PARTIAL METHYLATION OF METHYL 4,6-DIDEOXY-α-D-*xylo*--HEXOPYRANOSIDE AND METHYL 4,6-DIDEOXY-α-L-*lyxo*--HEXOPYRANOSIDE*

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The distribution of substituents during partial etherification of the title glycosides with methyl iodide and solid sodium hydroxide in acetonitrile has been determined. The differences in the reaction rates of methylation of single hydroxyl groups in the starting diols and monosubstituted ethers are explained by the steric effect of the vicinal methoxyl group and by the influence of intramolecular hydrogen bonds.

In the first communication of this series[1] we described the preparation of monosubstituted and disubstituted methyl ethers *II*, *III*, *IV*, *VI*, *VII*, and *VIII* by methylation of methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside (*I*) and methyl 4,6-dideoxy-α-L--*lyxo*-hexopyranoside (*V*) with methyl iodide and sodium hydroxide, in which the degree of substitution was regulated by the amount of the base used. In this paper we should like to discuss more closely the factors affecting the distribution of the methyl substituent among the hydroxyl groups of both mentioned substances during this reaction.

EXPERIMENTAL

Chemicals Used

Methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside (*I*) was prepared according to the procedure described by Jones and co-workers[2]; methyl 4,6-dideoxy-α-L-*lyxo*-hexopyranoside (*V*) and methyl 4,6-O-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (*IX*) were prepared in connection with other studies[3,4] in our laboratory; glycosides *II*—*IV* or *VI*—*VIII* all originate from our previous work[1]; methyl 4,6-O-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside (*X*), methyl 3,4,6-trideoxy-α-D-*erythro*-hexopyranoside (*XI*) and methyl 3,4,6-trideoxy-α-D-*threo*-hexopyranoside (*XII*) were prepared on $LiAlH_4$ reduction[5,6] of the corresponding 2,3-anhydro derivatives. The structure of all substances was checked either by comparison with authentic samples or on the basis of NMR and IR spectra.

* Part II in the series Partial Alkylations of Deoxy Sugars; Part I: see ref.[1]

Method

Partial methylation of glycosides *I* and *V* was carried out in this study predominantly in acetonitrile as solvent, using excess methyl iodide and a chosen amount of powdered sodium hydroxide, and working at room temperature. After the reaction was over, the mixture was analysed quantitatively by gas chromatography. In the same manner, the methylation of mixtures of monomethyl ethers to the second stage was also studied.

Partial Methylation of Glycosides *I* and *V*

To a cooled (0°C) solution of glycoside in acetonitrile and methyl iodide [ratio of substances in experiments with glycoside *I*: 324 mg (2 mmol) of glycoside, 10 ml of acetonitrile, 1 ml (16 mmol) of methyl iodide; in experiments with glycoside *V*: 200 mg (1·2 mmol) of glycoside, 6 ml of acetonitrile, 0·5 ml (8 mmol) of methyl iodide], powdered sodium hydroxide was added under stirring over 10—15 minutes, the amount of base corresponding to molar ratios 0·6, 0·9 and 1·2 with respect to the etherified glycoside. The mixture was stirred for 24 hours at room temperature, neutralized with a corresponding amount of acetic acid, and, after evaporation of solvent, extracted with chloroform. A mixture of substances isolated from the chloroform solution was weighed and the amount of every component was determined by gas chromatography. The average values of two such experiments are shown in Table I. Etherifications in dimethylformamide were carried out and analysed in an analogous manner (see also ref.[1]).

Partial Methylation of Mixtures of Monomethyl Ethers

The pair of monomethyl ethers in combination and in amounts given in Table II was dissolved in acetonitrile to give a 3—5% solution and then stirred at room temperature in the presence of excess methyl iodide and powdered sodium hydroxide (in a molar ratio 0·5 : 1 with respect

TABLE I

Composition (mol. percents) of the Reaction Mixtures after Methylation of Glycosides *I* and *V* with Methyl Iodide in Acetonitrile (columns *a*) and in Dimethylformamide (columns *b*) in Dependence on the Amount of the Base Used (Molar Ratios of Sodium Hydroxide and the Starting Compound: 0·6, 0·9, and 1·2)

