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ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS BY NONENZYMATIC TRANSAMINATION. RATIONALIZATION FOR THE STEREOCHEMICAL RESULTS

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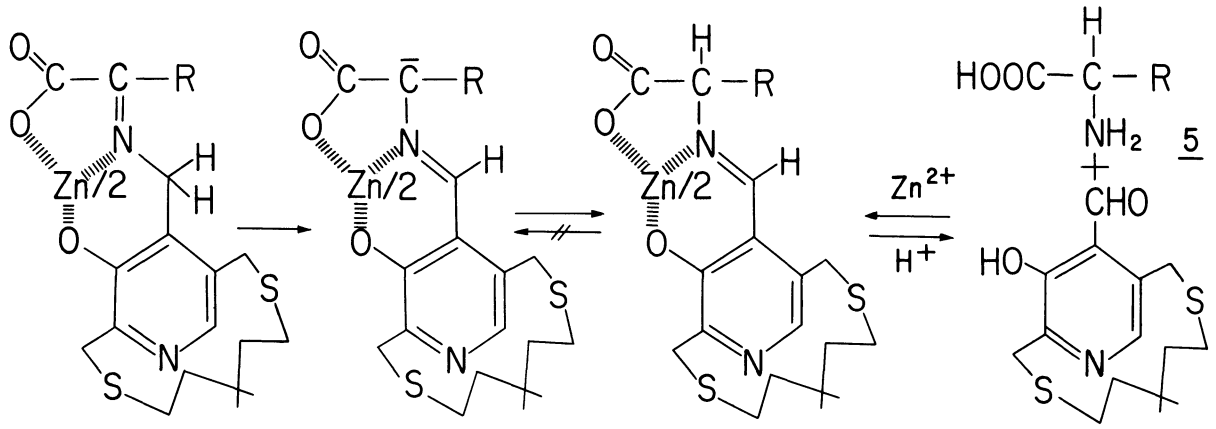
Asymmetric induction in the nonenzymatic transamination from the chiral pyridoxamine analog (1) to the α-keto acids in the presence of a limited amount of zinc ion can be explained by the kinetically controlled stereoselective protonation to the carbanion formed in an octahedral Zn^{2+} chelate intermediate during the reaction.

In the successful asymmetric synthesis of α-amino acids mimicking the reaction of vitamin B_6-dependent enzymes, we have found several interesting stereochemical features about the reactions: the transamination reactions between the chiral pyridoxamine analog, (R)- or (S)-enantiomer of 15-aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (1), and α-keto carboxyric acid, in the presence of Zn^{2+} in methanol.[2] First, reduction of the molar ratio of Zn^{2+} *vs.* 1 from 1/1 to 0.5/1 resulted in a remarkable increase of the enantiomeric excess of the amino acids produced. Second, employment of the S enantiomer of 1 (and half equimolar Zn^{2+}) gave the R enantiomer of the amino acids in excess, and *vice versa*.

This communication describes a rationalization for the foregoing stereochemical results through a discussion on the mechanism of the transamination reaction, presenting a clear image of the Zn^{2+} chelate intermediates.

The mechanism of the nonenzymatic transamination reaction between pyridoxamine and α-keto acid in the presence of metal ion has been explained as the initial formation of a metal chelate of ketimine from the three reactants and its isomerization to the aldimine chelate that follows.[3] Especially, one-way isomerization from the ketimine chelate to the aldimine chelate proceeds quite smoothly and completely in methanol when Zn^{2+} is employed as the metal ion.[4] This was also the case in the transamination reaction between chiral pyridoxamine analog (1) and α-keto acid, as the results of spectrophotometric examination. Figure 1 shows the change of the absorption spectra that occurs when chiral 1, sodium salt of α-keto acid and zinc perchlorate are mixed simultaneously.[5] The final absorption spectrum was identical with that of the aldimine chelate (4) prepared in the reverse direction from the sodium salt of the authentic amino acid (5), the chiral pyridoxal analog (6) and zinc perchlorate.



