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Aldol Condensations Catalyzed by Co(II) Complexes of Pyridine-containing Copolymers

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The cross aldol condensations of aldehydes and ketones catalyzed by Co(II) complexes of pyridine-containing copolymers proceed under neutral conditions in DMF or DMSO to afford α,β-unsaturated ketones without any by-product. The solid complex catalysts are capable of repeated use. The reactions of aromatic aldehydes and ketones give good results but not those of aliphatic compounds. Effects of substituent groups in chalcone formation are observed. The catalytic reaction features with the polymer-complex catalysts are compared with that with Co(II)-pyridine complex. The polymer-complex-catalyzed aldol condensations are discussed briefly in relation to the enzymatic reaction of Class II aldolase (metalloenzyme).

Aldol condensation reactions are generally catalyzed by strong bases or acids. Recently, we have found that the condensation reactions are catalyzed by 2,2′-bipyridine complexes of the first-row transition metals[1] and Co(II) complexes of polymers[2] under neutral conditions. The reactions of aldehydes and ketones with these complex catalysts afford only cross condensation products, α,β-unsaturated ketones, in satisfactory yields. With regard to polymer-catalyzed aldol condensations, catalysis of ion exchange resins have been known, but the product yield of the reactions is low along with some by-products.[3] In this paper, the scope and limitation of the aldol condensation reactions promoted by the Co(II) complexes of pyridine-containing copolymers will be described in detail together with the catalytic behavior of the polymer complexes. Some consideration is also given to the catalysis of Class II aldolase.

Results and Discussion

Polymer Complex Catalysts. The polymers employed for the ligand are as follows: Poly(4-vinylpyridine):[4] PVP, crosslinked poly(4-vinylpyridine):[4] VP, crosslinked 4-vinylpyridine-styrene copolymer:[5] VP–St (1 : 3), crosslinked 4-vinylpyridine-methyl methacrylate copolymer:[6] VP–MMA (1 : 3), crosslinked 4-vinylimidazol-methyl acrylate copolymer:[7] VIm–MA (1 : 10).

These polymers were prepared by conventional methods in the literature cited.[4–7] 1,4-Divinylbenzene was used as a crosslinking agent, 1 mol% to the polymers, and the crosslinked polymers were insoluble in the common organic solvents. The metal(II) complexes of these polymers were prepared by adding a solution of cobalt(II) acetate in *N,N*-dimethylformamide (DMF) to the swelled polymers in DMF and subsequent stirring at room temperature for 24 h. The cobalt(II) complexes thus obtained were reddish to light purple in color and the content of the Co(II) ion in the complexes was calculated from the difference of the initial amount to the residual untrapped amount of the Co(II) ion. The estimated ratio of the Co(II) ion to the pyridine or imidazol moiety in the complexes was about 1 : 1, which suggested the existence of vacant coordination sites for the ligand reactions (Table 1). In the IR spectra of the copolymer VP–St, absorption at 1600 cm^{-1} was observed and was attributed to the pyridine ring. This absorption shifted to 1620 cm^{-1} in the case of the Co(II) complex of the polymer.

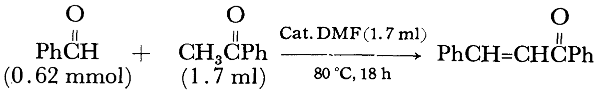
Effects of Cross Linkage and Copolymer. In order to examine the activity of the Co(II)–polymer-complex catalysts thus prepared, aldol condensations of benzaldehyde with excess of acetophenone were carried out in the presence of the catalyst in DMF at 80 °C for 18 h. The amount of Co(II) ion in the polymer complex used was about 16 mol% of the aldehyde employed. After the reaction, the catalyst was removed from the reaction mixture by filtration. No change in appearance of the catalyst was observed. The filtrate was analyzed by means of GLC to determine the yield of the reaction product, 1,3-diphenyl-2-propen-1-one (chalcone). To isolate the chalcone, the filtrate was evaporated *in vacuo*

TABLE 1. Co(II)–POLYMER COMPLEXES

Ligand (crosslinked)	py-Unit (mmol/g)	Co(II) ion (mmol/g)	py-Unit to Co(II) ion
VP	6.0	4.0	1.5
VP–St	2.38	2.4[a]	0.99
VP–MMA	3.5	3.5	1.0
VIm–MA	1.4	1.55	0.9

a) Ni(OAc)$_2$ complex: 1.9 mmol/g.