Compound	0·6		0·9		1·2	
	a	*b*	*a*	*b*	*a*	*b*
I	49·8	44·3	30·0	36·5	25·5	17·2
II	34·0	34·7	48·3	32·6	52·5	38·4
III	12·8	8·3	11·5	9·9	9·4	10·3
IV	3·4	1·0	10·2	17·8	12·5	26·0
V	51·3	—	27·1	—	23·9	15·7
VI	21·0	—	29·7	—	31·7	28·9
VII	21·7	—	18·7	—	20·0	13·1
VIII	6·0	—	24·5	—	24·4	15·0

to the mixture of glycosides; in the case of the pair *II* and *VI* this ratio was 0·75) for 24 hours. The reaction mixtures were worked up and analysed in the same manner as in the preceding case. The mixture of substances formed on etherification of glycosides *III* and *VIII*, for which we could not find a suitable packing for gas chromatography, was partly separated on a column of alumina (elution with benzene or benzene +0·5% of ethanol) to a mixture of corresponding di-O--methyl derivatives and a mixture of starting compounds, the composition of which was determined on the basis of optical rotation values. The results of analyses, expressed as per cents of reacted starting material, are summarized in Table II.

Analysis of Substances by Gas Chromatography

Mixtures of substances were analysed on a Chrom III instrument (Laboratorní přístroje, Prague, Czechoslovakia) with FID using nitrogen as carrier gas and a 180 × 0·4 cm column packed with 10% Versamide 900 on Chromaton N—AW. Operating temperature for compounds *I*—*IV* was 200°C, gas flow 15 ml/min; for compounds *V*—*VIII* the temperature raising was programmed within the 150—165°C interval to 2°C/min, and in the interval 165—200°C it was 10°C/min. The injection had a 0·4 μl volume (of an approximately 50% chloroform solution). The composition of each analysed mixture was read from the integration records of three determinations and it was corrected using a calibration curve obtained by analysis of a mixture of the same substances, of known composition.

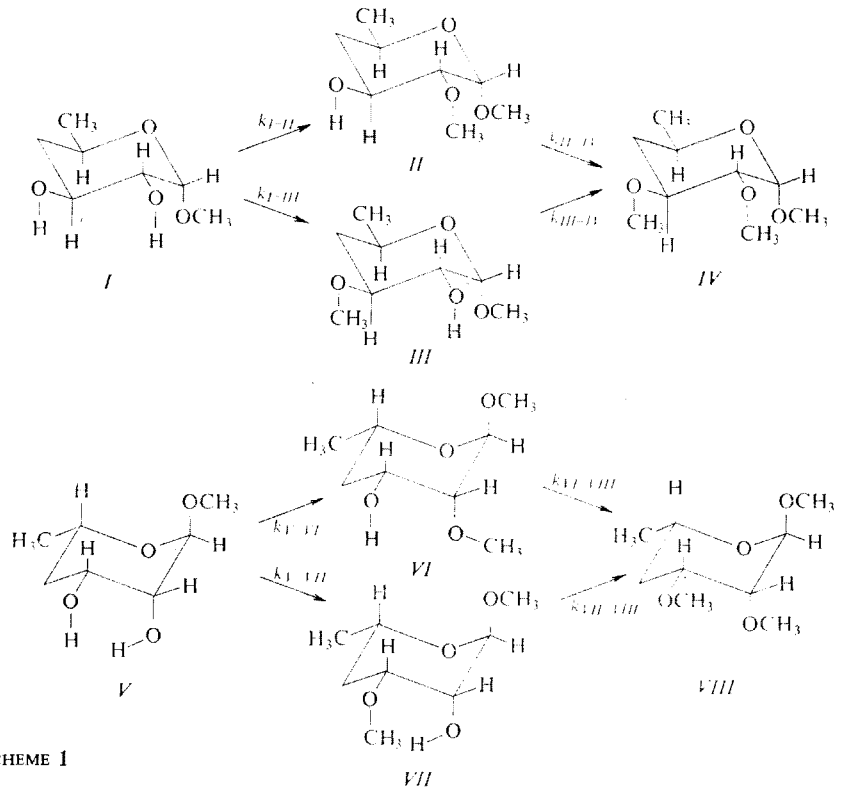
Infrared Spectrometry

IR spectra were measured on a Perkin-Elmer 325 apparatus in 20 mm quartz cells, spectral slit width 1·2 cm^{-1} at 3400 cm^{-1}. Concentrations used for recording the O—H vibration region in tetrachloromethane varied from 0·001 to 0·003M.

