*Inorganica Chimica Acta*, 57 (1982) 107–110



# Stereoselective Aldol Reactions on Mixed α-Aminoacidato Copper Complexes Cu(L-aaO)(GlyO)*

MICHAEL GIRNTH-WELLER and WOLFGANG BECK**

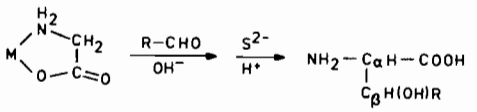
*Institut für Anorganische Chemie der Universität München, D-8000 Munich 2, F.R.G.*

Received April 4, 1981

*Aldol reactions at the α-$CH_2$-functions of Cu(L-aaO)(GlyO) (L-aaO = anion of L-Val, L-Pro, L-Lys, L-Glu) with benzaldehyde or butanal yield β-phenylserine or β-hydroxynorleucine, respectively. An excess of threo-over erythro-diastereoisomers (1.6–3.1:1) is obtained; the ratio depending both on the aldehyde reacting and the L-amino acid present. The observed stereoselectivity is discussed in terms of a mechanism involving a bicyclic oxazolidine complex.*

## Introduction

The α-CHR-group of metal-coordinated amino acids exhibits C–H-acidity, giving rise to racemisation [1, 2] and H/D-exchange under basic conditions [3]. Consequently, glycinato complexes **1** undergo aldol reactions with aldehydes, yielding free β-hydroxy-α-amino acids **2** after cleavage of the product (Scheme 1).



**1** **2**

Scheme 1

Akabori *et al.* [4] first studied the formation of threonine and allo-threonine from $Cu(GlyO)_2$ and acetaldehyde; the reaction has been extended to various metals and aldehydes [5–8]. In Δ- and Λ-$[Co(en)_2GlyO]^{2+}$, the 'pro L' – and 'pro D' – positions of the methylene group were found to undergo H/D-exchange at different rates, *i.e.* stereoselectively [9]. Accordingly, aldol reactions with these compounds lead to preferred formation of D- or L-**2** [10, 11].

However, aldol reactions on $Cu(GlyO)_2$ yielded 1.6–1.8:1 -ratios of threo- to erythro-**2** products. Thus, with all aldehydes used, an excess of threo-product, *i.e.* Cα(R), Cβ(S) or Cα(S), Cβ(R) (*e.g.* threonine), over the erythro-form, *i.e.* Cα(R), Cβ(R) or Cα(S), Cβ(S) (*e.g.* allothreonine), is obtained. We now wish to report some reactions of mixed complexes Cu(L-aaO)(GlyO) with benzaldehyde or butanal, together with an explanation of the observed stereoselectivity.

## Results and Discussion

To elucidate the effect of a higher amino acid-ligand on the stereochemistry of aldol reactions of copper(II)-glycinate, mixed complexes are desired. Due to kinetic lability, the availability of these species is governed by equilibrium constants of the reaction

$$Cu(L\text{-}aaO)_2 + Cu(GlyO)_2 \overset{K}{\rightleftarrows} 2\ Cu(L\text{-}aaO)(GlyO).$$

For a complete random distribution logK = 0.6; but in many cases is known to be higher than that expected statistically. The mixed complexes are generally slightly more stable than the bis-species [12–15].

In weakly basic aqueous solutions of Cu(II) and amino acid in a 1:2-molar ratio, N-O–coordinated bis-chelate complexes in the N-*trans* configuration predominate [16, 17]. The octahedral or distorted octahedral environment of $Cu^{2+}$ is completed by axially bound water. Thus, in the reaction mixtures used, *i.e.* pH 9.5 aqueous solutions of copper(II), glycine and a L-amino acid, (molar ratio 1:1:1) at least 50% of the overall complex concentration is N-*trans*-Cu(L-aaO)(GlyO)$(H_2O)_2$ (**3**).

For reactions of $Cu(GlyO)_2$ with aldehydes it was reported that highly basic conditions (pH 10–12) were required [4–6]. However, to minimize problems of racemisation, the present reactions were carried out at pH 9.5 with a 10-fold excess of aldehyde, yielding acceptable amounts of β-hydroxy-amino acids (70–80%) in reasonable times (7 days, RT).

