Tetrahedron Letters,Vol.28,No.22,pp 2529-2532,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

PHOTOCHEMICALLY INDUCED RING-OPENING IN PROLYL PEPTIDES

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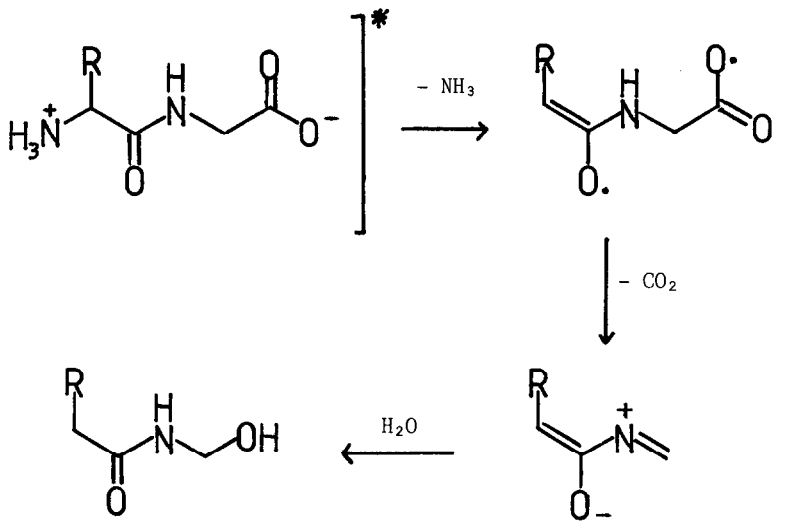
Abstract: Irradiation of prolylglycine in neutral, aqueous solution results in decarboxylative ring-opening to 5-amino-N-hydroxymethylpentanamide.

Simple aliphatic peptides undergo efficient photodegradation when exposed in aqueous solution to 254 nm radiation. Reaction in the excited state appears to be initiated by electron transfer from carboxylate to the adjacent peptide group, followed by deamination and decarboxylation, giving the N-hydroxymethylamide as a primary product[1] (Scheme 1).



SCHEME 1

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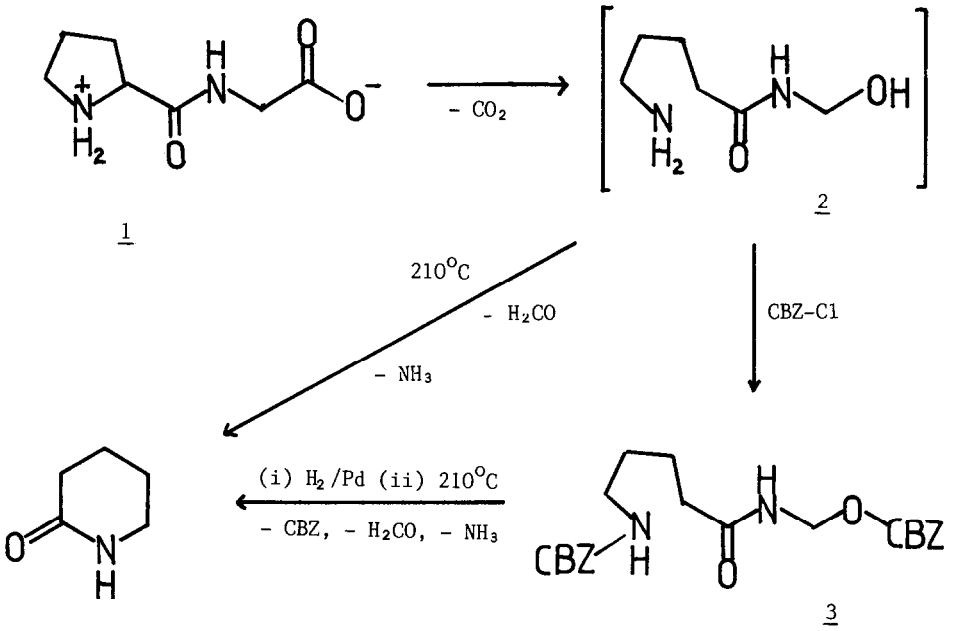
Early extension of this work to the study of prolyl peptides is of interest for two reasons. First, the above mechanism would be characterised by ring-opening rather than loss of ammonia, and second, prolyl and hydroxyprolyl residues are major components of dermal connective tissue, the known photodegradation of which may be important in the context of sunlight-induced skin damage[2]. The results reported below confirm that the predicted pattern of degradation occurs in prolylglycine.