RESULTS AND DISCUSSION

The percentual composition of substances in mixtures formed in the above mentioned experiments are given in Table I and II. From Scheme 1 it is evident (the symbols k_{I-II}, k_{I-III}, k_{II-IV}, k_{III-IV}, k_{V-VII}, k_{V-VI}, $k_{VI-VIII}$ and $k_{VII-VIII}$ mean the rate constants of single processes) that no conclusions can be expressed concerning the partial reactivity in the first reaction step during the methylation of compounds *I* or *V*, *i.e.* on the ratio of rate constants k_{I-II}/k_{I-III} or k_{V-VI}/k_{V-VII}, on the basis of the knowledge of the reaction mixture composition in a single point of the reaction co-ordinate only.* Therefore, we submitted various pairs of monomethyl ethers *II*, *III*, *VI* and *VII* to further reaction with methyl iodide in acetonitrile in the presence of one half of the equivalent of the base only and we again analysed the obtained mixtures by gas chromatography.

* This is possible with a certain degree of inaccuracy only with those values which were obtained in experiments with 0·6 mol NaOH/mol glycoside in acetonitrile, where the amount of disubstituted derivatives is very low. By neglecting them, the values $k_{I-II}/k_{I-III} = 34·0/12·8 = 2·7$, or $k_{V-VI}/k_{V-VII} = 21·0/21·7 = 0·97$ (*cf.* the values in Table III) were calculated.



SCHEME 1

TABLE II

Parallel Methylation of Pairs of Monomethyl Ethers with Methyl Iodide and Sodium Hydroxide in Acetonitrile

Starting mixture (mmol) of monomethyl ethers	Amount of base, mol	mol.% of the reacted compound			
		II	*III*	*IV*	*VII*
0·35 *II* 0·20 *III*	0·23	21·2	81·3	—	—
0·56 *VI* 0·17 *VII*	0·36	—	—	18·6	60·6
0·26 *II* 0·21 *VI*	0·35	47·2	—	42·1	—
0·23 *III* 0·22 *VII*	0·27	—	76·7	—	54·9

The results of these analyses (Table II) when put into the relationship for this type of parallel reactions[7] (equation (*1*))

$$k_A/k_B = (\ln c_{A_0} - \ln c_A)/(\ln c_{B_0} - \ln c_B) = \left(\log \frac{100 - a\%}{100}\right) \Big/ \left(\log \frac{100 - b\%}{100}\right) \qquad (1)$$

(where c_{A_0} and c_{B_0} are the initial concentrations of starting monomethyl ethers, c_A and c_B their concentrations at time t, and $a\%$ and $b\%$ percentual amounts of the reacted starting monomethyl ethers) enabled us to calculate the ratios of rate constants k_{III-IV}/k_{II-IV}, $k_{VII-VIII}$: : $k_{VI-VIII}$, $k_{II-IV}/k_{VI-VIII}$ and $k_{III-IV}/k_{VII-VIII}$. The ratio of the rate constants in the first reaction step of the methylation of methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside (*I*), *i.e.* k_{I-II} : : k_{I-III}, as well as the ratios necessary for an unambiguous determination of the effect of the neighbouring substituent on the methylation rate of the remaining hydroxyl group, *i.e.* k_{III-IV} : : k_{I-II}, k_{II-IV}/k_{I-III}, k_{III-IV}/k_{I-II}, and k_{III-IV}/k_{I-III}, were obtained from the solution of the system of equations[8] (*2*) and (*3*)*

$$c_{II} = \frac{p}{(q-1)}(c_I - c_{I_0}{}^{(1-q)} \cdot c_I^q), \qquad (2)$$

$$c_{III} = \frac{(1-p)}{(kq-1)}(c_I - c_{I_0}{}^{(1-kq)} \cdot c_I^{kq}), \qquad (3)$$

which describe the kinetics of the reactions in Scheme 1 for the unknowns $p = k_{I-II}/(k_{I-II} + k_{I-III})$ and $q = k_{II-IV}/(k_{I-II} + k_{I-III})$. In the calculation carried out on a Hewlett-Packard 2116B computer, the concentrations of substances given in Table I were substituted for c_I, c_{II}, and c_{III}, the experimentally determined ratio k_{III-IV}/k_{II-IV} (see equation (*1*)) for the value k, and 100% for the starting concentration c_{I_0}.

The ratios of the rate constants were then determined from the calculated p and q values by simple algebraic arrangements, for example $p/q = k_{I-II}/k_{II-IV}$, *etc.* In an analogous manner the ratios of the rate constants in the case of the derivatives of L-*lyxo* configuration were determined, which were then utilised together with the other ones for the calculation of the k_{I-II}/k_{V-VI} and k_{I-III}/k_{V-VII}. The values of all these ratios of rate constants are listed in Table III.

