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Intermolecular Aminolyses of 1-Thioglycosyl Esters of *N*-Acylamino Acids

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Fully acetylated 1-thioglycopyranosyl esters of *N*-acylamino acids (**1–3**), comprising different 1-thio sugars, undergo aminolysis with glycine methyl ester in dichloromethane at 40° to form the corresponding *N*-acyldipeptide methyl esters. The relative reactivity of the C-1 thioester bond towards aminolysis depends *inter alia* on the structure of the sugar moiety. Acylating efficiency of the 1-thioesters was additionally demonstrated by aminolysis of 2,3,4,6-tetra-*O*-acetyl-1-*S*-(*N*-*tert*-butyloxycarbonyl-L-tyrosyl)-1-thio-β-D-glucopyranose (**3h**) with peptidoglycan monomer (PGM, a disaccharide-pentapeptide) in *N,N*-dimethylformamide at room temperature to give the corresponding disaccharide-hexapeptide.

INTRODUCTION

Thioesters are a biologically important class of compounds. They take part in acyl transfer reactions in biological systems,[1–3] such as peptide bond formation in non-ribosomal biosynthesis of peptides (*e.g.* gramicidin S),[4] enzymic hydrolyses of peptides catalyzed by papain[5,6] and other cysteine proteases.[7] During the activation process of C3 and C4 components of human

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complement and human α_2-macroglobulin (a protease inhibitor),[8,9] their internal thioester bonds react with hydroxyl- and amino-residues on bacterial membranes. The importance of thioesters as prebiotic energy sources has been emphasized,[10–12] as well. Furthermore, the chiral inversion of 2-arylpropionic acids nonsteroidal anti-inflammatory drugs proceeded *via* their CoA-thioester.[13] Also, thiobenzyl esters of *N*-protected amino acids were efficiently used for the preparation of *N*-protected amino aldehydes, chiral building blocks in the synthesis of peptides.[14]

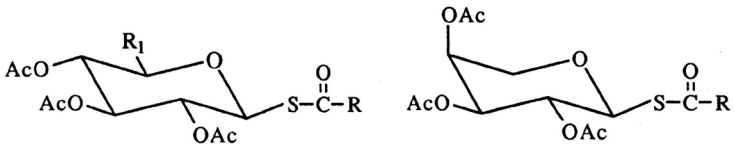
The use of carbohydrate-derived active esters for the preparation of peptides has been previously described.[15] The report has also been given on the formation of peptides using fully acetylated *N*-acylaminoacyl-1-thio-β-D-glucopyranoses[16–19] which can undergo intermolecular aminolyses by small nucleophiles, such as amino acids or dipeptides to form short peptides. We now report on the aminolytic reactivities of 1-thioglycosyl esters[17,20] of *N*-acylaminoacyl acids comprising different 1-thio sugar moieties (D-thioglucuronic acid, L-thioarabinose, and D-thioglucose) with glycine methyl ester and with a more complex molecule such as the peptidoglycan monomer[21] [PGM, GlcNAc-(1→4)-MurNAc-L-Ala-D-*iso*Gln-*meso*-diaminopimelyl(εNH2)-D-Ala-D-Ala], respectively.

RESULTS AND DISCUSSION

Compounds **1a–g**, **2a–g**, and **3a–h** were synthesized as described previously.[17,20] 2,3,4,6-Tetra-*O*-acetyl-1-*S*-(*N*-*tert*-butyloxycarbonyl-L-tyrosyl)-1-thio-β-D-glucopyranose (**3h**) was prepared by condensation of the appropriate thiosugar and the commercially available *N*-*tert*-butyloxycarbonyl-L-tyrosine in the presence of DCC. Under conditions used, the phenolic hydroxyl group of tyrosine was unprotected and did not cause unwanted side reactions. However, the isolation of **3h** was difficult due to its contamination with dicyclohexylurea and products formed by the decomposition of the starting sugar. The structure of **3h** was confirmed by analytical and physical methods.

The previously demonstrated susceptibility of 2,3,4,6-tetra-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-β-D-glucopyranoses (**3a–3g**)[17,18] towards aminolysis with an amino acid or dipeptide esters prompted us to examine two new series of compounds comprising 1-thio-β-D-glucopyranuronic acid or 1-thio-α-L-arabinopyranose as a sugar moiety.

