rate constants of the aldol condensation

Cat[b,c]	$k'_{\text{obsd}} \times 10^5/\text{s}^{-1}$
Co(II)	1.26
Co(II)–bpy	12.3
Co(II)–en	1.41
Co(II)–4-dm-bpy	1.49
Co(II)–6-dm-bpy	0.33
Mn(II)–bpy	0.85

a) The reaction of benzaldehyde[b)] with acetophenone[b)] was carried out in DMF at 82 °C. b) [cat] = 0.008 mol/dm^3, [aldehyde] = 0.2 mol/dm^3, [ketone] = 4 mol/dm^3. c) The molar ratio of the ligand molecule to anhydrous Co(II)acetate is 1.

It is observed that the catalytic activity of Co(II)–bpy complex in the reaction increases remarkably in comparison with the k'_{obsd} of Co(OAc)$_2$, while bpy itself has no catalytic activity at all. The activity of Co(II)–ethylenediamine(en) complex is almost similar to that of Co(OAc)$_2$. The effect of 4,4′-dimethyl-2,2′-bipyridine ligand(4-dm-bpy) containing methyl groups as electro-donative substituent is surprisingly low. Furthermore, 6,6′-dimethyl-2,2′-bipyridine ligand(6-dm-bpy) deactivates the catalytic activity of the complex extremely probably owing to steric hindrance of the ligand molecule to the reaction. With regard to the enhanced effect of 2,2′-bipyridine on the metal complex catalysts, seveal studies on other organic catalytic reactions were already reported.[3] According to their accounts, the net plus charge of M(II) will increase by π-back donation of M(II) to 2,2′-bipyridine in the complex, then the resulting enhanced coordination force of substrates to M(II) naturally accelerate the reactions. The ligand effects on the aldol condensations are also explainable by the similar π-back donation between M(II) and bpy. Table 2 also shows low catalytic activity of Mn(II)–bpy complex in comparison with that of Co(II)-bpy complex. It is assumed that this result is due to the different stabilities of general complexes in Irving-Williams series.[4]

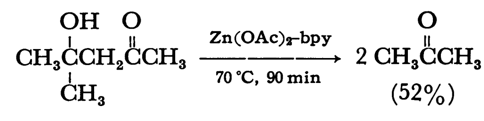
The Feature of the Catalysis. In order to show a feature of the complex catalysts, two different reactions catalyzed by the complex catalyst were investigated. One example is the condensation of benzaldehyde with 2-butanone. It was known that the base-catalyzed reaction gave, preferentially, the condensation product at C$_1$ of the ketone, while the acid-catalyzed reaction occurred preferentially at C$_3$.[5] In our reaction system with Co(OAc)$_2$–bpy complex, the regioselective condensation product at C$_1$-position was obtained in high yield as well as that with base catalysts.



$$\text{PhCH=O} + \text{CH}_3\text{C(=O)CH}_2\text{CH}_3 \xrightarrow{\text{base}} \text{PhCH=CHC(=O)CH}_2\text{CH}_3\ (\text{C}_1)$$
$$\text{PhCH=O} + \text{CH}_3\text{C(=O)CH}_2\text{CH}_3 \xrightarrow{\text{acid}} \text{PhCH=C(CH}_3)\text{C(=O)CH}_3\ (\text{C}_3)$$

$\text{C}_1 : \text{C}_3 = 96 : 4$

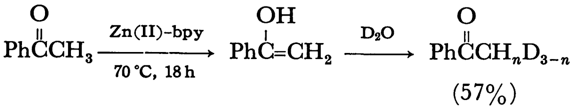
Another reaction, the decomposition of 4-hydroxy-4-methyl-2-pentanone, which has been also known to take place only by the use of base catalysts,[6] was examined in the presence of Zn(OAc)$_2$–bpy (1 : 1) complex in the NMR tube. It was observed that the reaction proceeded smoothly as follows:



$$\text{CH}_3\text{C(OH)(CH}_3)\text{CH}_2\text{C(=O)CH}_3 \xrightarrow[\text{70 °C, 90 min}]{\text{Zn(OAc)}_2\text{-bpy}} 2\ \text{CH}_3\text{C(=O)CH}_3\ .\ (52\%)$$

These findings show that the complex catalysts behave as a base catalyst. Both reactions do not commonly proceed in the presence of bpy itself. Accordingly, it is assumed that the basic function in the complex catalyst is not by bpy ligand but by the counter ion, AcO⁻, of the metal salts. It is widely recognized that the metal ion is considered as an acid and the counter ion is considered as a base.

