PARTIAL METHYLATION OF METHYL α-D- AND β-D-THREOFURANOSIDE

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The methylation rate of hydroxyl groups of the title glycosides *I* and *II* has been studied in their reaction with methyl iodide and sodium hydroxide in acetonitrile. From the relative rate constants determined for the side and consecutive reactions taking place the differences in methylation rate of the individual hydroxyl groups have been deduced and are discussed from the standpoint of possible steric and polar effects.

Methyl ethers of saccharides are primarily important for determination of constitution of monosaccharides and for structural analysis of oligo- and polysaccharides[1]. Therefore, preparation of partially methylated saccharides has been paid considerable attention. Predominant majority of papers adopts the way of preparation of these compounds which makes use of syntheses of intermediates with suitably blocked groups not designed for the methylation, which method is often very time-consuming and experimentally difficult[2]. On the other hand, development of separation and analytical methods in organic chemistry has made it possible to prepare partially alkylated saccharides by direct etherification of the polyfunctional saccharidic material. However, an optimization of conditions for preparation of partially alkylated monosaccharides needs a deeper insight into the regularities governing the different reactivity of individual hydroxyl groups along the saccharidic chain. In our earlier papers we studied the partial methylation of methyl 2,6-dideoxy-α-D--hexopyranosides[3-5] and methyl 4,6-dideoxy-α-D-hexopyranoside[6,7], i.e. saccharide derivatives with two free hydroxyl groups at various positions of pyranoside ring.

Continuing these studies we have now focused our attention on the simplest glycosides with two free hydroxyl groups, i.e. methyl tetrosides which present an interesting problem of reactivity of the hydroxyl groups in connection with the stereochemistry of furanoside ring. In contrast to all derivatives of higher saccharides containing this five-membered ring (pentofuranoses, hexofuranoses), the reactivity of the OH groups in tetrosides is not affected by the presence of any saccharidic exo-

cyclic carbon atoms and the corresponding functional groups. In this present work reactivity has been studied of the hydroxyl groups of methyl α-D-threofuranoside (*I*) and methyl β-D-threofuranoside (*II*) during partial methylation with methyl iodide and sodium hydroxide in acetonitrile medium.

The preparation of the starting glycosides *I* and *II*, as well as their methylation products, i.e. methyl 2-O-methyl-α-D-threofuranoside (*III*), methyl 3-O-methyl-α-D--threofuranoside (*IV*), methyl 2,3-di-O-methyl-α-D-threofuranoside (*V*), methyl 2-O-methyl-β-D-threofuranoside (*VI*), methyl 3-O-methyl-β-D-threofuranoside (*VII*), and methyl 2,3-di-O-methyl-β-D-threofuranoside (*VIII*) was described in our previous report[8] and their structure was confirmed by means of ^{1}H NMR (ref.[8]) and ^{13}C NMR spectra[9].

The mixtures of the unreacted starting material and its etherification products, i.e. in the case of the α-anomers the starting glycoside *I* and methyl ethers *III* – *V* (see Scheme 1) and in the case of the β-anomers the starting glycoside *II* and its methyl ethers *VI* – *VIII* (see Scheme 2), were analyzed by means of gas chromatography. The analytic results were evaluated graphically as dependence of the content of the monomethyl ethers *III* + *IV* and *VI* + *VII* on the decrease of the starting diols *I* and *II*, respectively (Figs 1 and 2). From these figures alone it is obvious that in both starting glycosides the hydroxyl group at C-2 reacts faster than that at C-3, which is especially distinct with the β-anomer *II*. For determination of quantitative de-