TABLE 2. ALDOL CONDENSATIONS WITH Co(II)–POLYMER COMPLEX CATALYSTS



$$\underset{(0.62\ \text{mmol})}{\mathrm{Ph\overset{O}{\overset{\|}{C}}H}} + \underset{(1.7\ \text{ml})}{\mathrm{CH_3\overset{O}{\overset{\|}{C}}Ph}} \xrightarrow[80\,^{\circ}\mathrm{C},\,18\,\mathrm{h}]{\text{Cat. DMF}(1.7\ \text{ml})} \mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}Ph}$$

No.	Catalyst		Yield/%[a]
1	Co(II)–PVP	[Co(II) : py=1 : 1.5]	41
2	Co(II)–VP	[Co(II) : py=1 : 1.5]	53
3	Co(II)–VP–St	[Co(II) : py=1 : 1]	100(84)
4	Co(II)–VP–MMA	[Co(II) : py=1 : 1]	(84)[b]
5	Co(II)–VIm–MA	[Co(II) : Im=1 : 0.9]	(64)[c]
6	Co(II)–py	[Co(II) : py=2 : 3]	80
7	Co(II)–Im	[Co(II) : Im=1 : 1]	(75)
8	Co(OAc)$_2$4H$_2$O		31
9	Am. IR-120		36

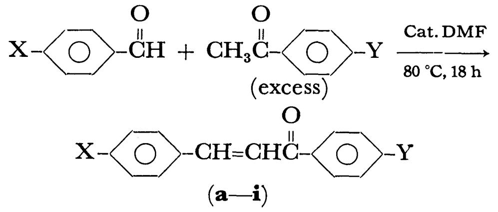
a) By GLC analysis, based on benzaldehyde used. The values in parentheses are isolated yields. b) 84% in DMSO and 59% in MeOH (isolated). c) 83% in DMSO (isolated); 81% by reused catalyst in DMSO.

to give a yellow oil which was treated by preparative TLC, determined by means of mp, IR, and NMR. For example, in the reaction with the complex Co(II)–VP–St, the yield of chalcone by GLC was 100% and the isolated yield was 84%, mp 55—58 °C. The reaction conditions and the results are summarized in Table 2 together with some other data for comparison. The reaction did not proceed in the absence of the catalyst, and all the ligand polymers themselves without the Co(II) ion showed no catalytic activity. The reactions did not proceed at room temperature even over prolonged reaction periods in the presence of the polymer-complex catalyst. Only PVP was soluble in DMF and the Co(II)–PVP complex catalyst as a solution in DMF (Co(II) : pyridine unit = 1 : 1.5) was used for the reaction No. 1 (homogeneous). The Co(II) ion itself showed some catalytic activity (No. 8). The PVP ligand seemed to enhance the reaction somewhat by co-ordination of the pyridine ring to Co(II) ions (No. 1). Crosslinking further enhanced the catalytic activity as observed in the reaction with Co(II)–VP (No. 2), affording higher product yield (53%) than that with Co(II)–PVP (41%) though it was not as good as that obtained with the Co(II)–py complex (No. 6, 80%). On the other hand, the crosslinked copolymer of 4-vinylpyridine and styrene Co(II)–VP–St showed a predominant result (No. 3, 100%). The reaction with the ion exchange resin Amberlite IR-120 (No. 9) afforded chalcone in low yield (36%) accompanying a considerable amount of the self-condensation product of acetophenone, 1,3-diphenyl-2-buten-1-one, and other by-products under similar reaction conditions (GLC). On the contrary, no side reactions were observed with the Co(II)–VP–St catalyst. The $\mathrm{Ni(OAc)_2}$–VP–St copolymer was also prepared (Table 1, footnote), but, it showed almost no catalytic activity for chalcone formation under similar reaction conditions.

