Asymmetric Synthesis of *allo*-Threonine and Threonine; the Use of a Chiral Pyridoxal-like Pyridinophane–Zinc Complex as an Enzyme Mimic

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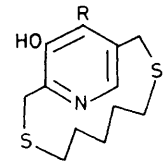
allo-Threonine and threonine having 88 and 74% enantiomeric excess (e.e), respectively, were obtained in 1.7 : 1 ratio, by a biomimetic aldol condensation between acetaldehyde and the zinc chelate of a Schiff base produced from glycine and a chiral, pyridoxal-like pyridinophane derivative (**2**).

The well-known finding by Snell[1] that various transformations involved in amino acid metabolism, catalysed by vitamin B_6-dependent enzymes, can be simulated by simpler model systems, was further developed by Martell,[2] who showed the advantages of using non-aqueous solvents in such model reactions. Many studies have been carried out mimicking various B_6 enzymes on the basis of this pioneering work. In particular, much attention has been focused in recent years on transaminase models with enantioface differentiation.[3] We have also succeeded in constructing one such transaminase model, using the pyridoxamine-like pyridinophane derivative (**1**) with planar chirality[4] and Zn^{2+} (0.5 equiv.).[5] The present

Table 1. Aldol condensation between glycine and acetaldehyde using the (**2**)–Zn^{2+} system.

Reaction conditions			Products			
Configuration of (**2**)	Buffer ph	Reaction time/h	Total yield (%)	*allo*-Thr.: Thr.	E.e./%[a] *allo*-Thr.	Thr.
(*S*)	9.15	46	41	1.6:1	78 (*S*)	61 (*S*)
(*S*)	10.23	24	73	1.7:1	88 (*S*)	74 (*S*)
(*R*)	10.23	24	76	1.7:1	82 (*R*)	70 (*R*)
(*S*)	11.17	24	83	1.6:1	74 (*S*)	50 (*S*)
(*R*)	11.17	100	—	—	60 (*R*)	36 (*R*)

[a] Configuration produced in excess is shown in parentheses.



(1) R = CH_2NH_2
(2) R = CHO

communication deals with an application of such a chiral system to the asymmetric synthesis of β-hydroxy-α-amino acids, stimulating B_6-dependent aldolase reactions.[6] The use of a Zn^{2+} chelate complex for aldol condensation† revealed some characteristic and advantageous features not found with other metal chelates.[7]

Treatment of a Schiff base derivative of glycine and the *R* or *S* enantiomer of 15-formyl-14-hydroxy-2,8-dithia[9](2,5)-pyridinophane (**2**) with Zn^{2+} (0.5 equiv.) resulted in two chelate complexes showing absorption maxima at 397 and 308 nm respectively, in approximately 3 : 1 ratio, of which only the former product underwent the subsequent aldol condensation. Routine column chromatographic separation of these complexes was unsuccessful but the major product was enriched in the methanol–water (3 : 7 v/v) eluate of a QAE Sephadex A-25 column which was saturated with the product mixture in advance. Re-elution with 0.2 M KCl in the same solvent gave the minor product, and repetition of these procedures accumulated the major product corresponding to 64% of the mixture. The isolated major product resisted crystallization, but was surmised to have a structure containing a 6-co-ordinate Zn atom (Figure 1‡), based on its Zn content (9.23%),§ m.p. >270 °C (decomp.); $\nu_{max.}$ (KBr) 1615 cm^{-1}; $\lambda_{max.}$ 397 nm (ε 1.5 × 10^4).

Aldol condensations between the isolated chelate complex and acetaldehyde (in large excess) were conducted at room temperature for 24—100 h in 1 : 1 methanol–water (v/v) buffered to pH 9.15, 10.23, or 11.17 with $NaHCO_3$–NaOH. After decomposition of the resulting complex by addition of 1 M HCl followed by evaporation, the residue was extracted with ethyl acetate and water. The pyridinophane (**2**) with full chirality was recovered almost quantitatively from the organic extract. The neutralized aqueous extract was repeatedly chromatographed on Amberlite CG 120 (first in H^+ form and eluted with aqueous NH_3; then in pyridinium form and eluted with pyridine–HCO_2H buffer), giving a mixture of *allo*-threonine and threonine;¶ δ (D_2O, 100 MHz) 3.74 [d, –C*H*(NH_2)– of *allo*-threonine, *J* 3.9 Hz], 3.48 [d, –C*H*(NH_2)– of threonine, *J* 4.9 Hz]. The mixture was esterified in 10% HCl–methanol, *N*-acylated with 3,5-dinitrobenzoyl chloride and Et_3N,[8] and analysed by h.p.l.c. on chiral Sumipax OA-1000 column (10 : 4 : 1 n-hexane–1,2-dichloroethane–ethanol), to give 4 well separated peaks corresponding to 2 enantiomers of each amino acid. Integration gave enantiomeric excess (e.e.) values for the amino acids. As shown in Table 1, *allo*-threonine and threonine having 88 and 74% e.e., respectively, were obtained in 1.7 : 1 ratio in a total yield of 73% by the reaction conducted at pH 10.23 for 24 h. Furthermore, Table 1 shows that (i) the use of (*S*)-(**2**) in the aldol condensation produces (*S*)-amino acids in excess, and *vice versa*; (ii) higher pH increases the total yield of amino acids but does not change the amino acid ratio; and (iii) e.e. values for both amino acids are decreased by higher pH and longer reaction time. These results are well rationalized by assuming a kinetically controlled stereoselective attack of acetaldehyde on one of the enantiofaces of the carbanion (Figure 1). The other enantioface is sterically hindered by one of the bulky sulphur atoms (circled in Figure 1). That the β-hydroxy-α-amino acid residues within the chelate seem to be well protected against rapid racemization, under mild conditions, may indicate an advantage of the use of the present Zn chelate system in asymmetric synthesis.

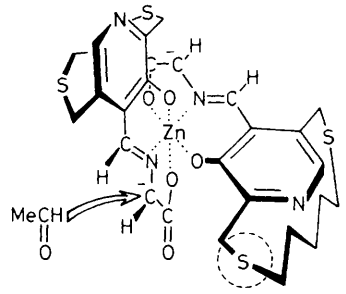


Figure 1. Λ-Isomer of the octahedral Zn^{2+} chelate complex containing (*S*)-(**2**) Schiff base and glycine anion.

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† The role of Zn^{2+} chelate complexes in the transamination reaction was first demonstrated by Martell.[2]

‡ This is drawn as a Λ isomer. The alternative helical isomer, Δ, is unlikely to exist.[9]

§ Calculated for $(C_{30}H_{36}O_6N_4Zn)^{2-}2H^+$: Zn, 8.78%.

¶ Satisfactory elemental analyses were obtained.

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