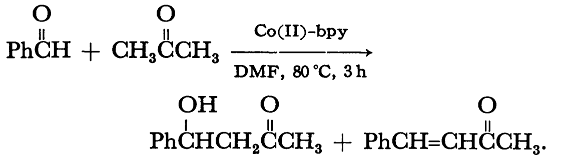
Consideration of the Reaction Process. It has been known that enolization of ketone is the first stage in the aldol condensation catalyzed by acid or base.[5] In our reaction system with M(II)–bpy complexes, H-D exchange reaction of acetophenone with deuterium oxide in the presence of Zn(OAc)$_2$–bpy catalyst was carried out in order to ascertain the formation of enolate anion. The reaction was remarkably catalyzed and the ratio of H-D exchange was 57% determined by NMR. When bpy itself was used, however, the reaction did not proceed.



$$\mathrm{Ph\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[70\,^{\circ}C,\ 18\,h]{Zn(II)\text{-}bpy} Ph\overset{\overset{OH}{|}}{C}{=}CH_2 \xrightarrow{D_2O} Ph\overset{\overset{O}{\|}}{C}CH_nD_{3-n}}$$

(57%)

At the second stage, it has been known that the reaction of aldehyde with the enolated ketone affords β-hydroxy ketone (aldol type product). However, the compound is easily dehydrated to give α,β-unsaturated ketone. In order to ascertain the formation of the aldol type product, the condensation of benzaldehyde with acetone in the place of acetophenone was carried out in the presence of Co(II)–bpy complex (1 : 1) at 80 °C in DMF for 3 h. The reaction gave yellow oil that was analyzed by ^{1}H-NMR and GC-MS spectra, and two kinds of product, 4-hydroxy-4-phenyl-2-butanone(**1**) and benzylideneacetone(**2**) were determined as follows:



$$\mathrm{Ph\overset{\overset{O}{\|}}{C}H + CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[DMF,\ 80\,^{\circ}C,\ 3\,h]{Co(II)\text{-}bpy} Ph\overset{\overset{OH}{|}}{C}HCH_2\overset{\overset{O}{\|}}{C}CH_3 + PhCH{=}CH\overset{\overset{O}{\|}}{C}CH_3.}$$

1 **2**

25% 11%

NMR: 2.10 (CH$_3$) : 2.28 (CH$_3$)

MS: 164 (M$^+$) : 146 (M$^+$)

When the similar reactions were carried out for longer time, it was observed that the yields of **1** decreased with the increasing yields of **2**. Consequently, it was assumed that the reaction afforded the product **1** in the first instance which was succesively dehydrated to give the product **2** as well as acid or base catalyzed reaction.

Consideration of Coordination. A coordination of aldehyde to the metal ion was examined by absorption spectroscopy. A solution of nickel(II) acetate in DMF showed an absorption maximum at 430 nm as shown in Fig. 3. When bpy was added to this solution, an absorption maximum appeared at 630 nm, which was attributed to the d-d band of Ni(II)–bpy chelation. When benzaldehyde was added to this solution of Ni(II)–bpy complex, the absorption maximum at 630 nm shifted to 622 nm. The fact might suggest that the carbonyl oxygen atom of aldehyde entered the first coordination sphere of Ni(II). While, no similar shift was observed by addition of acetophenone to the Ni(II)–bpy system.

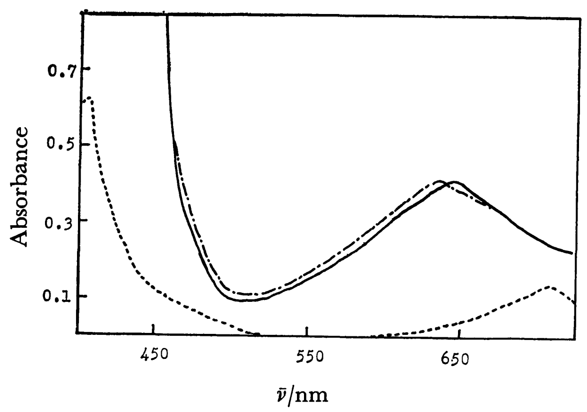


Fig. 3. Electronic absorption spectra of nickel (II) acetate–bpy–benzaldehyde and nickel (II) acetate–bpy–acetophenone complexes in DMF. [Ni(OAc)$_2$] = 0.060 mol/dm^3, [bpy] = 0.060 mol/dm^3, [aldehyde] = 0.075 mol/dm^3, [ketone] = 0.075 mol/dm^3.
⋯⋯: Ni(OAc)$_2$ ($\lambda_{\max}$ 430 nm), ——: Ni(OAc)$_2$–bpy ($\lambda_{\max}$ 630 nm) and Ni(OAc)$_2$–bpy acetophenone ($\lambda_{\max}$ 630 nm), —·—: Ni(OAc)$_2$–bpy–benzaldehyde ($\lambda_{\max}$ 622 nm).