Various Aldol Condensations with Co(II)–VP–St Catalyst. It was proved above that the Co(II)–VP–St-copolymer-complex in DMF was the most effective catalyst system for the reaction. Therefore, various aldol condensations with this catalyst were subsequently investigated. The reaction conditions were similar to that of Table 2. The reaction products were isolated and identified as α,β-unsaturated ketones, and no side reactions were observed. The results of the reactions of *p*-substituted benzaldehyde or *p*-substituted acetophenones are shown in Table 3, and the reactions with some aliphatic carbonyl compounds are summarized in Table 4. The purity of the products thus obtained was consistently high, probably because the polymer-complex-catalyzed reactions took place under neutral conditions.

In general, reactions between aromatic aldehydes and ketones gave good results, but not those of aliphatic compounds. The reactions shown in Table 3 yielded the corresponding chalcones and the product yields were remarkably affected by the substituent groups of either aldehydes or ketones: reactants having electron-attractive substituents gave high yields (products: **a**, **b**, **g**, **h**) and those having electron-donative ones gave low yields (products: **e**, **f**, **i**). The reaction of 2-butanone with benzaldehyde gave only 1-phenyl-1-penten-3-one (Table 4, **k**), though the yield was low. This regioselectivity was the same for reactions catalyzed by Co(II)–bpy complex, namely base-catalyzed type.[1]

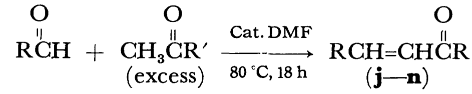
Table 3. Aldol condensations with Co(II)–VP–St catalyst(I)



X	Y	Product	Yield/%	Mp θ_m/°C	(Lit)
CN	H	**a**	98	162—163	
$\mathrm{NO_2}$	H	**b**	93[a)]	164—165	(8)
Cl	H	**c**	81	117—118	(8)
H	H	**d**	84[b)]	55—58	(9)
$\mathrm{OCH_3}$	H	**e**	55	75—77	(9)
$\mathrm{CH_3}$	H	**f**	44	97—98	(10)
H	CN	**g**	98	120—121	
H	$\mathrm{NO_2}$	**h**	93	151—152	(11)
H	$\mathrm{OCH_3}$	**i**	44	109—110	(12)

a) By reused catalyst(three times): 90—92%. b) By reused catalyst: 82%.

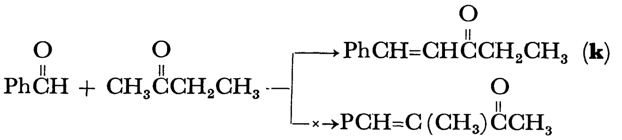
Table 4. Aldol condensations with Co(II)–VP–St catalyst(II)



$$\mathrm{R\overset{O}{\overset{\|}{C}}H + \underset{(excess)}{CH_3\overset{O}{\overset{\|}{C}}R'} \xrightarrow[80\,^{\circ}C,\,18\,h]{Cat.\,DMF} \underset{(\mathbf{j}\text{—}\mathbf{n})}{RCH{=}CH\overset{O}{\overset{\|}{C}}R'}}$$

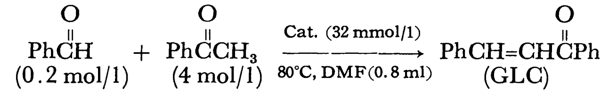
R	R′	Product	Yield/%	Mp θ_m/°C	(Lit)
Ph	$\mathrm{CH_3}$	**j**	66[a)]	41—42	(13)
Ph	$\mathrm{C_2H_5}$	**k**	28[b)]	39—40	(14)
PhCH=CH	Ph	**l**	50	103—106	(8)
$\mathrm{(CH_3)_2CH}$	Ph	**m**	29	Oil	(15)
$\mathrm{CH_3CH{=}CH}$	$\mathrm{CH_3}$	**n**	6	Oil	(16)

a) Reflux 40 h. b) Co(II)–VP–MMA was used (in sealed tube, *in vacuo*).



