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STERIC EFFECTS OF CHIRAL LIGANDS IN A NEW TYPE OF ALDOL CONDENSATIONS CATALYZED BY ZINC(II) COMPLEXES OF α-AMINO ACID ESTERS

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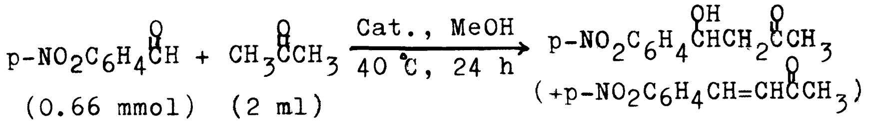
The aldol condensations of p-nitrobenzaldehyde with acetone have been found to be catalyzed by Zn^{2+} complexes of α-amino acid esters under mild and neutral conditions to afford enantiomeric excess aldol type product along with some of the dehydrated product. The complexes with ligands containing benzene ring such as esters of Phe, Tyr, and Trp are much more effective both on catalytic activity and asymmetric induction.

We previously reported that the aldol condensations were catalyzed by Co^{2+} complexes of bipyridine[1)] and pyridine-containing copolymers[2)] in DMF at 80 °C to afford α,β-unsaturated ketones in good yield. Recently, we have newly found that the aldol reactions of p-nitrobenzaldehyde with acetone are catalyzed by Zn^{2+} complexes of α-amino acid esters in MeOH at 30-40 ℃ to afford enantiomeric excess aldol type product and the reactions are largely affected by structure of the ligand. Many studies have been reported in regard to the aldol reactions utilizing organometallic compounds as auxiliary reagent for diastereoselective additions through metal enolate intermediates.[3)] However, studies on the asymmetric aldol reactions catalyzed by Zn^{2+} complexes of α-amino acid esters under neutral conditions have not been reported yet. We wish to report features of the reactions by use of several kinds of amino acid esters from a view point of steric effects.

Amino acid esters employed for the ligands were ethyl esters of L-alanine (AlaOEt), SerOEt, PheOEt, TyrOEt, and TrpOEt. α-Methylbenzylamine(MeBA) was also examined for reference. $Zn(NO_3)_2 \cdot 6H_2O$ as metal species of the complexes was sperior to $ZnCl_2$, $Zn(OAc)_2$, and other metal salts. The reactions of p-nitrobezaldehyde with acetone were mainly carried out in order to examine effects of ligands of the complex catalysts. As a result, it was inferable that structures of the amino acids and the ester group affected on the reactions very much. The complexes with ligands containing benzene ring such as PheOEt, TyrOEt, and TrpOEt were much more effective both on catalytic activity and asymmetric induction.

Table 1. Preliminary examinations of aldol reactions



$$\text{p-NO}_2\text{C}_6\text{H}_4\overset{\text{O}}{\overset{\|}{\text{C}}}\text{H} + \text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_3 \xrightarrow[40\ ^{\circ}\text{C},\ 24\ \text{h}]{\text{Cat., MeOH}} \text{p-NO}_2\text{C}_6\text{H}_4\overset{\text{OH}}{\overset{|}{\text{C}}}\text{HCH}_2\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_3$$

(0.66 mmol) (2 ml)

$(+\text{p-NO}_2\text{C}_6\text{H}_4\text{CH=CH}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{CH}_3)$

No.	Catalyst	(mol%)	Aldol type product yield/%NMR	Aldol type product $[\alpha]_D$	Conversion %/NMR
1	None		0	—	0
2	$Zn(NO_3)_2 \cdot 6H_2O$	16	52	0	52
3	Tyr	32	trace	—	trace
4	Zn^{2+}-$(tyr)_2$	16	3.7	—	11.3[a]
5	TyrOEt	32	26	-4	46[b]
6	Zn^{2+}- TyrOEt	16	40	-6.4	53
7	Zn^{2+}-$(TyrOEt)_2$	16	58[c]	-11.2	100

a) Acetal 7.6%. b) Unidentified by-product.
c) 46% at 30 °C reaction, $[\alpha]_D = -19°$.

As a preliminary test, catalytic behavior of the components of the complexes were first examined as shown in Table 1. Zinc salt itself showed catalytic activity to some extent but no asymmetric induction was expected at all(Entry No. 2). Tyr itself and its complex showed almost no catalytic activity (Nos. 3 and 4). While, the reaction with TyrOEt itself afforded 26% of the aldol type product[4] and 20% of the dehydrated product[5] accompanied with some unidentified by-product (NO. 5). In conclusion, Zn^{2+}-$(TyrOEt)_2$ in MeOH was the effective catalyst system(No.7). An examination of UV spectra of the Zn^{2+}-$(TyrOEt)_2$ complex was of no use because absorption maxima of the Zn^{2+} and TyrOEt overlapped at around 250 nm. However, UV spectra of $Ni(OAc)_2 \cdot 4H_2O$ in EtOH showed λmax 670 nm and when twice mol of the TyrOEt was added to this solution, λmax shifted to 650 nm and hyperchromic effect was observed. On the other hand, $[\alpha]_D$ value of the TyrOEt itself in EtOH was +19.8° but that of $Ni(OAc)_2$-$(TyrOEt)_2$ changed to -2.5°. These facts indicated the complex formation in the solution evidently.