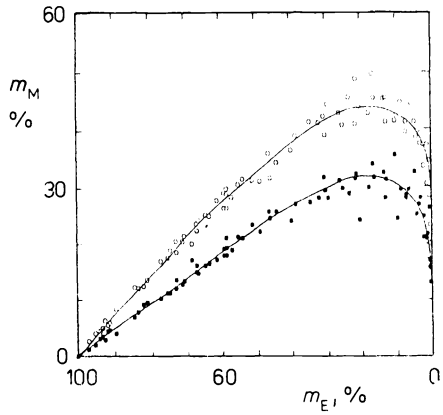


FIG. 1

Dependence of molar fraction m_M of methylation intermediate from methyl α-D-threofuranoside (*I*), ○ methyl 2-O-methyl-α-D--threofuranoside (*III*), ● methyl 3-O-methyl--α-D-threofuranoside (*IV*) on reacted amount m_E of starting compound

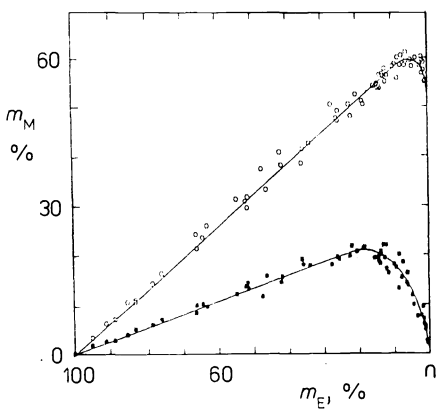
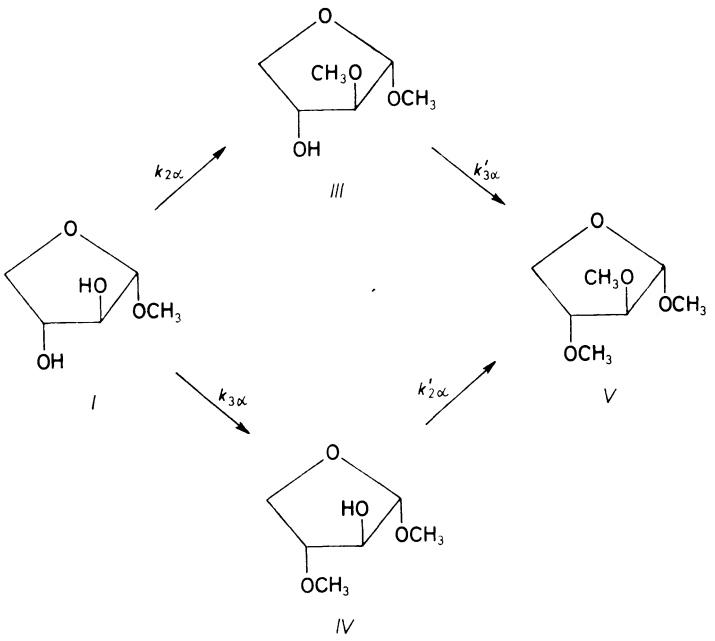
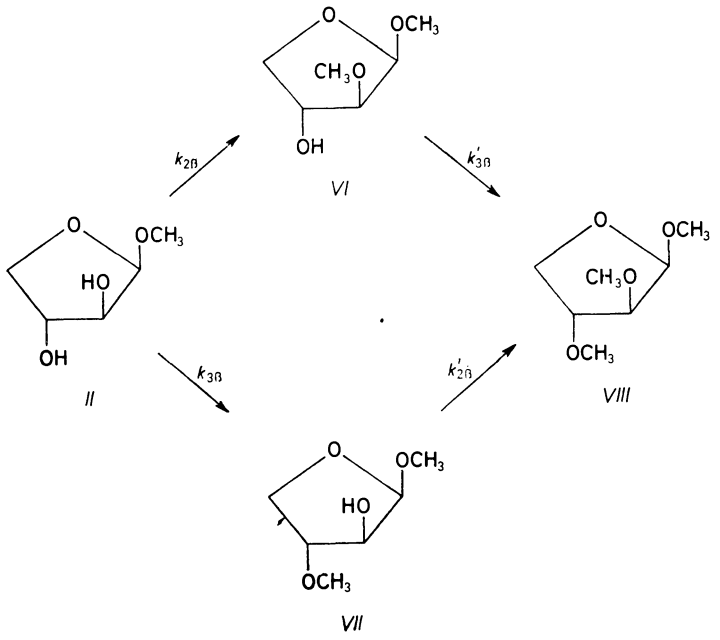