Following metal ion separation the amino acid mixture was analysed by TLC and ion exchange chromatography (automatic amino acid analyzer) giving four detectable species: unreacted glycine, unchanged L-amino acid, and the threo- and erythro-diastereoisomers of the β-hydroxyamino acid. With benzaldehyde, threo- (αD, βL or αL, βD; D,L-PseOH) and erythro- (αD, βD or αL, βL; D,L-allo-PseOH) phenylserine **4** is obtained; with n-butanal, D,L-threo- and erythro-β-hydroxy-norleucine **5**. As it turned out to be impossible to separate the molar

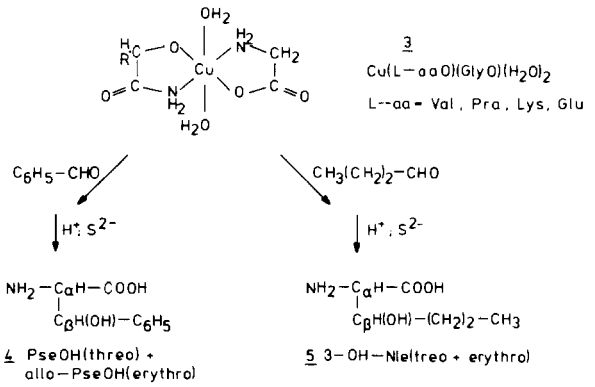
*Metal Complexes with Biologically Important Ligands XIX. XVIII: W. Beck, W. Petri and J. Meder, *J. Organometal. Chem.*, *191*, 73 (1980).

**Author to whom correspondence should be addressed.

TABLE I. Diastereomeric Ratios.[a]

| L-aa in Cu(L-aaO)(GlyO) | aldehyde | β-hydroxy amino acid | ratio threo:erythro |
|---|---|---|---|
| L-Val | benzaldehyde | Pse | 1.9:1 |
| L-Val | butanal | β-OH-Nle | 1.6:1 |
| L-Pro | benzaldehyde | Pse | 1.95:1 |
| L-Pro | butanal | β-OH-Nle | 1.75:1 |
| L-Lys | benzaldehyde | Pse | 2.5:1 |
| L-Lys | butanal | β-OH-Nle | 2.15:1 |
| L-Glu | benzaldehyde | Pse | 3.1:1 |
| L-Glu | butanal | β-OH-Nle | 2.7:1 |

[a]Pse = phenylserine; β-OH-Nle = β-hydroxynorleucine.




Scheme 2

amounts of diastereoisomers required for optical rotation measurements on Dowex 50X8 ion exchange columns, no assessment of the enantiomeric yields (*e.g.* excess of D- or L-phenylserine, respectively) could be made. However, with the amino acid analyzer, operating on the nanomolar scale, quantitative separation of diastereoisomers was achieved. Results are given in Table I. In all reactions an excess of threo-relative to erythro-product was found (1.75:1 to 3.1:1).

The threo-erythro ratios of 1.6:1–1.8:1 for reactions of $Cu(GlyO)_2$ with acet-, benz- and i-butyraldehyde [5] were only understood when the isolation of primary products, copper-coordinated oxazolidines, was accomplished [18, 19]. This would suggest formation of intermediate complexes **6**, via a mechanism [7, 20] involving initial attack of the $NH_2$-group by an aldehyde, with subsequent reaction of another aldehyde at the less acidic α-$CH_2$-group and concurrent ring closure to give the coordinated oxazolidine (scheme 3).

The aldehyde-residues R will be directed preferably to exo-positions in the bicyclic system formed. Hence, for Cα and Cβ, opposite configurations are required. Following acid hydrolysis and removal of copper(II) the D,L-threo-β-hydroxyamino acid is obtained. In the light of this, the observed diastereomeric excess of the threo-form in phenylserine than

The bulkier benzyl-group, compared with the $CH_3(CH_2)_2$-residue (R in **6**) is more restricted to the two exo-positions, thus leading to a higher diastereomeric excess of the threoform in phenylserine than in β-hydroxynorleucine.

The influence of the L-amino acid present, however, is more significant. Yields of threo-product increase according to the order Gly = L-Val < L-Lys < L-Glu, indicating steric interaction of R′ in **6a** with groups in the endo-positions (no such interaction is possible in **6b**). Steric interaction of R′ in **6a** with the endo positions of the oxazolidine ring should give an excess of L-threo. The analogous *cis*-chelate complex would then yield an excess of D-threo. Identical threo- to erythro-product ratios are observed using Cu(L-Val) (GlyO) (Table I) and $Cu(GlyO)_2$ [21]. The pyrrolidine ring of L-proline appears to distort coordinated water from its axial site towards the oxazolidine ring to be formed. The ω-$NH_2$-function of lysine reacts with the aldehyde to give a Schiff-base -$(CH_2)_4$–N=CH–R. The high threo-excess obtained both in the presence of L-lysine and L-glutamic acid may suggest axial coordination of the Schiff-base-N and the ω-$COO^-$-group, rendering the adjacent endo-positions highly unfavourable for the incoming aldehyde residues.

