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PEPTIDE BOND FORMATION BY INTERMOLECULAR AMINOLYSIS OF D-GLUCOPYRANOSYL ESTERS OF AMINO ACIDS*

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ABSTRACT

The reaction of HO-protected and -unprotected D-glucopyranosyl esters of *N*-acylamino acids (Gly, Ala, Phe) with glycine and phenylalanine methyl esters in *N,N*-dimethylformamide at 38° and dichloromethane at 40°, respectively, led to rupture of the C-1 ester bond and formation of the corresponding *N*-acyldipeptide methyl ester. The relative reactivity of the C-1 ester bond toward aminolysis was greatly influenced by the structure of the amino acid nucleophile, the nature of the aglycon side-chain group, and the anomeric configuration of the D-glucopyranosyl ester involved. Evidence for a substantially lower acylating efficiency of the ester at C-2, as compared to that at C-1, was obtained by aminolysis of two fully acetylated 2-*O*-(acylaminoacyl)-β-D-glucopyranoses. Treatment of 1-*O*-(glycylglycylglycyl)-β-D-glucopyranose with phenylalanine methyl ester in *N,N*-dimethylformamide led to parallel hydrolysis and intermolecular aminolysis, to give the tripeptide and tetrapeptide methyl ester.

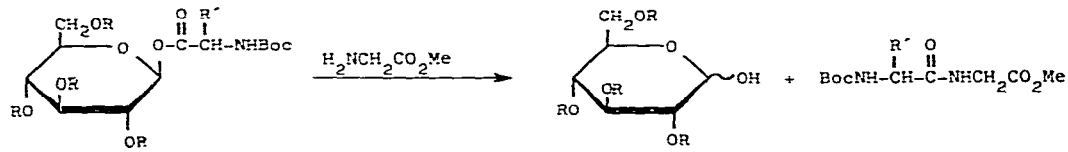
INTRODUCTION

We have reported[1] on the tendency of some 1-*O*-dipeptidyl-D-glucopyranoses to undergo intramolecular aminolysis with cleavage of the C-1 ester bond and formation of the corresponding piperazine-2,5-dione derivatives. D-Glucopyranosyl esters of tripeptides are resistant to this reaction, because of an unfavourable spatial disposition of the terminal amino and the 1-ester carbonyl groups[2]. D-Glucopyranosyl esters of amino acids, although readily hydrolysed, may also undergo intra- and inter-molecular transesterification through nucleophilic attack at the glycosyl ester carbonyl group[3,4]. Since the reactions mentioned point to enhanced electrophilic properties of the 1-ester carbonyl carbon, it seemed of interest to examine the susceptibility of these compounds toward amino acids as the nucleophile. We now report on the aminolytic reactivities of HO-protected and -unprotected D-glucopyranosyl esters of *N*-acylamino acids under various conditions.

*Glycosyl Esters of Amino Acids: Part XIV. For Part XIII, see ref. 23.

RESULTS AND DISCUSSION

The susceptibility of glycosyl esters of amino acids to nucleophilic attack by the amino group of a second amino acid was first examined (Scheme 1) with 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*N*-*tert*-butoxycarbonyl-glycyl- and -L-phenylalanyl)-β-D-glucopyranose[5] (**1** and **3**) as model substrates and the methyl ester of glycine as nucleophile. The aminolysis, performed with 3 molar equivalents of glycine methyl ester in *N*,*N*-dimethylformamide at 38°, proceeded (t.l.c. monitoring) slowly and without competing hydrolysis. After 4 days, the mixtures contained only unreacted starting-material, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, and the corresponding *N*-*tert*-butoxycarbonyl(Boc)-dipeptide methyl ester. Under the same conditions, the HO-unprotected 1-esters **2**[6] and **4**[7] underwent a partial (~10%) hydrolysis of the C-1 ester bond, to yield D-glucose and the Boc-dipeptide methyl ester, together with a small proportion of Boc-glycine and Boc-phenylalanine, respectively. The reaction mixtures were fractionated by column chromatography, and the products isolated and characterised. A comparison of the yields (Scheme 1) of the dipeptide derivatives implies that the nature of the aglycon amino acid affects the extent to which peptide formation occurs: the 1-esters **1** and **2**, involving Boc-glycine as the acid component, were more susceptible to the nucleophilic reagent than **3** and **4**, which contain Boc-phenylalanine.