Table I presents the results of aminolysis reactions carried out with the 1-thioglycopyranosyl esters of *N*-protected glycine, alanine, and phenylalanine as acylating agents and the methyl ester of glycine as a nucleophile; for comparison, the reported[18] yields of dipeptide methyl esters formed by aminolyses of corresponding 1-thioglucopyranosyl esters are also included in Table I.



1a-g $R_1 = CO_2Me$
3a-h $R_1 = CH_2OAc$

2a-g

RCO = N-acylaminoacyl residue

a	Z-Gly	e	Boc-D-Ala
b	Z-L-Ala	f	Z-L-Phe
c	Z-D-Ala	g	Boc-L-Phe
d	Boc-L-Ala	h	Boc-L-Tyr

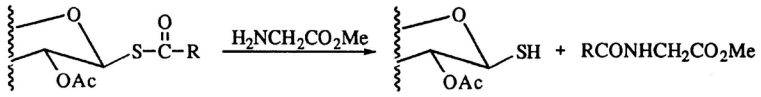
$Z = C_6H_5\text{-}CH_2\text{-}OCO$

$Boc = (CH_3)_3C\text{-}OCO$

Figure 1.

TABLE I

Aminolyses of 1-thioglycopyranosyl esters of N-acylamino acids **1** and **2**[a]



1-thioesters **1-3** thiosugars dipeptides

R-CO	**1a–1g**[b] %	**2a–2g**[c] %	**3a–3e**[d] %	Dipeptide isolated[Ref.]
Z-Gly	50	55	38	Z-Gly-Gly-OMe[22]
Z-L-Ala	58	54	52	Z-L-Ala-Gly-OMe[23]
Z-D-Ala	80	41	77	Z-D-Ala-Gly-OMe[24]
Boc-L-Ala	73	55	62	Boc-L-Ala-Gly-OMe[25]
Boc-D-Ala	85	53	70	Boc-D-Ala-Gly-OMe[24]
Z-L-Phe	92	46	54	Z-L-Phe-Gly-OMe[26]
Boc-L-Phe	48	48	89	Boc-L-Phe-Gly-OMe[27]

[a]All reactions were performed with 2×10^{-2} M 1-thioglycosyl esters **1** or **2**, respectively, and 3 equiv. of glycine methyl ester at 40° in dichloromethane. [b]Reaction time 12 h, if not stated otherwise. [c]Reaction time 3 days. [d]Reported[18] peptide yields for 1-thioglucosyl esters **3** after 16 h of reaction.

From the data presented (Table I) it can be concluded that the relative reactivities of the 1-thioglycosyl esters **1–3** are highly dependent upon the structure of the sugar moiety and the configuration of amino acids.

Aminolysis reactions studied in this work were performed with appropriate 1-thioglycosyl esters and 3 equivalents of glycine methyl ester in dichloromethane at reflux temperature of the solvent. The aminolysis reaction led to the rupture of the C-1 thioester bond and formation of the corresponding *N*-acyldipeptide ester. Under the conditions used, all 1-thioglycosyl esters were resistant to hydrolysis.

The aminolyses of methyl 2,3,4-tri-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-1-thio-β-D-glucopyranuronates (**1a–1g**),[20] under the above conditions, were practically complete in 12 hours. The corresponding *N*-protected dipeptide methyl esters formed were isolated and characterized.[22–27] Similar yields of isolated *N*-protected dipeptide methyl esters were obtained within 16 h when 2,3,4,6-tetra-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-1-thio-β-D-glucopyranoses were used as starting materials in aminolysis reactions. Under the same conditions, the aminolyses of 2,3,4-tri-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-L-α-arabinopyranoses (**2a–2g**)[20] proceeded at a much lower rate, *e. g.* even after 3 days, unreacted starting 1-thioesters **2** were detected (monitoring by t.l.c.).