$$\mathrm{Ph\overset{O}{\overset{\|}{C}}H + CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3} \begin{cases} \longrightarrow \mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}CH_2CH_3}\ (\mathbf{k}) \\ \xrightarrow{\times} \mathrm{PCH{=}C(CH_3)\overset{O}{\overset{\|}{C}}CH_3} \end{cases}$$

Catalysis of the Copolymer Complexes. On the basis of the above studies, the scope of the catalytic ability of the Co(II) copolymer complex is fairly wide, though it is limited for reactions with aliphatic carbonyl compounds. In order to examine this catalysis feature in detail, the polymer-complex-catalyzed reaction was compared with a pyridine-complex-catalyzed reaction under similar reaction conditions. As the polymer- and pyridine-complex catalysts, Co(II)–VP–St and Co(II)–4-isopropylpyridine complexes (1 : 1) were employed respectively. The yield of chalcone was determined by GLC analysis: the correlation of the yield with reaction



$$\underset{(0.2\,\mathrm{mol/l})}{\mathrm{Ph\overset{O}{\overset{\|}{C}}H}} + \underset{(4\,\mathrm{mol/l})}{\mathrm{Ph\overset{O}{\overset{\|}{C}}CH_3}} \xrightarrow[80\,^{\circ}\mathrm{C},\,\mathrm{DMF}(0.8\,\mathrm{ml})]{\mathrm{Cat.}\,(32\,\mathrm{mmol/l})} \underset{(\mathrm{GLC})}{\mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}Ph}}$$

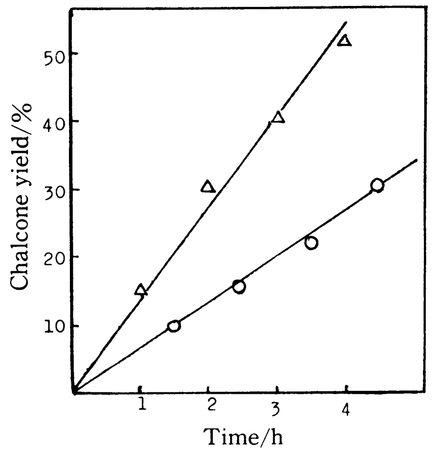


Fig. 1. Reaction profile of the aldol condensations of benzaldehyde and acetophenone catalyzed by polymer and monomer Co(II) complexes.
—○—: Co(II)–VP–St, —△—: Co(II)–*i*-Pr-py (1 : 1).

time is shown in Fig. 1. The catalytic activity of the polymer complex was lower than that of the pyridine complex for the initial stage of the reaction. However, Co(II)–VP–St is superior to Co(II)–py in the reactions for 18 h as shown in Table 2 (100% and 80%). Further, in an equimolar reaction, Co(II)–VP–St was also superior to Co(II)–py. When 0.62 mmol of benzaldehyde and acetophenone was used respectively under similar reaction conditions to that of Table 2 (18 h), the reaction with Co(II)–VP–St gave chalcone in a 70% yield (isolated), but Co(II)–py gave only 50% yield (isolated).

As mentioned above, the electron-attractive groups in the aromatic aldehydes or ketones enhance the reactivity of the substrates in these reactions (Table 3) as well as acid or base catalyzed aldol condensations.[17] On the contrary, no substituent effect was observed in the reactions with Co(II)–bpy complex (1 : 1) catalyst under similar reaction conditions, *e.g.* chalcone 81%, *p*-$NO_2C_6H_4CH{=}CHCOPh$ 88%, *p*-$ClC_6H_4CH{=}CHCOPh$ 72%, *p*-$CH_3OC_6H_4CH{=}CHCOPh$ 88% *etc.*[1] Therefore, the fact that the substituent effect is observed in the aldol condensations with the polymer complex may be one of the unique features of the polymer complex catalyst though the reason of it is not clear.