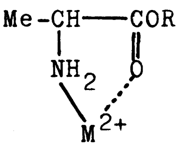
On the basis of above examinations, the reactions by use of various kind of Zn^{2+} complexes(M:L=1:2) were carried out as shown in Table 2. The complex catalysts were prepared mixing $Zn(NO_3)_2 \cdot 6H_2O$ and ligand compounds in MeOH(7 ml), stirred for a while, and the complex solution was subsequently used as catalyst without isolation of the complex as a crystal form. After the reaction, the reaction mixture was diluted with excess water, extracted with ethyl acetate for the isolation of the reaction products by means of column chromatography (silica-gel, ethyl acetate-hexane). Optical purity of the aldol type product obtained in the reactions has been still unkown although the enantiomeric excess of it was tried to determine by means of ^{1}H-NMR spectroscopy with shift reagents($Eu(tbc)_3$ and $Eu(tfc)_3$) and by some other methods but definite values were not obtained.

Table 2. Aldol condensations with Zn^{2+} complex catalysts.[a] Effects of chiral ligands

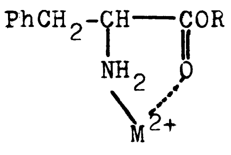
No.	Ligand (M:L=1:2)	($[\alpha]_D$)	Aldol type product yield/%NMR	$[\alpha]_D$[b]	Conversion %NMR
1	AlaOEt	(+4)	39	-2	54
2	PheOEt	(+27)	57	-20	85
3	Phe	(-35)	trace	——	trace
4	+MeBA[c]	(+38)	51	+6.6	76
5	-MeBA	(-39)	53	-4	77
6	TyrOEt	(+20)	58	-11.2	100
7	TyrOMe	(+28)	50	-8.3	70
8	SerOEt	(+1)	37	-1.7	41
9	TrpOEt	(+27)	40	-30[d]	76
10	Trp	(-33.7)	trace	——	trace[e]

a) Reactions and the reaction conditions are similar to that shown in Table 1, catalyst: 16 mol% of the aldehyde. b) In EtOH at room temperature. c) MeBA: α-methylbenzylamine. d) Mean value. e) Unidentified by-product.

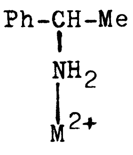
In Entry No. 2 (Table 2), effect of benzene ring in the PheOEt complex catalyst is observed apparently both in reactivity and asymmetric regulation as compared with the reaction with the AlaOEt complex (Entry No. 1). This effect is also observed in the reactions with the TyrOEt(No. 6) and the TrpOEt(No. 9) complexes. In Entry No. 8, effect of SerOEt is poor as compared with that of TyrOEt. The complexes of α-methylbenzylamine(Nos. 4 and 5) are much more catalytic active than the AlaOEt and SerOEt complexes probably because of steric effect of the benzene ring in the ligands, but are inferior to the PheOEt and TyrOEt complexes.



AlaOEt



PheOEt



MeBA

It seems that carbonyl groups of the amino acid esters form weak coordination together with strong coordination of amino groups, but the α-methylbenzylamine has no ester group. Therefore, an assistant effect of the ester group may contribute to favorable catalytic activity, especially to the asymmetric induction. As is seen in Entry No. 7, the TyrOMe is inferior to the TyrOEt as ligand probably because of less steric effect of the COOMe group. The TrpOEt is the most bulky molecule among the ligands in Table 2 and $[\alpha]_D$ value of the aldol type product in the reaction with its complex is higher than that in other reactions(No. 9), but the conversion(%) is lower than that with the PheOEt and TyrOEt complexes. Values of specific rotation of the PheOEt, TyrOEt, and TrpOEt are relatively high(Table 2) but relation between their $[\alpha]_D$ values and their catalytic effects on asymmetric regulation is not elucidated.

When the reaction with Zn^{2+}-$(TyrOEt)_2$ complex catalyst was carried out in H_2O solvent(pH 7, 40 °C, 24 h), only the aldol type product was obtained in a 100% yield but almost no asymmetric induction was observed(racemic modification). Thus, effect of solvent on the enantioselective reactions are very important.

References

1) K. Irie and K. Watanabe, Bull. Chem. Soc. Jpn., 53, 1366(1980); 54,1195(1981).

2) K. Watanabe and A. Imazawa, Bull. Chem. Soc. Jpn., 55, 3208(1982).

3) C. H. Heathcock, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press (1984), Vol. 3B, p. 111.

4) Aldol type product: 4-hydroxy-4-(4-nitrophenyl)-2-butanone.

   a) Racemic modification: yellowish crystals, mp 63 °C. D.S. Noyce and W. L. Reed, J. Am. Chem. Soc., 80, 5539(1958).

   b) Enantiomeric excess mixture: yellowish oil. Optical rotation was measured in EtOH slovent at room temperature.

   IR(cm^{-1}): 3400(OH), 1710(C=O), 1600(ArH). ^1H-NMR($CDCl_3$):δ 2.19(s, 3H), 2.88(d, 2H), 4.10(br, s, OH), 5.18(t, 1H), 7.66-8.15(q, aromatic).

5) Dehydrated product: 4-(4-nitrophenyl)-3-buten-2-one. mp 114-116 °C. D. S. Noyce and W. L. Reed, J. Am. Chem. Soc., 80, 5539(1958). ^1H-NMR($CDCl_3$):δ 2.42(s, 3H), 6.68-6.96(d, 1H), 7.30-7.46(d, 1H), 7.64-8.37(q, aromatic).

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