2 3 4 6

By a further experiment using 4 prepared from 5 and 6, it was confirmed that deprotonation at the α-position of the carboxylate group in 4 did not occur in the presence of the sodium salt of the α-keto acid[6] as the base. Thus, 4 prepared from authentic chiral amino acids, (S)-6, and Zn^{2+} was kept for 48 h at room temperature with three molar equivalents of sodium salt of the corresponding α-keto acids, and decomposed by addition of 1 M hydrochloric acid. The amino acids recovered retained the full original chirality. These results lead to the following conclusion: asymmetric induction in this transamination reaction is not ascribed to the production of the thermodynamically stable diastereomer of 4 through equilibration between 4 and 3 but, to the kinetically controlled stereoselective protonation to one of the enantio-faces of the carbanion in 3. That the attacking proton comes only from methanol but not intramolecularly from the methylene group bearing the imino nitrogen in 2[7] was confirmed by the observation that the treatment of 4-methyl-2-oxo-pentanoate with Zn^{2+} and (R)-1 (0.5:1) in methanol-d_1 gave only α-deuterated leucine.[8]

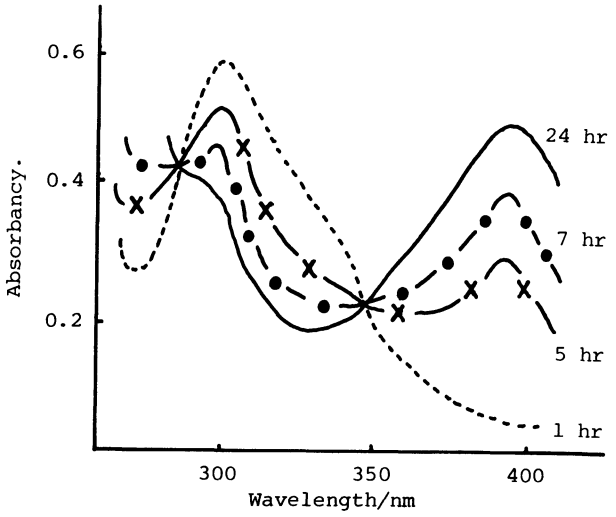


Figure 1. Changes of electronic absorption spectra with time for a methanolic solution of (S)-1 (1.0×10^{-4} M), zinc perchlorate (0.5×10^{-4} M), and sodium 4-methyl-2-oxo-pentanoate (2.0×10^{-4} M).

The combination of α-keto acid, chiral 1, and half equimolar Zn^{2+} should predominantly form a 6-coordinated Zn^{2+} chelate complex in an octahedral form, involving two molecules of the Schiff base arising from the keto acid and 1 because the Schiff base behaves as a typical tridentate ligand.[9] It is possible for a couple of ketimines to isomerize smoothly to the corresponding aldimines within

this complex. This was the reason why, after acidic hydrolysis of the zinc-aldimine chelate complex (4), the amino acids (5) was obtained in more than 50% yields on the basis of the pyridoxamine analog used[2] in spite of the presence of only half molar equivalent of zinc ion to the pyridoxamine analog. As discussed later, the rigid structure of this chelate intermediate is required for controlling the direction of the attack of the proton on the carbanion in 3. This explains that employment of Zn^{2+} half equimolar to 1 gave the amino acid in higher enantiomeric excesses than the case using equimolar Zn^{2+} that allows the formation of the chelate complexes coordinated by one molecule of the Schiff base and a few molecules of methanol or water.