Concerning the reaction solvent, an aprotic polar solvent such as DMF or DMSO was favorable (Table 2, footnote), and almost no reaction product was obtained in C_6H_6. Further, it was notable that no reaction took place in neat reaction. These facts suggest that an adequate solvent makes the polymer complex swell enough to ingest the substrates into the polymer and so helps good catalysis. A polymer complex catalyst has an advantage of being removed easily from the reaction mixture by filtration and so it can be used repeatedly. In our catalyst system, the polymer complex catalysts were also proved to be reusable with retention of almost the same catalytic activity (Tables 2 and 3, footnote).

Aldol condensations in biological systems are known to be catalyzed by aldolase enzymes, Class I and Class II;[18] the latter is a metalloenzyme containing zinc(II) ion in the active sites. In the reaction of Class II aldolase, however, catalysis of the enzyme has not been elucidated enough, although some models of the reaction mechanism have been proposed by biochemists.[19–21] We also prepared $Zn(OAc)_2$–VIm–MA (Zn : VIm = 1 : 1.35) complex by a procedure similar to that for Co(II) complex, and the yield of chalcone was 40% (isolated) under similar reaction conditions. The effect of a pyridine- or imidazol-containing copolymer as ligand may be important in the metalloenzyme if there is an interaction between metal(II) ion and imidazol ring of a histidine residue, since imidazol as well as pyridine can form π-bonding by coordination to the metall(II) ion.[22] The facts described in this paper might indicate the possibility that polymer complexes can be developed and applied to the aldolase model reaction system. Our catalyst system may present a new model for understanding the Zn(II) ion catalysis in the Class II aldolase.

Experimental

Instruments. The NMR and IR spectra were taken with a Hitachi Perkin-Elmer R-20A spectrophotometer (60 MHz) and a Hitachi 215 Grating Infrared spectrophotometer respectively. The GLC was carried out with a Hitachi K-53 gas chromatograph with a flame ionization detector, using a 1 m stainless steel tube column packed with 10% Carbowax 20 M on Diachrom A (career gas, N_2; temp 220—270 °C). The product yields were determined by GLC and NMR analysis using *p*-$CH_3OC_6H_4COCH_2Ph$ (or PhCOPh) and $Cl_2CHCHCl_2$ as the internal standard respectively. The atomic absorption spectra was taken with a Shimadzu Atomic Absorption-Flame Emission Spectrophotometer AA-640-13.

Preparation of Co(II) Complex of Copolymer VP–St. 4-Vinylpyridine (1.05 g, 10 mmol), styrene (4.17 g, 40 mmol), divinylbenzene (66 mg, 0.5 mmol), 2,2′-azobisisobutyronitrile (82 mg, 0.5 mmol), and benzene (10 ml, solvent) were mixed together in a 20 ml ampule. The contents were degassed by a vacuum system, and the ampule was sealed off under vacuum and heated at 70 °C for 40 h. The transparent copolymer thus obtained was washed with benzene in a Soxhlet extractor (10 h), dried under reduced pressure at 70 °C, yield 3.06 g. Found: C, 88.08; N, 3.06; H, 7.70%. Calcd (pyridine: benzene unit = 1 : 3.2): C, 89.31; N, 3.02; H, 7.50%. The copolymer (1.043 g) was swelled in 16 ml of DMF and then added to a solution of $Co(OAc)_2 4H_2O$ (3 mmol, 1.5 × pyridine unit) in 5 ml DMF, and stirred for 24 h at room temperature. The reddish purple copolymer complex thus obtained was filtered off and washed with 179 ml of warm DMF. The filtrate and the washings were combined and the content of Co(II) ion in the solution was determined by atomic absorption spectrophotometry. The content of Co(II) ion in the polymer complex was calculated as 2.4 mmol; accordingly the pyridine unit co-ordinated to the Co(II) ion unit was 0.99 (Table 1). The polymer complex was washed with diethyl ether and dried under reduced pressure at 70 °C, yield 1.23 g.

