Tetrahedron Letters,Vol.30,No.21,pp 2841-2844,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

DECARBOXYLATION OF α-AMINO ACIDS BY PYRUVIC ACID AND ITS DERIVATIVES. EVIDENCE FOR AZOMETHINE YLIDES IN IN VITRO ANALOGUES OF PYRUVOYL ENZYMIC PROCESSES

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Abstract. Reaction of α-amino acids with pyruvic acid, ethyl pyruvate or pyruvamide in hot DMF results in imine formation followed by decarboxylation to generate azomethine ylides stereospecifically. The azomethine ylides undergo stereo specific cycloaddition to N-methylmaleimide via an endo-transition state. Pyruvate dependant decarboxylases are suggested to give rise to analogous azomethine ylide intermediates in vivo.

A wide range of biochemical transformations of α-amino acids are mediated by enzymes which employ pyridoxal 5'-phosphate as the catalytic centre. Many of the mechanistic features of these processes are understood.[1] We became interested in these processes as a result of our discovery of a new general type of prototropy, 1,2-prototropy, in X=Y-ZH systems which generates 1,3-dipoles, $X=\overset{+}{Y}(H)-\overset{-}{Z}$, under thermal activation.[2] Analogous prototropic processes occur in pyridoxal imines of α-amino acid esters[3] and were able to duplicate in vitro the in vivo decarboxylation processes mediated by pyridoxal enzymes and to demonstrate that these processes also involve intermediate azomethine ylides.[4] In this latter process the immediate precursor of the azomethine ylide is an oxazolidin-5-one whose stereochemistry dictates the stereochemistry of azomethine ylide.[5]

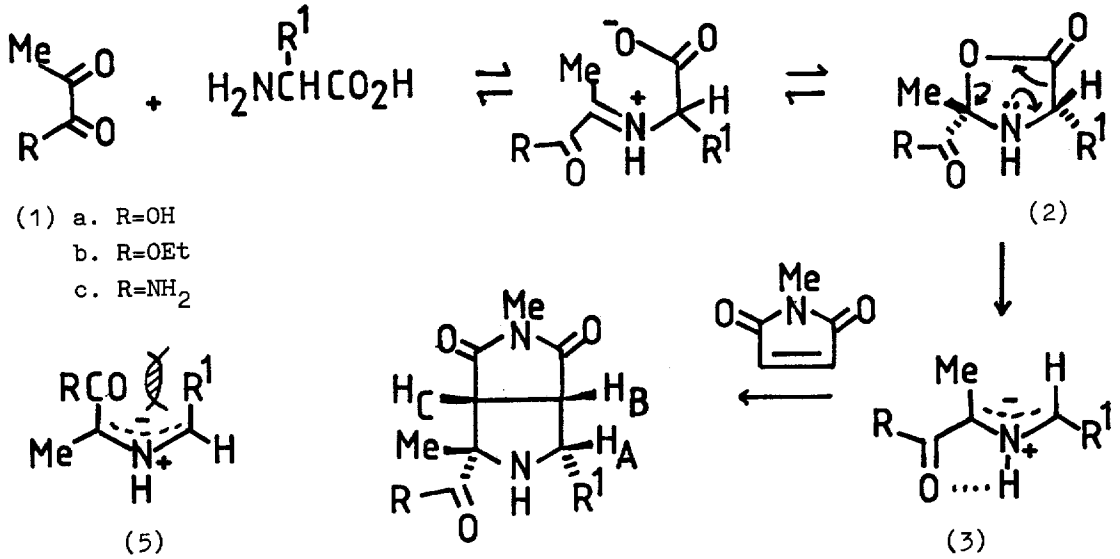
Although less ubiquitous than pyridoxal phosphate dependant enzymes, a second group of enzymes based on pyruvate also employ imine formation as an essential step in their mode of action.[6] Of particular interest are the pyruvate dependant decarboxylases[7-8], of which histidine decarboxylase[7] is the best known.