The results obtained may be summarized as follows:

1) During the methylation to the first stage the hydroxyl group on $C_{(2)}$ of the glycoside *I* reacts approximately two to three times faster than the hydroxyl group on $C_{(3)}$; in glycoside *V* hydroxyl groups react at approximately the same rate. From the mutual comparison of the reactivity of both starting glycosides it follows that the reactivity of glycoside *I* is higher, especially on the hydroxyl group in the position 2 (approx. three to four times higher in comparison with the same hydroxyl group in glycoside *V*).

2) In both configurational series methylation of the hydroxyl group on $C_{(2)}$ leads to a distinct (up to fourfold) decrease in reactivity of the hydroxyl group in the posi-

* Under the supposition that a single mechanism is operative.

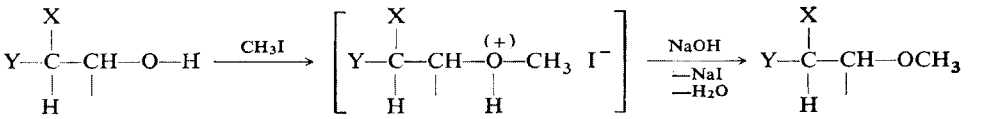
TABLE III

Ratios of Rate Constants of Partial Methylation of Glycosides *I*—*III* and *V*—*VII*

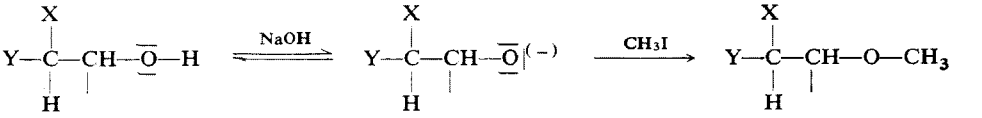
Ratio	Amount of base (mol/mol glycoside)		
	0·6	0·9	1·2
k_{I-II}/k_{I-III}	2·3	2·8	3·4
k_{III-IV}/k_{II-IV}	7·0	—	—
$k_{II-IV}/k_{VI-VIII}$	1·2	—	—
$k_{III-IV}/k_{VII-VIII}$	1·8	—	—
k_{V-VI}/k_{V-VII}	0·8	0·9	1·0
$k_{VII-VIII}/k_{VI-VIII}$	4·5	—	—
k_{II-IV}/k_{I-II}	0·1	0·13	0·14
k_{II-IV}/k_{I-III}	0·2	0·4	0·5
k_{III-IV}/k_{I-II}	0·7	0·9	1·0
k_{III-IV}/k_{I-III}	1·5	2·7	3·3
$k_{VI-VIII}/k_{V-VI}$	0·3	0·4	0·4
$k_{VI-VIII}/k_{V-VII}$	0·2	0·4	0·4
$k_{VII-VIII}/k_{V-VI}$	1·3	2·0	1·7
$k_{VII-VIII}/k_{V-VII}$	1·0	1·9	1·6
k_{I-II}/k_{V-VI}	3·4	3·9	3·1
k_{I-III}/k_{V-VII}	1·2	1·6	1·0

tion 3 in comparison with the reaction rate of etherification of the same hydroxyl group in glycosides *I* or *V*. In contrast to this the methylation of the hydroxyl group on $C_{(3)}$ does not lead to a substantial change in the reaction rate of the hydroxyl group in the position 2. In the mixtures of monosubstituted derivatives *II* and *III*, or *VI* and *VII*, resp., the hydroxyl group on $C_{(2)}$ reacts seven times, or four and

Mechanism *A*



Mechanism *B*



SCHEME 2

a half times faster, respectively, than the hydroxyl group in the position 3. In the mixtures of equally substituted monomethyl ethers of different configurations, derivative *III* reacts approximately twice as fast as *VII*, while derivative *II* reacts approximately at the same rate as *VI*.