Prolylglycine (1) in degassed, distilled water ($450cm^3$-0.03M) was photolysed in a quartz water-cooled reactor fitted with a 400W medium-pressure mercury arc. The reaction was monitored by reverse-phase HPLC (three sets of conditions) for loss of 1 and growth of products, by pH, and by estimation of carbon dioxide gravimetrically[3] as $BaCO_3$. After 70% conversion, the photolysis mixture was extracted with dichloromethane and the aqueous portion fractionated on cation exchange resin by washing first with water and then with 1M aqueous pyridine. The amine mixture in the latter fraction was derivatized with benzyl chloroformate using standard procedures, and separated by preparative normal phase HPLC. The principal component was isolated as a white crystalline product (8mg,mt 75-6°C) whose spectroscopic data[4] showed it to be the bis-CBZ derivative (3) of 5-amino-N-hydroxymethylpentanamide (2). Removal of the CBZ-groups by hydrogenolysis gave a solution that was shown by HPLC, under five different conditions, to be that of a mjaor constituent of the original photolysis mixture. Both this solution and the photolysis mixture afforded the gas phase spectrum of δ-valerolactam when analysed by GC-FTIR (Scheme 2).

The monitoring data showed a 23% yield of carbon dioxide was sustained throughout the period of photolysis, whereas that of 2 fell rapidly from an initial value of 25±5% to 12±2% and 6±1% at 30% and 70% conversion, respectively. Correspondingly, the pH of the photolysis solution increased from 5.8 to 7.6 and 8.6. This behaviour is typical of all the peptides we have studied[1], although the pH increase was somewhat greater and was shown by Nessler's reagent not to be due to the release of ammonia. The formation of amines via ring-opening is also consistent with our observation that a much higher proportion of the products was both retained on cation exchange resin and sensitive to ion-pair reagents in HPLC.

Thus prolylglycine in neutral aqueous solution appears to undergo photochemical degradation via intramolecular electron transfer in the excited state from carboxylate to peptide groups, followed by ring-opening and loss of carbon dioxide. This pathway is consistent with reports of analogous ring opening following external electron addition in the radiolysis of prolyl peptides[5]. Prolyl residues in dermal connective tissue could be



SCHEME 2

similarly photoreduced by excited dermal pigments[6] or excited aromatic side-chains within the protein[7], followed by secondary deamination[8].

Acknowledgements We thank the SERC for spectroscopic services at the University of Warwick and at the P.C.M.U., Harwell, and the Open University Research Committee for support.

References and Notes

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4. Compound 3: 1H NMR ($CDCl_3$): δ1.47(2H,p),1.62(2H,p),2.20(2H,t),3.13(2H,q), 3.99(2H,d),4.82(1H,broad t),5.02(2H,s),5.11(2H,s),5.99(1H,broad t),7.28 (10H,m), related signals were checked by decoupling experiments; ^{13}C NMR ($CDCl_3$): δ22.3,29.2,35.4,40.3,41.2,66.5,67.1,128.0,128.3,128.4,128.45, 128.54,135.0,136.5,155.0,156.4,160.8; IR(KBr): 3324,1736,1683,1658,1532, cm^{-1}; MS(EI): no parent ion observable but M-$(C_6H_5CH_2O)_2$-CO_2 (156.0881) and other ions (e.g C_7H_8O) expected for CBZ- derivatives (R.T. Aplin, J.H. Jones and B. Liberek, *J. Chem. Soc. (C)*, 1968,1011).

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(Received in UK 11 March 1987)