The source of the asymmetric induction of this transamination reaction is the planar chirality of 1; i.e., the presence of the "ansa-chain"[10] in its molecule. In order to explain the result that the employment of (S)-1 gave (R)-amino acids in excess, it is necessary to take into consideration the relative orientation of two neighboring "ansa-chains" in the octahedral chelate complex. Examination with CPK space-filling molecular models suggested that one of the two possible helical isomers (Λ and Δ) of the chelate complex was improbable because the two "ansa-chains" partially overlapped with each other. This situation is schematically shown in Figure 2 as the Δ isomer. On the contrary, the alternative Λ isomer is not inhibited by any interaction between the two "ansa-chains". Consequently, the Λ isomer will play an essential role in this transamination reaction and undergo stereoselective protonation to the carbanion. As Figure 3 shows, the bulky sulfur atom and its neighboring alkyl groups in the Λ isomer containing (S)-6 moieties cover the re-face of the carbanion, preventing the protonation from this side. Thus the protonation has to take place on the si-face of the carbanion and gave amino acid of R configuration as the result. The other of the carbanions that constitute the Λ isomer is in the completely same situation, though not shown in Figure 3. These explanations are in accord with the stereochemical aspects of the

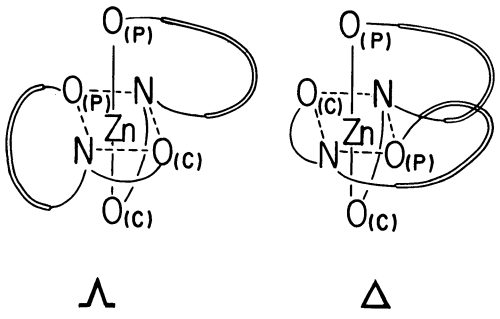


Figure 2. Schema showing the relative orientation of the two "ansa-chains" in the octahedral chelate complex constituted from vitamin B_6 analogs of S configuration. $O_{(p)}$ and $O_{(c)}$ indicate phenolic and carboxylic oxygen atoms respectively. Broad open line shows the approximate position of the "ansa-chains".

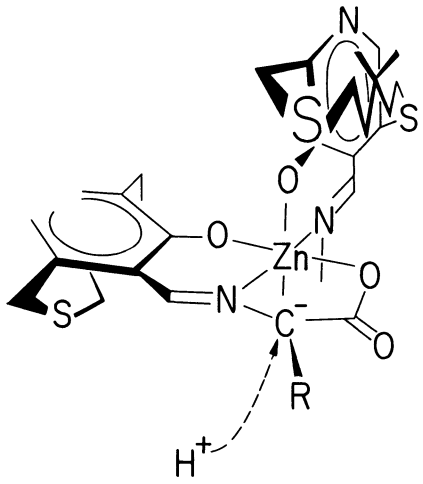


Figure 3. Stereoselective protonation to the carbanion in the Λ isomer.

experimental results. In short, the "ansa-chain" of the chiral pyridoxamine analogs seems to serve doubly for the stereoselective transamination reaction; i.e., the selection between helical isomers Δ and Λ (Figure 2), and the restriction of the direction of protonation.

Hitherto, several efforts have been made to elucidate the structure of the metal chelate intermediates in the model reactions mimicking the vitamin B_6-dependent enzymes by means of n.m.r spectroscopy,[11] X-ray analysis,[12] and so on. In the case of Zn^{2+} chelates, however, their structure is still obscure because of the diversity of the coordination mode and the difficulty in the X-ray analyses.

This paper could disclose the structure of such Zn^{2+} chelate intermediates under the limited reaction conditions owing to the employment of the special ligands having the definite absolute configurations.

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5) This change corresponds to the isomerization from the ketimine chelate (2) to the aldimine chelate (4). When $Zn(ClO_4)_2 \cdot 6H_2O$ equimolar to pyridoxamine analog was used, an essentially similar change was also observed, but the reaction rate was different.
6) Sodium 2-oxo-carboxylate was used in excess for the synthesis of amino acids through the transamination reaction.
7) This fact is completely opposite to that in the enzymatic transaminations.
8) The obtained leucine ($[\alpha]_D^{23}$ -8.4° (c 0.8, H_2O)) completely lacked the signal due to the α-proton in the p.m.r spectrum.
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