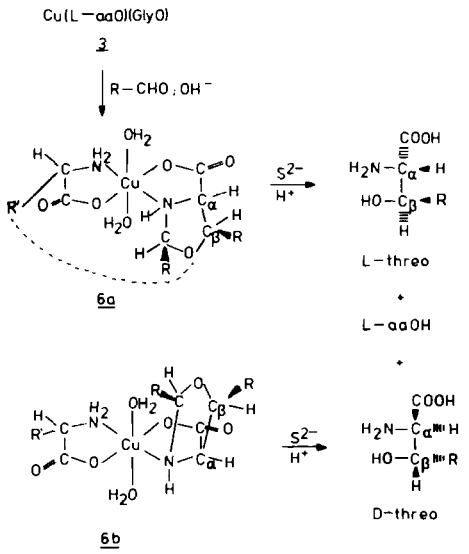
However, it may be noted that coordination of ω-$COO^-$ in copper-glutamic acid complexes has been found to be weak or non-existent [22].

For the stereoselectivity observed, it has to be taken into account that oxazolidine-formation can take place as outlined in Scheme 3, and additionally at $Cu(GlyO)_2$ (see Scheme 2). Assuming that $Cu(GlyO)_2$ [21] and the intermediate product **6b** both yield a threo-excess of 1.6–1.8:1, and further that the ratio Cu(L-aaO)(GlyO): $Cu(GlyO)_2$ = 2:1, a maximum threo-erythro-distribution of ~3:1 can be achieved, provided the reaction pathway via **6a** proceeds in high yields with exo-orientation. Thus, with L-glutamic acid present on reaction with benz-

TABLE II. $R_f$-Values and Retention Times of Amino Acids.

| L-aa in (Cu(L-aaO)(GlyO) | R in R–CHO | product | eluent in TLC | $R_f$ of L-aa (authentic sample) | $R_f$ of product | Retention time [min. s.] of product | |
|---|---|---|---|---|---|---|---|
| | | | | | | threo | erythro |
| L-Val | $-C_6H_5$ | Pse | baw[a] | 47 (48) | 70 | 37.20 | 40.07 |
| L-Val | $-(CH_2)_2CH_3$ | β-OH-Nle | eaw[b] | 90 (89) | 69 | 32.23 | 35.44 |
| L-Pro | $-C_6H_5$ | Pse | baw[a] | 28 (29) | 69 | 37.22 | 40.07 |
| L-Pro | $-(CH_2)_2CH_3$ | β-OH-Nle | ea [c] | 30 (30) | 50 | 32.25 | 35.43 |
| L-Lys | $-C_6H_5$ | Pse | baw[a] | 6 (6) | 70 | 37.21 | 40.04 |
| L-Lys | $-(CH_2)_2CH_3$ | β-OH-Nle | eaw[b] | 18 (19) | 67 | 32.26 | 35.47 |
| L-Glu | $-C_6H_5$ | pse | baw[a] | 48 (49) | 70 | 37.18 | 40.08 |
| L-Glu | $-(CH_2)_2CH_3$ | β-OH-Nle | ea [c] | 23 (21) | 48 | 32.25 | 35.43 |

[a]baw = n-butanol/acetic acid/water (4:2:5). [b]eaw = ethanol/conc. ammonia/water (9:1:12). [c]ea = ethanol/conc. ammonia (4:1).




Scheme 3

aldehyde (product ratio Pse: allo-Pse = 3.1:1), there is apparently high stereoselection within this pathway.

## Experimental

Aldol-reactions: To 1 mmol $Cu(OH)_2$, freshly prepared from $CuCl_2$ and NaOH and separated by centrifugation, in water (50 $cm^3$), 1 mmol L-amino acid (L-valine, L-proline, L-lysine or L-glutamic acid) and 1 mmol glycine was added. The pH of the resulting deep blue solution was adjusted to 9.5 with $Na_2CO_3$. Three mmoles of benzaldehyde (or n-butanal) were added at room temperature followed by 1 mmol every 24 h, with maintainance of pH 9.5. After 7 days, reactions were quenched by the addition of HCl (5 mol $dm^{-3}$, 1 $cm^3$). Isolation of amino acids: $H_2S$ was led into the quenched reaction mixture until it became completely colourless and the precipitated CuS was filtered off. The filtrate was shaken with $CH_2Cl_2$ to remove unreacted aldehyde and organic byproducts. After evaporation of the aqueous layer, the remaining colourless solid residue was dissolved in a few $cm^3$ of $H_2O$ and transferred to an ion exchange column (Dowex 50X8, 400 mesh; $NH_4^+$-form; 50 X 1 cm). Inorganic salts were removed by elution with 100 $cm^3$ water and the amino acids then eluted with $NH_3$ (2 mol $dm^{-3}$, 20 $cm^3$). Evaporation of this fraction yielded the mixed amino acids. TLC: The residue was dissolved in HCl (5 mol $dm^{-3}$, 10 $cm^3$) and analysed on Kieselgel layers (Merck 60, ascending method, identification 1% ninhydrine spray), together with authentic samples. Various eluants were required for complete resolution depending on the composition of the particular amino acid mixture (Table II).

