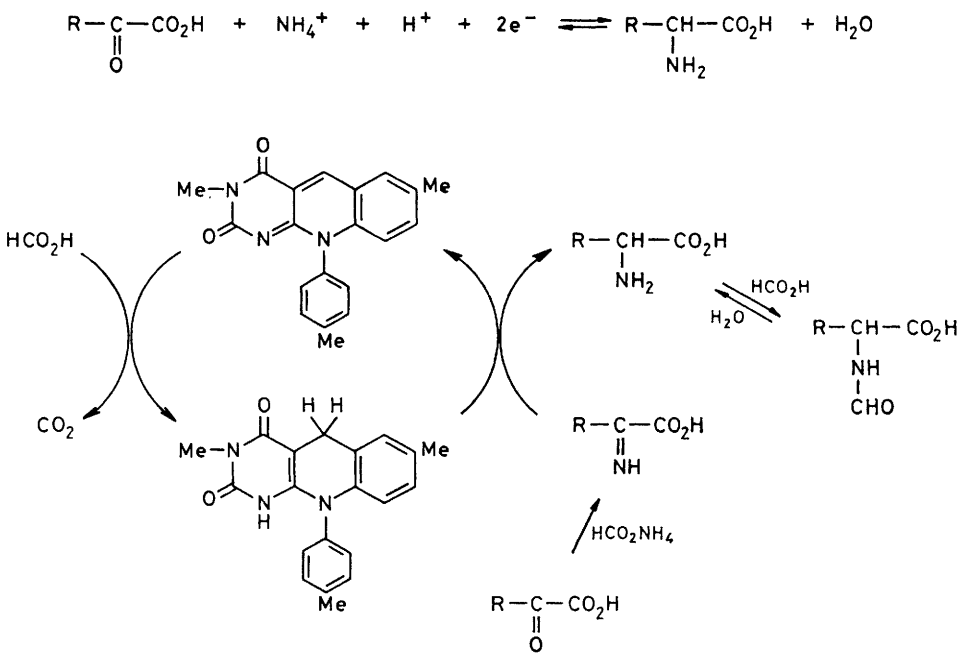
Autorecycling System for the Synthesis of α-Amino-acids by the Reductive Amination of α-Keto-acids catalysed by 1,5-Dihydro-5-deazaflavin

Fumio Yoneda* and Kazunori Kuroda

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

An effective autorecycling system for the biomimetic synthesis of α-amino-acids by the reductive amination of α-keto-acids has been achieved for the first time using 10-aryl-5-deazaflavin, ammonium formate, and formic acid; each mole of the 5-deazaflavin catalyses the reduction, by formic acid, of up to 20 moles of the α-imino-acids formed *in situ* from the α-keto-acids and ammonium formate.

The reversible reductive amination of α-keto-acids to α-amino-acids shown in equation (1) is catalysed by NAD(P)-dependent dehydrogenases such as L-glutamate dehydrogenase.[1] The reaction is known to proceed through the intermediate α-imino-acids. Chemical syntheses of amino-acids which involve the catalytic reduction of α-imino-acids in the presence of a variety of metal catalysts have been known for some time.[2] Several amino-acids have been prepared by electro-



Scheme 1

chemical reductive amination of the corresponding keto-acids in aqueous ammonia at mercury,[3] platinum,[4] or palladium black[4] electrodes. Recently, Shinkai *et al.*[5] demonstrated that α-amino-acids could be synthesised from α-keto-acids by the biomimetic reduction of the intermediary α-imino-acids with 1-benzyl-3-carbamoyl-1,4-dihydroquinoline as an NADH model. Here we report the first example of autorecycling reductive amination of α-keto-acids catalysed by 1,5-dihydro-5-deazaflavin, which offers a biomimetic and useful synthesis of α-amino-acids. This procedure consists of the treatment of α-keto-acids with ammonium formate in formic acid in the presence of a small amount of 5-deazaflavin catalyst (Scheme 1). We selected 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin to be the catalyst, as this exhibited the strongest reducing ability in the reduction of benzaldehyde to benzyl alcohol.[6]

For example, to a mixture of pyruvic acid (2.84 mmol), ammonium formate (9.51 mmol), and formic acid (20—30 ml) was added 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin (0.075 mmol) and the mixture was refluxed at 120 °C for 25 h under stirring. The reaction mixture was evaporated *in vacuo* to dryness to yield crude *N*-formylalanine, which was refluxed in 6M hydrochloric acid (20 ml) for 10 h. The hydrolysate was evaporated to dryness *in vacuo*, the residue was dissolved in a small amount of water and the aqueous solution applied to an i.r. 120B column. The column was eluted with 1M ammonia and the fractions containing amino-acid were evaporated to dryness *in vacuo* to give almost pure alanine (102 mg, 40.8%). The recycling number of the 5-deazaflavin catalyst was 15.16. Under these conditions, the 5-deazaflavin is initially hydrogenated by formic acid to the corresponding 1,5-dihydro-5-deazaflavin, which acts as turnover catalyst to reduce the α-imino-acid (probably protonated with formic acid), formed from α-keto-acid and ammonium formate, to yield the corresponding α-amino-acid. The α-amino-acid is readily formylated with the excess of formic acid to give the *N*-formyl-amino-acid which accumulates in the reaction mixture.

In complete agreement with this result, other α-amino-acids were prepared by the reductive amination of the corresponding α-keto-acids (Table 1). One exception was the reaction with oxala-acetic acid as the starting material which did not give any aspartic acid but only alanine resulting from the β-decarboxylation, as shown in Table 1. This decarboxylation to give alanine is reminiscent of the enzymic β-decarboxylation of aspartic acid to alanine by the aspartate β-decarboxylase.[7] A similar β-decarboxylation was reported in the reaction of oxala-acetic acid with an optically active amine followed by reduction to yield an optically active alanine.[8]

Table 1. Results of the reductive amination of α-keto-acids to α-amino-acids by 5-deazaflavin, ammonium formate, and formic acid at 120 °C for 25 h.

α-Keto-acid	α-Amino-acid	Recycling number of the catalyst[b]	Yield[a] (%)
Pyruvic acid	DL-Alanine	15.16	40
Glyoxalic acid	DL-Glycine	19.55	52
Phenylpyruvic acid	DL-Phenylalanine	7.88	21
Benzoylformic acid	DL-Phenylglycine	16.37	44
2-Ketoglutaric acid	DL-Glutamic acid	14.48	39
Oxala-acetic acid	DL-Alanine	10.16	27

[a] Yields, based on the starting α-keto-acids, have not been optimised. [b] A recycling number of one indicates 100% yield based on the catalyst.

In control experiments without the 5-deazaflavin only a trace of amino-acids at most was detected.

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