Modification of Glycine-containing Peptides Induced by Visible Light

By D. ELAD,* M. SCHWARZBERG, and J. SPERLING
(*Department of Chemistry, The Weizmann Institute of Science, Rehovoth, Israel*)

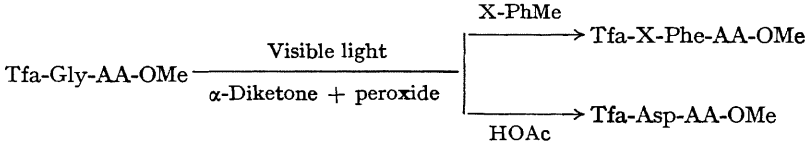
Summary Glycine residues in peptides have been converted into residues of a variety of branched amino-acids through the use of an appropriate reagent and visible light.

AN u.v. light-induced modification of glycine-containing di- and polypeptides has been reported by us recently.[1-3] This modification involves an alkylation process by which glycine residues in the peptides are selectively converted into residues of branched α-amino-acids with aliphatic or aromatic side chains. Thus, while using but-1-ene or toluene as reactants glycine residues were converted into norleucine or phenylalanine, respectively. These reactions were initiated photochemically with acetone using u.v. light of $\lambda > 260$ or > 290 nm. The extension of these reactions to polypeptides and proteins containing u.v. sensitive amino-acids, as well as the incorporation of sensitive amino-acid residue (*e.g.*, tyrosine) into a protein molecule, may require the use of light of longer wavelength, and consequently, the employment of suitable photoinitiators. The use of a variety of photoinitiators might also lead to a broader scope of these modification reactions through the incorporation of side chains which are not derived from olefins or aromatic hydrocarbons (*e.g.*, aspartic acid or serine derived from acetic acid[4] or methanol,[5] respectively). We report the photochemical modification of glycine-containing di- and poly-peptides initiated with visible light, using a combination of an α-diketone and a peroxide as a photoinitiator. Such modifications have been applied also for the incorporation of tyrosine or aspartic acid residues through the reactions of glycine with *p*-methoxytoluene or acetic acid, respectively. These reactions with the dipeptides are summarized in the Scheme.

The α-diketone (*e.g.*, biacetyl or camphorquinone) serves as the visible light absorbing system, while the peroxide serves as an hydrogen atom abstraction agent.[1,6] Some of the reactions studied and the major products obtained are described in the Table.

Typically, a mixture of *N*-trifluoroacetyl-dipeptide methyl ester (2 mmol), toluene (5 ml), biacetyl (0·4 ml), di-t-butyl peroxide (3 ml), and t-butyl alcohol (40 ml) was exposed to visible light at room temperature for 24 h. The progress of the reactions was followed by acid hydrolysis of samples and analysis on an Amino-acid Analyzer. Dipeptides were isolated by chromatography on silica gel and characterized by direct comparison with authentic samples.[1,3]

The preferential reactivity of glycine residues observed in reactions of glycine-containing di- and poly-peptides



SCHEME

Tfa = Trifluoroacetyl
AA=Gly, Ala, Val, Phe, or Tyr (OMe)
X = *p*-H or *p*-OMe

Alkylation products of glycine-containing peptides (initiated by visible light and biacetyl + di-t-butyl peroxide)[a]

Peptide derivative	Substrate	Product	Yield[b] (%)
Tfa-Gly-Gly-OMe	Toluene	Tfa-Gly-Phe-OMe	30
		Tfa-Phe-Gly-OMe	29
		Tfa-Phe-Phe-OMe	10
Tfa-Gly-Gly-OMe	*p*-Methoxytoluene	Tfa-Tyr(OMe)-Gly-OMe	21
		Tfa-Gly-Tyr(OMe)-OMe	20
Tfa-Gly-Gly-OMe	Acetic acid or anhydride	Tfa-Asp-Gly-OMe	30
		Tfa-Gly-Asp-OMe	30
Tfa-Gly-L-Ala-OMe	Toluene	Tfa-Phe-L-Ala-OMe	50
Tfa-Gly-L-Val-OMe	Toluene	Tfa-Phe-L-Val-OMe	50
Tfa-Gly-L-Phe-OMe	Toluene	Tfa-Phe-L-Phe-OMe	57
Tfa-Gly-L-Tyr(OMe)-OMe	Toluene	Tfa-Phe-L-Tyr(OMe)-OMe	43
Tfa-L-Phe-Gly-OMe	*p*-Methoxytoluene	Tfa-L-Phe-Tyr(OMe)-OMe	35
(L-Pro-Gly-L-Pro)$_n$	Toluene	(L-Pro-Phe-L-Pro)$_x$ ··· ··(L-Pro-Gly-L-Pro)$_{n-x}$	[c]
(Ala)$_m$(Gly)$_n$[$m:n$ = 9 : 1]	Toluene	(Ala)$_x$(Gly)$_y$(Phe)$_z$	[d]

[a] Fluorescent lamps were used as source of visible light; GWV filters (transmitting light of $\lambda > 370$ nm) were employed. [b] Yields are based on consumed starting peptide. Conversions ranged from 25—60%. [c] Amino-acid composition (residues/100 total residues) in product: Pro-64; Gly-25·3; Phe-10·7. [d] Ala-89; Gly-10; Phe-1.

initiated with acetone–u v light,[1,3] was preserved in the present cases too, but with some quantitative differences On the other hand, this diketone–peroxide combination has been shown to be less selective than acetone towards the non-peptidic substrates, *e g* acetic acid, thus enabling the conversion of glycine residues into aspartic acid derivatives, which could not be achieved by the acetone–u v light method under similar conditions [6b]

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