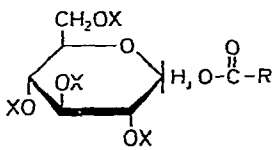
		Dipeptide	Yield(%)
1	R = CH_2Ph, R' = H	R = CH_2Ph	R' = H	55
2	R = R' = H	R = H	R' = H	57
3	R = R' = CH_2Ph	R = CH_2Ph	R' = CH_2Ph	27
4	R = H, R' = CH_2Ph	R = H	R' = CH_2Ph	33

Boc = Me_3COCO

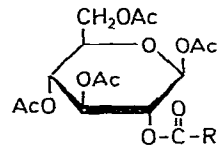
Scheme 1

Solvents are potent catalysts for aminolysis, and active aryl esters of amino acids couple with an amino component very much faster in dipolar aprotic solvents (*e.g.*, *N*,*N*-dimethylformamide) than in solvents having low dielectric constants (*e.g.*, dichloromethane)[8]. In order to avoid polar effects of the solvent, further experiments were performed with dichloromethane. As expected, aminolysis of D-glucopyranosyl esters in this solvent proceeded at a much lower rate; however, the reaction could be promoted when performed at reflux temperature (40°). Under these conditions, all of the 1-esters investigated were completely resistant to hydrolysis.

Thus, treatment of 2,3,4,6-tetra-*O*-benzyl- and 2,3,4,6-tetra-*O*-acetyl-1-*O*-(*N*-benzyloxycarbonylglycyl)-β-D-glucopyranose (**5β**[9] and **6β**) with 3 equivalents of D,L-phenylalanine methyl ester in dichloromethane at 40° for 4 days afforded *N*-benzyloxycarbonyl(Z)-glycyl-D,L-phenylalanine methyl ester in yields of 49 and 50%, respectively. Since no appreciable differences in reactivity were found between the *O*-benzylated and *O*-acetylated 1-esters bearing the same aglycon, the more accessible members of the latter series were examined.



		X
5	Z-Gly	CH_2Ph
6	Z-Gly	Ac
7	Z-Phe	Ac
8	Ac-Phe	Ac
9	Boc-Ala	Ac
10	Boc-D-Ala	Ac
11	Z-Ala	Ac
12	Z-D-Ala	Ac
13	Ac-Ala	Ac
14	Ac-D-Ala	Ac
17	H-Gly-Gly-Gly	H



15	Z-Gly
16	Boc-Ala

Boc = Me_3COCO

Z = $PhCH_2OCO$

Table I summarises the results obtained with the fully acetylated D-glucopyranosyl esters of *N*-protected-glycine (**6**), -phenylalanine (**7**, **8**), and -alanine (**9–14**) as the acylating agents and the methyl esters of glycine and D,L-phenylalanine as the coupling amines. From the data presented, it can be concluded that the relative reactivities of the 1-esters investigated were highly dependent upon the structure of the amino acid nucleophile. Under the conditions studied, glycine methyl ester was markedly more effective than an equal concentration of D,L-phenylalanine methyl ester (Expts. 1 and 2; 4 and 6). On the other hand, the different reactivities of β-D-glucopyranosyl esters of Z-glycine, Z-L-phenylalanine, and Z-L-alanine (**6β**, **7β**, and **11β**[10]) toward glycine methyl ester (Expts. 1, 4, and 11) and D,L-phenylalanine methyl ester (Expts. 2 and 6), respectively, point to the influence of the side chain of the aglycon amino acid upon the acylating ability (*i.e.*, relative electrophilicity) of the glycosyl carbonyl carbon. In general, these results accord with those acquired from kinetic studies[8,11–13] on the coupling rates and relative activity of amino acid active-esters having different side-chains. However, complete failure of the fully acetylated 1-esters of *N*-benzyloxycarbonyl- and *N*-acetyl-L-phenylalanine (**7β** and