General Procedure for Aldol Condensations. The complex catalyst, Co(II)–VP–St (51 mg) was kept in 0.5—1.7 ml DMF for swelling in 10 ml flask, then benzaldehyde (63 mg, 0.62 mmol) and excess acetophenone (1.7—2.5 ml) were added together into the flask and stirred at 80 °C for 18 h. The polymer catalyst was removed by filtration and the filtrate condensed to some extent under reduced pressure for GLC analysis. The yield of chalcone was calculated on the basis of the benzaldehyde used (Table 2). In the reaction for Fig. 1, the reaction mixture was analyzed directly without filtration of the catalyst. To isolate the chalcone or its derivatives, the filtrate was evaporated *in vacuo* to expel the solvent, aldehyde and the excess ketone; the residue was then submitted to preparative TLC on silica gel (developed with hexane–ethyl acetate) and the reaction product extracted with ethyl acetate, dried and weighed (Tables 3 and 4).

Condensation Products (Tables 2, 3, and 4). **a**: 4-Cyanochalcone, mp 162—163 °C; IR 2210 cm^{-1} (CN), 1670 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 7.50—8.15 (aromatic proton); Ms: *m/e*, 233 (M^+), 156 ($M^+-C_6H_5$), 128 ($M^+-C_6H_5CO$). **b**: 4-Nitrochalcone, mp 158—160 °C (lit,[8] 158—160 °C); IR 1670 cm^{-1}, 1520 cm^{-1} (NO_2); ^{1}H-NMR ($CDCl_3$): δ 7.50—8.50 (aromatic proton). **c**: 4-Chlorochalcone, mp 117—118 °C (lit,[8] 114 °C); IR 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.00—8.00 (aromatic proton). **d**: Chalcone, mp 57—58 °C (lit,[9] 57—58 °C); IR 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.98—7.98 (aromatic proton). **e**: 4-Methoxychalcone, mp 75—77 °C (lit,[9] 72—74 °C); IR 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.76 (3H, s, CH_3), 6.78—8.65 (aromatic proton). **f**: 4-Methylchalcone, mp 97—99 °C (lit,[10] 96 °C); IR 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.32 (3H, s, CH_3), 7.12—8.10 (aromatic proton). **g**: 4′-Cyanochalcone, mp 120—121 °C; IR 2230 cm^{-1} (–CN), 1660 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 7.38—8.17 (aromatic proton). ***h***: 4′-Nitrochalcone, mp 151—152 °C; IR 1660 cm^{-1}, 1510 cm^{-1} (NO_2); ^{1}H-NMR ($CDCl_3$): δ 7.26—8.44 (aromatic proton). **i**: 4′-Methoxychalcone, mp 109—110 °C; IR 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.78 (3H, s, CH_3), 6.90 (2H, d, aromatic proton),7.20—7.67 (7H, aromatic proton). **j**: Benzylideneacetone, mp 41—42 °C (lit,[13] 41.5 °C); IR 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.39 (3H, s, CH_3), 6.75 (1H, d, –CH=), 7.35—7.72 (aromatic proton). **k**: 1-Penyl-1-penten-3-one, mp 39—40 °C (lit,[14] 38.5—39.5 °C); ^{1}H-NMR ($CDCl_3$): δ 1.18 (3H, t, CH_3), 2.7 (2H, q, –CH_2–), 6.84 (1H, d, –CH=), 7.38—7.78 (aromatic proton). **l**: Cinnamylidenacetophenone, mp 103—106 °C (lit,[8] 102—103 °C); IR 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ, 6.95—8.10 (aromatic proton). **m**: 1-Phenyl-4-methyl-2-penten-1-one, IR 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.15 (6H, d, CH_3), 1.70 (1H, m, CH), 6.90—8.00 (aromatic proton); MS: *m/e*, 174 (M^+), 159 (M^+-CH_3), 144 (M^+-2CH_3), 131 ($M^+-CH(CH_3)_2$). **n**: 2,4-Heptadien-1-one, ^{1}H-NMR ($CDCl_3$): δ 1.84 (3H, d, CH_3), 2.20 (3H, s, CH_3).

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