The obtained results show that the structure of the sugar moiety affects the extent to which peptide formation occurs; the degree of activation of an amino acid linked to different 1-thiosugars strongly depends on the nature of the sugar. Fully protected 1-*S*-(*N*-acylaminoacyl)-1-thio-β-D-glucopyranuronates (**1a–1g**) were more reactive than 2,3,4-tri-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-α-L-arabinopyranoses (**2a–2g**). The reactivity of 1-thioglucosyl esters **3a–3e** is lower than that of **1** but still much higher than that of **2**. These results indicate that the 1-thioglucopyranuronic moiety acts as a better leaving group than the other two thiosugar moieties studied. This is in accord with the generally accepted mechanism of aminolysis of esters,[28,29] thioesters,[30,31] and 1-thioglucosyl esters of amino acids[19] involving the tetrahedral intermediate. It is known[32,33] that an increase in electron-withdrawal potential increases the leaving group's ability to depart. The electron-attracting esterified uronic carboxyl group (COOMe) might, therefore, shift the equilibrium of the aminolytic reaction to the tetrahedral intermediate and accelerate its collapse to products.

Within the series of 1-thioglucopyranuronate esters **1**, different reactivities regarding the configuration of the amino acid were shown. The 1-thioesters comprising D-amino acids were slightly more reactive than their L-counterparts, most probably due to the steric factors. These data are in agreement with the previously reported[19] greater activity of 1-thioglucosyl esters of D-amino acids over the L-amino acids derivatives. In the case of 1-thioarabinose esters **2**, aminolysis of which occurs at much lower rates, this difference was not observed and similar yields of protected dipeptides were obtained.

The influence of the *N*-amino acid protection on the rate of aminolysis of 1-thioglycosyl esters was not significant in the series of compounds studied. Thus, methyl 2,3,4-tri-*O*-acetyl-1-*S*-(*N*-*tert*-butyloxycarbonyl-L(D)-alanyl)-1-thio-β-D-glucopyranuronates (**1d** and **1e**) were slightly more reactive than the corresponding *N*-benzyloxycarbonyl-L(D)-alanyl-derivatives (**1b** and **1c**). Practically no difference was noticed in the arabinose series of thioesters. Some differences in yields of isolated compounds were observed between Z- and Boc-protected thioesters of the methyl 1-thioglucopyranuronate and 1-thioglucopyranose series comprising phenylalanine as an amino acidic residue (**1f–g** and **3f–g**). This is most probably due to purification difficulties encountered during isolation procedures. These data are in accord with the findings of Plass and Boissonnas[34] who found that the *N*-*tert*-butyloxycarbonyl-(Boc) and *N*-benzyloxycarbonyl-(Z) amino acid esters have nearly identical aminolytic reactivities in the reaction with an amine. Similar observation was made[19] for fully acetylated 1-thioglucosyl esters **3** bearing the Boc- and Z-protected amino acids. It is interesting to note that kinetic studies of aminolyses of 1-thio-β-D-glucopyranosyl esters of *N*-acylalanines have shown[19] that the type of *N*-protecting groups exerts a significant influence on the rate of aminolysis. 1-Thioesters which contain an amide (*e.g.* Ac) type of protection were more reactive than those containing a urethane (Boc- and Z-) type of amino protection. Intramolecular hydrogen bond existing in *N*-acetyl-alanines enhances the electrophilic character of the carbonyl group which then becomes more liable to the nucleophilic attack of an amine. As Boc- and Z-belong to the same (urethane) type of *N*-protection, the differences in aminolytic activities of 1-thioglycosyl esters **1** and **2** are not significant.

The acylating efficiency of 1-thioglycopyranosyl esters of *N*-acylamino acids was further investigated on the fully protected 1-*S*-(*N*-*tert*-butyloxycarbonyl-L-tyrosyl)-1-thio-β-D-glucopyranose (**3h**) with a more complex nucleophile such as the peptidoglycan monomer (PGM, a disaccharide-pentapeptide, Figure 2). Peptidoglycan monomer[21] is a repeating unit of the *Brevibacterium divaricatum* cell wall peptidoglycan. It exhibits strong immunomodulating, antitumour and antimetastatic activities.[35] Our interest was focused on the preparation of its derivatives that might possess better biological characteristics and that might be applied in the treatment of some diseases. Recently, a successful synthesis of Boc-L-tyrosyl derivative of peptidoglycan monomer (Boc-Tyr-PGM) was achieved by condensation of unprotected peptidoglycan monomer and *N*-hydroxysuccinimidester of Boc-L-tyrosine in the presence of triethylamine for 16 h at ambient temperature, yielding 46% of chromatographically pure compound.[36] An alternative approach to its synthesis is reported in this work.