FIG. 2

Dependence of molar fraction m_M of methylation intermediate from methyl β-D-threofuranoside (*II*), ○ methyl 2-O-methyl-β-D--threofuranoside (*VI*), ● methyl 3-O-methyl--β-D-threofuranoside (*VII*) on reacted amount m_E of starting compound



SCHEME 1



SCHEME 2

pendences between the individual side and consecutive reactions taking place according to Schemes 1 and 2 we calculated[10] the relative rate constants of these reactions (vide infra). From the relative rate constants found in Scheme 1 the following conclusions can be made:

1) In the methylation of α-glycoside *I* with methyl iodide and sodium hydroxide in acetonitrile the 2-O-methyl derivative *III* is formed faster than the 3-O-methyl derivative *IV* by the factor of about 1·5 ($k_{2\alpha}/k_{3\alpha} = 1{\cdot}48$).

2) Further methylation of both the monomethyl ethers *III* and *IV* proceeds at almost the same rates to give the dimethyl ether *V* ($k'_{2\alpha}/k'_{3\alpha} = 0{\cdot}99$).

3) When comparing the etherification reaction rates of the same hydroxyl group at 2 position of nonsubstituted and monosubstituted derivative, we can see that diol *I* reacts at its hydroxyl group at 2 positions of furanoside ring c. 2·5 times faster than the 3-O-methyl derivative *IV* ($k_{2\alpha}/k'_{2\alpha} = 2{\cdot}48$).

4) In the etherification of hydroxyl group at the third carbon atom again the glycoside *I* reacts faster than the respective 2-O-methyl derivative *III*, but the reaction rate lowering after the methylation of neighbouring hydroxyl group is smaller (1·5 fold) than that in the previous case ($k_{3\alpha}/k'_{3\alpha} = 1{\cdot}65$).

The partial methylation of β-anomer *II* showed distinctly greater differences in reactivity of hydroxyl groups at C-2 and C-3 (see the relative rate constants in Scheme 2):

1) In the methylation of starting diol *II* under the given conditions the 2-O-methyl derivative *VI* is formed approximately 2·5 times faster than 3-O-methyl derivative *VII* ($k_{2\beta}/k_{3\beta} = 2{\cdot}41$).

2) In the subsequent methylation step the 3-O-methyl derivative *VII* reacts more than 5 times faster (to give the dimethyl ether *VIII*) than the 2-O-methyl derivative *VI* ($k'_{2\beta}/k'_{3\beta} = 5{\cdot}40$) does.

3) When comparing the methylation rates of the same hydroxyl group at 2 position of nonsubstituted and monosubstituted derivative, the diol *II* reacts (in the methylation of this OH group at C-2) approximately twice as fast as the 3-O-methyl derivative *VII* ($k_{2\beta}/k'_{2\beta} = 2{\cdot}26$).

4) In the methylation of OH at C-3 there takes place a distinct reactivity decrease after the substitution at the neighbouring hydroxyl group, the diol *II* being methylated at this position 5 times faster than the 2-methyl ether *VII* ($k_{3\beta}/k'_{3\beta} = 5{\cdot}06$). This decrease is substantially more marked than that in the case of the respective α-anomers.

In analogy to the case of partial methylations of methyl dideoxyhexopyranosides, when following the individual factors which affect the methylation rate of particular hydroxyl groups in the compounds studied we also considered the possibility of intramolecular hydrogen bond effect. A summarization of results of IR spectral studies[11]