Since acetophenone was enolized by M(II)–bpy complex, the interaction between acetophenone and M(II) seemed to be extremely weak. In other words, the ketone may be located in far distance from the metal ion. Considering in connection with the results described above, the aldol condensation reaction may proceed *via* a coordination of aldehydes to the M(II).

It has been known that aldol condensation in biological system are catalyzed by aldolase enzymes, Class I and II.[7] Class II aldolase is a metalloenzyme containing Zn(II) in the active site. In the reaction of Class II aldolase, however, catalysis of the enzyme has not been elucidated enough although some models of the reaction mechanism were presented by biochemists.[8–12] Therefore, our reaction system with Zn(II)–bpy complex may present a new example for understanding of the Zn(II) catalysis in Class II aldolase from a side of organic catalytic reactions.

Some information withdrawn from our study on the catalysis of M(II)–bpy complex are summerized as follows:

(1) 2,2′-Bipyridine ligand in the Co(II) complex enhanced the catalytic activity remarkably, though the ligand itself had no activity.

(2) M(II)–bpy complex showed a feature of basic catalyst. Such effect of (1) may be important in the metalloenzyme if there is interaction between the metal ion and imidazole ring of a histidine residue, since imidazole as well as bpy can form π-bonding by coordinating to the M(II). Ingram reported that Class II aldolase showed a basic catalysis.[8] Further, it was suggested that the basic group may be an appropriately located β-COO⁻ of aspartic acid or γ-COO⁻ of glutamic acid.[8] However, from a viewpoint of our metal(II)–bpy complex catalysis(2), another suggestion that basic group is the counter ion of the metal ion being located at active center of the metalloenzyme may be permitted. Further, a detail investigation of a model reaction of Class II aldolase is now in progress.

Experimental

Kinetics of Aldol Condensation. In order to study the rate of the aldol condensation of benzaldehyde with acetophenone, a sample of catalyst (for example; $Co(OAc)_2$ (0.0142 g, 0.08 mmol) and 2,2′-bipyridine (0.0125 g, 0.08 mmol)) was weighed into a volumeric flask (10 ml) and DMF (3 ml) was added to the flask to dissolve the catalyst. The solution was stirred at room temperature for 21 h. Benzaldehyde (0.212 g, 2 mmol) and acetophenone (4.8 g, 40 mmol) were poured in this flask and DMF was added to the mark. The solution was poured in each ampoule (1 ml × 8). The sealed ampoules were heated at 82 °C and were withdrawn from time to time and then were quenched in a freezer. p-MeO–$C_6H_4COCH_2C_6H_5$ as an internal standard was added to the solution in opened ampoules which were analyzed by GLC (column temp at 220 °C, 1 m, Carbowax 20 M). The solution showed only one product (chalcone) other than unreacted benzaldehyde and acetophenone. The amount of chalcone was determined by comparing the relative peak area of chalcone *vs.* the internal standard with those of the calibration chart.

Regioselectivity in the Reaction of Benzaldehyde with 2-Butanone. A DMF (5 ml) solution of benzaldehyde (1.875 mmol), 2-butanone (5 ml), $Co(OAc)_2$ (0.300 mmol), and 2,2′-bipyridine (0.300 mmol) was stirred at a reflux temperature for 6 h. After the completion of the reaction, the solvent was removed *in vacuo* and the residue was extracted with ether–water system. The organic layer was dried over anhydrous sodium sulfate and was evaporated to give a mixture of 1-phenyl-1-penten-3-one (a) and 3-methyl-4-phenyl-3-buten-2-one (b) in 95% yield. The ratio (a) : (b) was 96 : 4 which was determined by NMR spectra.

Decomposition Reaction of 4-Hydroxy-4-methyl-2-pentanone (DAA). DAA (2 mmol) was added to a solution of anhydrous zinc acetate (0.1 mmol) and 2,2′-bipyridine (0.1 mmol) in DMSO-d_6 (0.09 ml) in NMR tube. The tube was sealed off and heated at 70 °C for 90 min. For the calculation of the amount of unreacted DAA determined by NMR, 1,1,2,2-tetrachloroethane as an internal standard was added to the reaction mixture and DAA was decomposed in 52%.

H-D Exchange of Acetophenone. A solution of acetophenone (1.0 mmol), $Zn(OAc)_2$ (0.1 mmol), D_2O (2.75 mmol), and CD_3CN (0.4 ml) in sealed NMR tube was heated at 70 °C for 18 h. The integration ratio of methyl proton *versus* aromatic proton was determined by NMR and the H-D exchanged ratio of methyl group of acetophenone was calculated in 54%.

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