The following reaction was carried out in dimethylformamide due to the low solubility of PGM in other organic solvents. The treatment of 2,3,4.6-

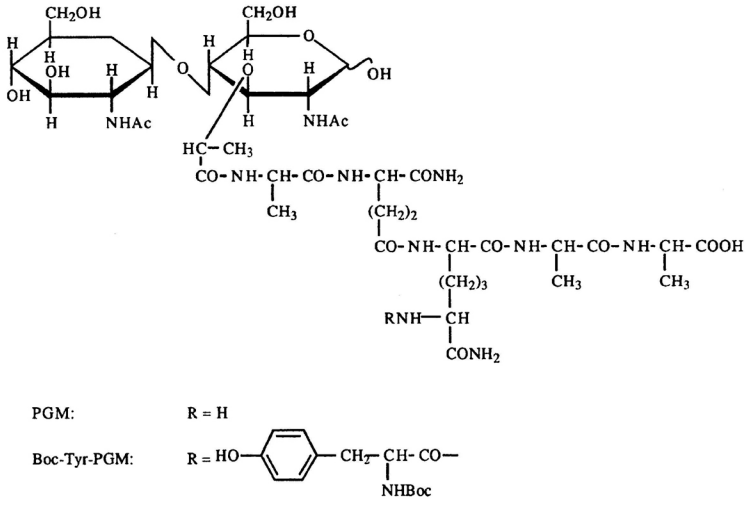


Figure 2.

tetra-*O*-acetyl-1-*S*-(*N*-*tert*-butyloxycarbonyl-L-tyrosyl)-1-thio-β-D-glucopyranose (**3h**) with peptidoglycan monomer at room temperature for 3 days yielded Boc-Tyr-PGM [GlcNAc-(1→4)-MurNAc-L-Ala-D-*iso*Gln-*meso*-diaminopimelyl-(ε-*N*-Boc-Tyr)-D-Ala-D-Ala], (Figure 2).

The product of aminolysis was isolated by column chromatography on Sephadex G-25, followed by silica gel and Bio Gel P-2 columns. The chromatographically homogeneous product co-migrated in t.l.c. (solvent B) with the authentic sample of Boc-Tyr-PGM. The structure of Boc-Tyr-PGM was confirmed by an amino acid analysis and ^{1}H-NMR spectroscopy. Total acid hydrolysis of Boc-Tyr-PGM, followed by t.l.c. in solvent system C confirmed the structure proposed. The ^{1}H-NMR spectrum (in D_2O) of Boc-Tyr-PGM was undistinguishable from the respective spectrum of the product previously prepared.[3]

The data presented show that 1-thioglycosyl esters of amino acids undergo intramolecular aminolysis to form new peptide bonds. During the process, small peptides as well as the more complex ones can be successfully prepared.

EXPERIMENTAL

General Methods

Column chromatography was performed on silica gel (Merck) and t.l.c. on Kieselgel G (Merck) with A, ethyl acetate/benzene (proportions are given in the text); B, *n*-propanol/conc. ammonia (7 : 3); C, *n*-butanol/glacial acetic acid/water (60 : 15 : 25),

and detection was effected by charring with sulphuric acid, the ninhydrin or the chlorine-iodine reagent for peptides. Sephadex G-25 was obtained from Pharmacia (Uppsala, Sweden) and Bio Gel P-2 from Bio Rad Laboratories (Richmond, USA). ^{1}H-NMR spectra (100 MHz, $CDCl_3$, internal Me_4Si) were recorded with a Jeol JNM FX-100 F.t. spectrometer. Absorbance was measured on a Perkin Elmer Lambda 3 UV-VIS spectrophotometer.

Methyl 2,3,4-tri-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-1-thio-β-D-glucopyranuronates (**1a-1g**),[20] 2,3,4-tri-*O*-acetyl-1-*S*-(*N*-acylaminoacyl)-L-arabinopyranoses (**2a-2g**),[20] and glycine methyl ester hydrochloride were prepared according to literature procedures. *N-tert*-butyloxycarbonyl-L-tyrosine (Boc-L-Tyr) was purchased from Fluka (Buchs, Switzerland). Peptidoglycan monomer (PGM) was supplied by PLIVA, Chemical and Pharmaceutical Industry (Zagreb, Croatia).