TABLE I

AMINOLYSIS OF FULLY ACETYLATED D-GLUCOPYRANOSYL ESTERS OF *N*-PROTECTED AMINO ACIDS WITH AMINO ACID METHYL ESTERS IN DICHLOROMETHANE[a]

Expt.	*D-Glucosyl ester*			*Nucleophile*	*Dipeptide methyl ester isolated*	
	No.	*Anomer*	*Aglycon group*	*Chemical structure*	*Chemical structure*	*Yield[b] (%)*
1	**6**	β	Z-Gly	H-Gly-OMe	Z-Gly-Gly-OMe	87[c]
2	**6**	β	Z-Gly	H-D,L-Phe-OMe	Z-Gly-D,L-Phe-OMe	50
3	**6**	α	Z-Gly	H-D,L-Phe-OMe	Z-Gly-D,L-Phe-OMe	28
4	**7**	β	Z-Phe	H-Gly-OMe	Z-Phe-Gly-OMe	51
5	**7**	α	Z-Phe	H-Gly-OMe	Z-Phe-Gly-OMe	8
6	**7**	β	Z-Phe	H-D,L-Phe-OMe	No reaction	—
7	**8**[d]	β	Ac-Phe	H-Gly-OMe	Ac-Phe-Gly-OMe	82
8	**8**	β	Ac-Phe	H-D,L-Phe-OMe	No reaction	—
9	**9**[e]	β	Boc-Ala	H-Gly-OMe	Boc-Ala-Gly-OMe	50[f]
10	**10**	β	Boc-D-Ala	H-Gly-OMe	Boc-D-Ala-Gly-OMe	78[f]
11	**11**[d]	β	Z-Ala-	H-Gly-OMe	Z-Ala-Gly-OMe	15
12	**12**[d]	β	Z-D-Ala	H-Gly-OMe	Z-D-Ala-Gly-OMe	33
13	**13**[e]	β	Ac-Ala	H-Gly-OMe	Ac-Ala-Gly-OMe	93
14	**14**[e]	β	Ac-D-Ala	H-Gly-OMe	Ac-D-Ala-Gly-OMe	48

[a]All reactions were performed with ~3 × 10^{-4}M glucosyl ester and 3 equiv. of nucleophile at the reflux temperature of the solvent for 4 days, if not stated otherwise. [b]Yields refer to the pure dipeptide derivative isolated after chromatography, and are calculated on the D-glucosyl ester used. [c]Isolated after 2 days of reflux. [d]Lit.[10]. [e]Lit.[6]. [f]Isolated after 16 h of reflux.

8β[10]) to react with D,L-phenylalanine methyl ester (Expts. 6 and 8) cannot be explained only by electronic effects and should, at least in part, be ascribed to steric factors connected with the bulky phenyl groups. The striking difference in reactivity between β-D-1-esters of Boc- and Z-protected L-alanine (**9β**[6] and **11β**; Expts. 9 and 11) appears to be a consequence of steric hindrance, because electronic effects of the two *N*-protecting groups on amino acid coupling-rates were found[8,11] to be very similar and not significant. Differences in aminolytic reactivity observed between two glycosyl esters bearing the same aglycon, but of opposite configuration (**9β** and **10β**; **11β** and **12β**[10]; **13β**[6] and **14β**[6]; Expts. 9–14), should also involve steric factors. The present data, however, are not sufficient to allow any conclusion on this phenomenon.

The results obtained with the α and β anomers of the fully acetylated 1-esters of Z-glycine and Z-L-phenylalanine (**6** and **7**; Expts. 2 and 3; 4 and 5) provide evidence for the influence of anomeric configuration upon the relative ease of peptide bond formation. The higher aminolytic activity of the β anomers may be explained by a greater negative charge of the glucosidic oxygen atom, thus suggesting more extensive protonation on the equatorial O-1 in the bond-breaking step[1].