of methyl tetrosides and their monomethyl ethers offers a possibility of explanation of the above conclusions: In the methylations of nonsubstituted methyl threosides *I* and *II*, C(2)—OH reacts faster than C(3)—OH in both the cases. The higher reactivity of C(2)—OH can be explained by the inductive effect of vicinal acetal group. However, a quite considerable difference was found in the rate constants ratio k_2/k_3 between both the glycosides. Therefore we suppose that the reactivity of OH groups is influenced also by formation of intramolecular hydrogen bonds. In the case of compound *II* the strong hydrogen bond O(2)—H···O(1) (υ = 3 562 cm^{-1}, ref.[11]) increases the nucleophilicity of O(2) oxygen atom whereby the influence of inductive effect of the acetal group at C-1 is further increased. On the other hand, the effect of strong hydrogen bond O(3)—H···O(1) in the α-anomer *I* (ν = 3 545 cm^{-1}) increases the nucleophilicity of O(3), whereby the inductive effect of acetal group at C(1) is partially compensated. Due probably to this reason the value of rate constant ratio $k_{2\alpha}/k_{3\alpha}$ measured for the α-anomer *I* is lower (1·48) than that found for the β-anomer *II* (2·41).

In the methylation to the second degree of the monomethyl ethers of methyl tetrosides, in the case of β-anomers the 3-O-methyl derivative *VII* reacts distinctly faster than the 2-O-methyl derivative *VI*, whereas the same compounds with α arrangement of OCH_3 at C-1 (i.e. *III* and *IV*) react practically at the same rates. This is probably due again to the increased reactivity of O(3)—H in compound *III* as a consequence of formation of very strong hydrogen bond O(3)—H···O(1) (ν = 3 543 cm^{-1}, ref.[11]).

When comparing the methylation rates of the same hydroxyl group having different substituents at the vicinal OH group, we found the largest difference between compounds *II* an *VI* during the methylation of their C(3)—OH group ($k_{3\beta}/k'_{3\beta}$ = = 5·06). The reactivity of OH group at C-3 can be affected by conformation differences between compound *II* and *VI* and, besides, the lowered reactivity of C(3)—-OH in compound *VI* can probably be due also to the lowered nucleophilicity of the oxygen atom in O(3)—H of compound *VI* as compared to that in the diol *II* as a consequence of weakening or elimination of the intramolecular hydrogen bond O(3)—H···O(4); for the 2-O-methyl derivative *VI* it is ν(OH) = 3 630 cm^{-1}, whereas for the compound *II* it is ν(OH) = 3 616 cm^{-1} (ref.[11]). The above-mentioned findings are important both theoretically and practically (application to syntheses of partially methylated methyl tetrosides). The direct methylation of the starting diols *I* and *II* is most advantageous for synthesis of methyl 2-O-methyl-β-D-threofuranoside (*VI*) which forms more than 60% of the reaction mixture. With regard to the maximum yield of this monomethyl ether the optimum methylation degree (found according to ref.[10]) corresponds to the situation when the reaction mixture contains about 5% starting diol *II*, which is achieved after addition of 1·2 equivalents of the reagent or base.

EXPERIMENTAL

Partial Methylation of α-Glycoside *I*

Powdered sodium hydroxide (9—45 mg, 0·23—1·13 mmol) was added to a mixture of 60 mg (0·45 mmol) compound *I*, 12 ml acetonitrile, and 1·8 ml (28·9 mmol) methyl iodide with stirring. The reaction mixture was stirred in a thermostated flask at 20°C. The methylation course was followed by means of gas chromatography using a Varian-Aerograph 2100 apparatus combined with a Hewlett–Packard 3380 A integrator, a 1 800 × 2 mm column packed with 5% Versamide 900 on Chromosorb T at the temperature of 140—180°C with the temperature gradient of 4°C/ /min and helium flow rate 20 ml/min. The amount of the reaction mixture analyzed was 0·7 μl, temperature of the inlet chamber 190°C, temperature of the flame-ionisation detector 200°C. At the conditions given the following retention times were found for the individual compounds: *V* 106 s, *III* 267 s, *IV* 530 s, *I* 971 s.

Partial Methylation of β-Glycoside *II*

The kinetic measurements of methylation of compound *II* were carried out at identical conditions to those used for the α-anomers *I*. At the above-mentioned conditions the following retention times were found for the individual compounds: *VIII* 126 s, *VII* 160 s, *VI* 517 s, *II* 625 s.

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