Table. Cycloadducts (4a-c) from the reaction of pyruvic acid derivatives with α-amino acids and N-methylmaleimide[a]

Pyruvate	Amino Acid	Time(h)	Product	Yield(%)[b]
1a	alanine	1.0	4a, R^1=Me	88
1a	phenylalanine	0.8	4a, R^1=CH_2Ph	64
1a	leucine	0.8	4a, R^1=CH_2CHMe_2	62
1a	phenylglycine	1.0	4a, R^1=Ph	59
1a	histidine	2.0	4a, R^1=4-imidazoylmethyl	53
1b	alanine	1.75	4b, R^1=Me	60
1b	phenylalanine	1.25	4b, R^1=CH_2Ph	66
1b	leucine	1.75	4b, R^1=CH_2CHMe_2	59
1c	methionine	1.0	4cr^1=CH_2CH_2SMe	55
1c	aspartic acid	2.0	4c, R^1=CH_2CO_2H	63
1c	serine	1.25	4c, R^1=CH_2OH	56

a. All reactions carried out in DMF at 80-100°C using a 1:1:1 molar ratio of amino acid, N-methylmaleimide and pyruvic acid derivative.[12]

b. Yield of isolated, crystallised product.



SCHEME

The ability of α-keto acid derivatives such as alloxan[9] and pyruvic acid[10] to effect decarboxylation of α-amino acids has been known for over a hundred years.[4,10] Much later pyruvamide derivatives were shown to behave in an analogous fashion and the reaction's relevance to pyruvate-containing enzymes was noted.[11]

We now report evidence for azomethine ylide intermediates in the reactions of α-amino acids with pyruvic acid derivatives (1a-c) and, by implication, in the corresponding biochemical processes referred to above. Thus pyruvic acid (1a) reacts with α-amino acids at 80-100°C in DMF in the presence of N-methylmaleimide to give the cycloadducts (4a)(Scheme), stereospecifically, and in good yield (Table). The decarboxylation is regiospecific and involves loss of the carboxyl group from the α-amino acid. Analogous stereospecific cycloadducts are obtained when ethyl pyruvate (1b) or pyruvamide (1c) are used in place of pyruvic acid (Table).

The stereochemistry of representative cycloadducts has been established by n.O.e. difference spectroscopy, e.g. for (4a, R^1=Ph) ^{1}H NOEDSY(%): irridation of H_A effects enhancement of the signals for H_B(12%) and C(Me)(5%), irradiation of H_C effects enhancement of H_B(5%) and H_A(3%). The stereochemistry of the cycloadducts (4a-c) implicates a dipole with configuration (3) and an endo-transition state for the cycloaddition. This result agrees with our previous studies of the cycloaddition of arylimines of α-amino acids and their esters to maleimides.[13] The alternative dipole (5), adjudged less favourable energetically due to steric interactions of the RCO and R^1 groups, could also give rise to (4a-c) but via an exo-transition state. Extensive studies with N-methylmaleimide have established that it traps the kinetically formed dipole and does not permit dipole stereomutation.[2,5] It is probable that formation of (3) proceeds via the oxazolidin-5-one (2) as previously established for aryl imines of α-amino acids.[5]

Further extensions of these decarboxylative cycloaddition processes are under active investigation.

We thank I.C.I., Colours & Fine Chemicals Division, and Queen's University for support.

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12. A mixture of alanine (440mg, 0.5mmol), N-methylmaleimide (550mg, 0.5mmol) and freshly distilled pyruvic acid (440mg, 0.5mmol) in DMF (50ml) was heated at 95°C for 1h. The solvent was then removed under reduced pressure and the resulting solid crystallised from chloroform to afford (4a, R^1=Me)(990mg, 88%) as colourless needles, m.p. 175-178°C, ($CDCl_3$) 3.72 (m,1H,H_A), 3.52 (d,1H, J 7.6Hz,H_C), 3.44 (t,1H,H_B), 2.89 (s,3H,NMe), 1.73 (s,3H,Me) and 1.48 (d,3H,Me)
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(Received in UK 29 March 1989)