*Synthesis of 2,3,4,6-Tetra-*O*-acetyl-1-*S*-(*N*-tert-butyloxycarbonyl-L-tyrosyl)-1-thio-β-D-glucopyranose (**3h**)*

To a cold solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose[37] (364 mg) and *N-tert*-butyloxycarbonyl-L-tyrosine (281 mg) in dichloromethane (5 mL), dicyclohexylcarbodiimide (240 mg) was added. The reaction mixture was kept at room temperature for 24 h (monitoring by t.l.c. in solvent A, 5 : 1). Dicyclohexyl urea was filtered off, the filtrate was evaporated and the residue was chromatographed on a silica gel column (solvent A, 5 : 1), followed by three recrystallizations (ethyl acetate-light petroleum) to give the 1-thio ester **3h** (130 mg, 21%), m.p. 161–162 °C. ^{1}H-NMR ($CDCl_3$) δ/ppm: 1.41 (s, 9 H, Me_3C), 1.99, 2.01, 2.04, and 2.09 (4 s, 12 H, 4 × OAc), 6.71 and 6.99 (2 d, 2 H each, $J_{H,H}$ = 7.55 Hz, $-C_6H_4-$).

Aminolysis Reactions

(a) To a stirred suspension of glycine methyl ester hydrochloride (1.5 mmol) in CH_2Cl_2 (25 mL) the equivalent amount of *N*-methylmorpholine was added, followed by the relevant 1-thioglycosyl ester **1** or **2** (0.5 mmol). The reaction mixture was refluxed (40–42° C) for a defined period of time, whereupon the reaction mixture was washed with water, dried (Na_2SO_4), and concentrated. The residue was subjected to chromatography on a silica gel column (solvent A, 3 : 1 or 2 : 1) to give the corresponding protected dipeptides in a pure form (Table I).

(b) To a solution of peptidoglycan monomer (PGM, 0.1 mmol) in DMF (5 mL) an equivalent amount of *N*-methyl morpholine was added, followed by an excess of 1-thioester **3h** (0.12 mmol). The reaction was carried out at room temperature for 3 days (t.l.c. in solvent B). The solvent was evaporated in high vacuum and the residue dissolved in water and acidified with hydrochloric acid to pH = 3. After extraction with ethyl acetate (3 × 10 mL) the aqueous layer was concentrated and applied to a Sephadex G-25 column (2.5 × 90 cm) and eluted with water. Fractions (3 mL) absorbance were measured at 230 nm and those corresponding to Boc-Tyr-PGM were pooled and evaporated. Complete purification of the product was achieved by fast chromatography of this material on a silica gel column (solvent B) followed by a Bio Gel P-2 column eluted with water to give the pure Boc-Tyr-PGM as a solid (28 mg, 22%). Total acid hydrolysis revealed the expected amino acid composition. ^{1}H-NMR (D2O) δ/ppm: 1.29 (s, Me_3C), 1.34–1.40 (m, partly overlapped with Me_3C, 21H, 3 × Me-Ala + lactoyl Me), 1.89 and 1.98 (2 s, 6H, 2 × *N*Ac), 7.07 (2 d, 2H each, $J_{H,H}$ = 8.55 Hz, $-C_6H_4-$).

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SAŽETAK

Intermolekularna aminoliza 1-tioglikozil estera *N*-acilaminokiselina

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Potpuno acetilirani 1-tioglikopiranozilni esteri *N*-acilaminokiselina (**1–3**) podliježu aminolizi s metilnim esterom glicina u diklorometanu, na 40 °C, pri čemu nastaju odgovarajući metilni esteri *N*-acildipeptida. Relativna reaktivnost C-1 tioesterske veze u reakcijama aminolize ovisna je, između ostaloga, i o strukturi šećerne komponente. Acilirajuće sposobnosti 1-tioestera dodatno su dokazane u reakciji aminolize 2,3,4,6-tetra-*O*-acetil-1-*S*-(*N*-*tert*-butiloksikarbonil-L-tirozil)-1-tio-β-D-glukopiranoze (**3h**) sa peptidoglikan monomerom (PGM, disaharid-pentapeptid) u *N*,*N*-dimetilformamidu, pri sobnoj temperaturi. U toj reakciji nastaje odgovarajući disaharid-heksapeptid.