The finding that the optical rotations of isolated dipeptide derivatives were identical, or very close, to those of the optically pure, authentic specimens indicates

that aminolysis occurred without epimerisation of the aglycon chiral center. The tendency of amino acid derivatives protected by urethane-type (Boc, Z) protecting-groups to racemise is generally very low, but the opposite is true for *N*-acetyl derivatives, which epimerise readily *via* oxazolone intermediates[14]. The absence of racemisation in Ac-Ala-Gly-OMe ($[\alpha]_D$ −59.4°) and Ac-D-Ala-Gly-OMe ($[\alpha]_D$ +64.7°) formation by aminolysis of **13β** and **14β**, respectively, suggests some intramolecular, anchimeric assistance by the sugar moiety during aminolysis.

In order to compare the degree of activation of an amino acid linked to HO-1 and HO-2 of D-glucopyranose, 1,3,4,6-tetra-*O*-acetyl-2-*O*-(*N*-benzyloxycarbonylglycyl)- and -(*N*-*tert*-butoxycarbonyl-L-alanyl)-β-D-glucopyranose (**15** and **16**[6]) were treated with glycine methyl ester in dichloromethane for 4 days, under the conditions described in Table I. Compound **15** afforded the dipeptide Z-Gly-Gly-OMe (15%) as the minor, and *N*-acetylglycine methyl ester (44%) as the major, product, whereas aminolysis of **16** led to equal amounts (36%) of Boc-Ala-Gly-OMe and *N*-acetylglycine methyl ester. Two conclusions may be drawn from these results and the data obtained for aminolysis of the isomeric 1-esters **6β** and **9β** (Table I, Expts. 1 and 9): (*a*) the degree of activation of the acid involved in the C-1 ester linkage was substantially higher than that of the isomeric C-2 ester, and (*b*) the acylating efficiency of the sugar–amino acid C-1 and C-2 esters was, in all cases, higher than that exerted by the corresponding 1- and 2-acetates.

Treatment of 1-*O*-(glycylglycylglycyl)-β-D-glucopyranose (**17β**[2]) with 2 molar equivalents of D,L-phenylalanine methyl ester in *N*,*N*-dimethylformamide at 38° for 3 days led (t.l.c. monitoring) to parallel hydrolysis and aminolysis of the C-1 ester bond, to give D-glucose (92%), glycylglycylglycine (67%), and glycylglycylglycyl-D,L-phenylalanine methyl ester (28%). Thus, under the conditions of the experiment, a minor part of **17β** underwent intermolecular aminolysis with scission of the glycosyl ester bond and elongation of the aglycon tripeptide-chain into tetrapeptide in which the nucleophilic reagent becomes the C-terminal amino acid.

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were determined for 1% solutions in chloroform, if not stated otherwise. Concentrations were performed at diminished pressure on a rotary evaporator at <35°. Column chromatography was performed on Silica Gel (Merck 0.05–0.2 mm), or cellulose powder (Whatman standard grade) packed as a slurry using a plunger. T.l.c. was performed on Silica Gel 60 (Merck), and detection was effected with sulphuric acid (charring), the ninhydrin reagent, or the chlorine–iodine reagent for peptides. Solvents used were: *A*, benzene–ethyl acetate (various proportions); *B*, chloroform–ethyl acetate (10:1); *C*, 1-butanol–acetic acid–water (60:15:25); and *D*, 2-propanol–light petroleum–water (55:30:11). P.m.r. spectra (100 MHz, internal Me_4Si) were recorded with a Jeol JNM FX-100 Fourier-transform NMR spectrometer.

Peptides. — Ac-Phe-Gly-OMe[15], Boc-Ala-Gly-OMe[16], Boc-Gly-Gly-OMe[16],

Boc-Phe-Gly-OMe[17], Z-Ala-Gly-OMe[18], Z-Gly-Gly-OMe[19], Z-Gly-D,L-Phe-OMe[20], and Z-Phe-Gly-OMe[21] were prepared according to literature procedures. Ac-Ala-Gly-OMe was prepared by treating Ac-Ala-Gly-OH {lit.[22] $[\alpha]_D$ −63° (water)} with diazomethane in ether at 0° for 1 h; m.p. 126–127°, $[\alpha]_D$ −64°.