Detection of diastereoisomers: The solution used for TLC was diluted 1:100, giving a concentration suitable for the amino acid analyzer (0.5–1 nmol/10 μl; Durrum 0-500, ion exchange column, 50 cm X 1.75 mm; eluent sodium citrate buffer (0.2 m–1.1 m) pH 2.9–7.9). Retention times see Table II.

## Acknowledgements

Support by Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie is gratefully acknowledged. We are indebted to Professor K. Kühn, Max-Planck-Institut für Biochemie, Martinsried/München and to Mr. Rasthofer for the measurements with the amino acid analyzer.

## References


1 R. D. Gillard and D. A. Phipps, *Chem. Commun.*, 800 (1970).
2 R. D. Gillard, P. O'Brien, P. R. Norman and D. A. Phipps, *J. Chem. Soc. Dalton*, 1989 (1977).
3 D. H. Williams and D. H. Busch, *J. Am. Chem. Soc., 87*, 4644 (1965).
4 S. Akabori, *Nature, 173*, 324 (1956);
S. Akabori, K. Okawa and M. Sato, *Bull. Chem. Soc. Japan, 29*, 608 (1956).
5 Review articles: D. A. Phipps, *J. Molecul. Catal., 5*, 8 (1979), and ref. therein;
A. Pasini and L. Casella, *J. Inorg. Nucl. Chem., 36*, 2133 (1974);
Metal Ions in Biological Systems, Ed. H. Sigel, Vol. 9, Marcel Dekker, New York (1979).
6 R. J. Geue, M. R. Snow, J. Springborg, A. J. Herlt, A. M. Sargeson and D. Taylor, *Chem. Commun.*, 285 (1976).
7 W. Beck and M. Girnth, *Chem. Ber., 109*, 965 (1976).
8 L. Casella, A. Pasini, R. Ugo and M. Visca, *J. Chem. Soc. Dalton*, 1655 (1980).
9 B. T. Golding, G. J. Gainsford, A. J. Herlt and A. M. Sargeson, *Tetrahedron, 32*, 389 (1976).
10 M. Murakami and K. Takahashi, *Bull. Chem. Soc. Japan, 32*, 308 (1956).
11 J. C. Dabrowiak and D. W. Cooke, *Inorg. Chem., 14*, 1305 (1975).
12 R. P. Martin, M. M. Petit-Ramel, J. P. Scharff, in Metal Ions in Biological Systems, Vol. 2, Ed. H. Sigel, Marcel Dekker, New York (1973).
13 G. Brookes and L. D. Pettit, *J. Chem. Soc. Dalton*, 1918 (1977).
14 H. Sigel, *Angew. Chem., 87*, 391 (1975).
15 A. Gergely, I. Sovago, I. Nagypal and R. Király, *Inorg. Chim. Acta, 6*, 435 (1972).
16 H. Sigel, *Inorg. Chem., 14*, 1535 (1975).
17 E. W. Wilson, M. H. Kasperian and R. B. Martin, *J. Am. Chem. Soc., 92*, 5365 (1970).
18 J. R. Brush, R. J. Magee, M. J. O'Connor, S. B. Teo, R. J. Geue and M. R. Snow, *J. Am. Chem. Soc., 95*, 2034 (1973).
19 J. P. Aune, P. Maldonado, G. Larcheres and M. Pierrot, *Chem. Commun.*, 1351 (1970).
20 D. A. Phipps, *Inorg. Chim. Acta, 27*, L103 (1978).
21 Y. I. Kutani, T. Okuda and S. Akabori, *Bull. Chem. Soc. Japan, 33*, 582 (1960).
22 S. T. Chow and C. A. McAuliffe, *Progr. Inorg. Chem., 19*, 51 (1975).