N-Benzyloxycarbonylglycylglycylglycyl-D,L-phenylalanine methyl ester, prepared (51%) by treating Z-Gly_3-OH with equimolar amounts of *N*-hydroxysuccinimide, dicyclohexylcarbodi-imide (DCC), and D,L-phenylalanine methyl ester in *N*,*N*-dimethylformamide, had m.p. 120–122° (from *N*,*N*-dimethylformamide–diethyl ether).

Anal. Calc. for $C_{24}H_{28}N_4O_7$: C, 59.49; H, 5.82; N, 11.56. Found: C, 59.22; H, 5.86; N, 11.65.

Catalytic hydrogenation of the above compound in methanol–acetic acid (5:1, 10 mL) afforded glycylglycylglycyl-D,L-phenylalanine methyl ester acetate salt; m.p. 122–126° (from methanol–diethyl ether). P.m.r. data (D_2O): δ 7.25 (Ph), 3.68 (CO_2Me), and 1.89 (AcOH).

Anal. Calc. for $C_{16}H_{22}N_4O_5 \cdot CH_3CO_2H$: C, 52.67; H, 6.39; N, 13.65. Found: C, 52.40; H, 6.42; N, 13.84.

*2,3,4,6-Tetra-*O*-acetyl-1-*O*-(*N*-acylaminoacyl)-*D*-glucopyranoses* (**6**, **7**, *and* **10**). — These compounds were prepared by the methods already described[5,9]: (*a*) accelerated active ester (AAE) method using tetra-*O*-acetyl-β-D-glucopyranose and the appropriate *N*-acylamino acid pentachlorophenyl ester in the presence of imidazole (5 equiv.) in dichloromethane; (*b*) DCC condensation of the same sugar component with the *N*-acylamino acid in the presence of imidazole (2 equiv.) in dichloromethane; (*c*) condensation of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with the silver salt of the *N*-acylamino acid in dry benzene at room temperature. After working-up, the products were purified by chromatography on silica gel (solvent *A*) and characterised by analytical and spectral (i.r., p.m.r.) data.

Tetra-*O*-acetyl-1-*O*-(*N*-benzyloxycarbonylglycyl)-β-D-glucopyranose (**6β**, 60%), prepared by method (*c*), was a solid foam, $[\alpha]_D$ +21°.

Anal. Calc. for $C_{24}H_{29}NO_{13}$: C, 53.43; H, 5.41; N, 2.59. Found: C, 53.19; H, 5.21; N, 2.45.

The α anomer of **6** (61%), prepared by method (*b*), was a solid foam, $[\alpha]_D$ +103° (Found: C, 53.69; H, 5.22; N, 2.75).

Tetra-*O*-acetyl-1-*O*-(*N*-benzyloxycarbonyl-L-phenylalanyl)-β-D-glucopyranose (**7β**, 70%), obtained by method (*c*), was a solid foam, $[\alpha]_D$ +13°.

Anal. Calc. for $C_{31}H_{35}NO_{13}$: C, 59.13; H, 5.60; N, 2.22. Found: C, 59.31; H, 5.63; N, 2.42.

The α anomer of **7** (84%), obtained by method (*a*), was a viscous oil, $[\alpha]_D$ +62° (Found: C, 59.09; H, 5.37; N, 2.47).

Tetra-*O*-acetyl-1-*O*-(*N*-*tert*-butoxycarbonyl-D-alanyl)-β-D-glucopyranose (**10β**, 23%), prepared by shaking tetra-*O*-acetyl-α-D-glucopyranosyl bromide, Boc-D-alanine, and freshly prepared silver carbonate in dry benzene, was a solid foam, $[\alpha]_D$ +10°.

Anal. Calc. for $C_{22}H_{33}NO_{13}$: C, 50.86; H, 6.40; N, 2.70. Found: C, 51.20; H, 6.22; N, 2.89.

1,3,4,6-Tetra-O-acetyl-2-O-(N-benzyloxycarbonylglycyl)-β-D-glucopyranose (**15**). — This compound was prepared by the AAE method (*a*) using 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose as the sugar component. The product was eluted from silica gel (solvent *A*, 2:1), to give **15** (54%) as a solid foam, $[\alpha]_D$ +15°.

Anal. Calc. for $C_{24}H_{29}NO_{13}$: C, 53.43; H, 5.41; N, 2.59. Found: C, 53.71; H, 5.29; N, 2.57.

Aminolysis reactions. — (*a*) *In* N,N-*dimethylformamide*. To a stirred suspension of amino acid methyl ester hydrochloride (0.9 mmol) in *N,N*-dimethylformamide (5 mL) was added, at room temperature, 4-methylmorpholine (0.1 mL, 0.9 mmol) followed by the D-glucopyranosyl ester of the *N*-protected amino acid **1–4** (0.3 mmol). The solution was kept at 38° for 4 days, and the reaction was monitored by t.l.c. (solvent *A*, 1:1). After removal of the solvent, the residues (from **1** and **3**, and **2** and **4**) were passed through silica gel with solvents *A* (1:1) and *B*, respectively, to give the corresponding *N*-protected dipeptide methyl ester (Scheme 1).

(*b*) *In dichloromethane*. Molar ratios and the order of addition of reactants were the same as described above, except that aminolysis (compounds **6–16**) was performed in dichloromethane (50 mL/mmol of glycosyl ester). The reaction mixtures were boiled under reflux (40°) for the times indicated in Table I, the solvent was then evaporated, and the residue was eluted from silica gel (solvent *A*), to afford the respective dipeptide ester as a chromatographically homogeneous solid (Table I).

Boc-D-alanylglycine methyl ester, obtained by aminolysis of **10β**, was an oil, $[\alpha]_D$ +17°.

Anal. Calc. for $C_{11}H_{20}N_2O_5$: C, 50.75; H, 7.74; N, 10.76. Found: C, 50.50; H, 7.96; N, 10.99.

Z-D-alanylglycine methyl ester, obtained by aminolysis of **12β** and crystallised from chloroform–light petroleum, had m.p. 91–93°, $[\alpha]_D$ +23° (methanol).

Anal. Calc. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.17; N, 9.52. Found: C, 57.37; H, 6.13; N, 9.70.

N-Acetyl-L-alanylglycine methyl ester, obtained by aminolysis of **13β** and crystallised from ethyl acetate–light petroleum, had m.p. 126–127°, $[\alpha]_D$ −59.4°.

Anal. Calc. for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.30; H, 7.00; N, 13.60.

N-Acetyl-D-alanylglycine methyl ester, obtained by aminolysis of **14β** and crystallised from ethyl acetate–light petroleum, had m.p. 128–130°, $[\alpha]_D$ +64.7° (Found: C, 47.62; H, 6.77; N, 13.86.)

(*c*) Aminolysis of 1-*O*-(glycylglycylglycyl)-β-D-glucopyranose (**17β**; 100 mg, 0.285 mmol) was performed with 2 equiv. of D,L-phenylalanine methyl ester as described under (*a*) for a total of 3 days; the reaction was monitored by t.l.c. (solvent *C*). After removal of precipitated glycylglycylglycine (36 mg, 67%), the filtrate was evaporated (0.1 Torr) to dryness, and the residue extracted with diethyl ether (to remove the unreacted phenylalanine methyl ester). The remaining solid was dissolved

in a minimum of solvent *D* and chromatographed on a column (81 × 1.5 cm) of cellulose (100 g) with the same solvent, to give D-glucose (47 mg, 92%), followed by chromatographically homogeneous glycylglycylglycyl-D,L-phenylalanine methyl ester (28 mg, 28%), which crystallised from methanol–diethyl ether; m.p. 119–122°, indistinguishable (mixture m.p., i.r., p.m.r.) from the sample prepared by direct synthesis.

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