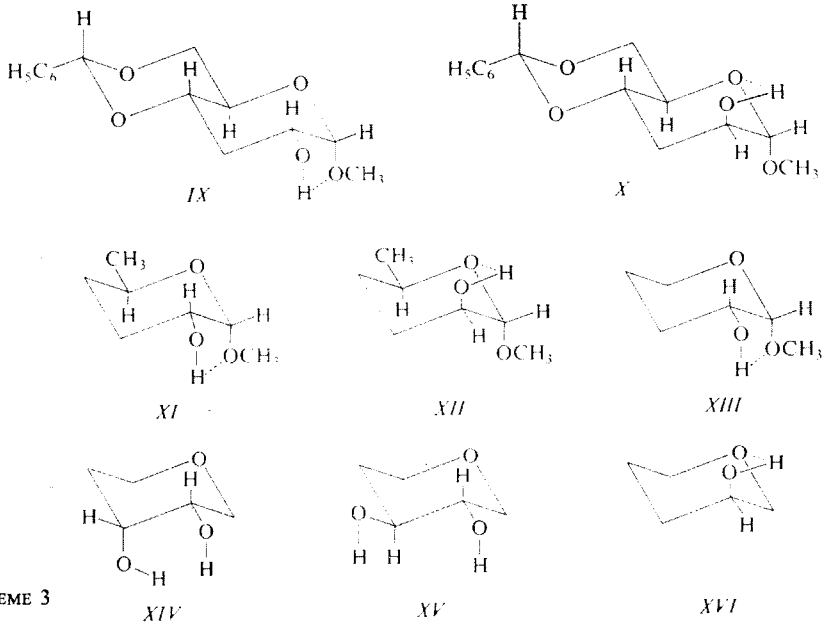
From the values presented it seems probable that under the conditions used the amount of base has not a too strong effect on the ratio of reactivities of the hydroxyl groups in positions 2 and 3, *i.e.*, it affects rather the degree of conversion than the ratio of the products. In view of the very low concentration of hydroxide in the solution it may be supposed that a possible contribution of the alkoxide form to the reactivity of the hydroxyl group will be insignificant. This is also indicated by the quite different course of the reaction when sodium hydride[9] was used instead of sodium hydroxide, *i.e.* when the reactivity is determined predominantly by the alkoxide anion, *i.e.* by the equilibrium distribution of Na^+. Hence, of the possible mechanisms of alkali catalysed etherification (Scheme 2) the mechanism *A* probably prevails, although a partial course according to *B* cannot be completely excluded; higher reactivity will be displayed by that hydroxyl group the oxygen atom of which has a higher nucleophilicity. A formation of the adducts of hydroxyl groups with sodium hydroxide molecule (that was considered during the discussion of the results of the reaction of N,N-diethylaziridinium chloride with methyl α-D-glucopyranoside in solutions of various concentrations of sodium hydroxide[10]) is in our case improbable, because of the very low concentration of the base in the solution (heterogeneous reaction mixture). Therefore, the sodium hydroxide present will probably serve mainly for the blocking of the hydrogen iodide formed. The inductive effect of the electrophilic substituents X and Y (Scheme 2) in the mechanism *A* slows down the reaction a little, because it leads to the decrease of the electron density on the oxygen atom of the hydroxyl group. The same situation will exist also for the mechanism *B* if the rate determining step is the reaction of alkoxide with methyl iodide; if not, an acceleration of the reaction takes place under the influence of the −I-effect.

The different reactivity of secondary hydroxyl groups during the etherification of sugar derivatives by various alkylating reagents was many times observed and explained either by steric hindrance, as for example in the case of decreased reactivity of the axial OH-group on the $C_{(4)}$ of derivatives with *galacto* configuration[11–13], or by the different polarity of the O—H bond of single hydroxyl groups, more or less affected by the inductive effect of the hemiacetal group. A number of authors[14–18] explain the increased reactivity of the OH group in the position 2 toward alkylating agents by this effect; the same is true of the increase in reactivity of the OH group in the position 3 after etherification of the hydroxyl group on the second carbon atom[13,16].

The results of the experiments summarized on p. 304 cannot be explained by steric or polar effects only. This is evident, for example, from the comparison of the values k_{I-II}/k_{V-VI} *versus* $k_{III-IV}/k_{VII-VIII}$ and similar values, which differ appreciably

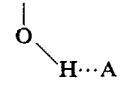
in spite of the fact that they compare the reaction rates of substances reacting on centres with unchanged (or similarly changed) steric factors and affected by the same inductive effect. We believe that an important role in the affecting of the reactivity of single hydroxyl groups of glycosides *I–III* and *V–VII* during their alkylation with methyl iodide and sodium hydroxide in acetonitrile is played by internal hydrogen bonds. The existence and the intensity of these bridges is due itself to steric and polar effects, as well as to the character of the solvent used. In spite of its considerable dielectric constant ($\mu = 37{\cdot}5$) acetonitrile is a relatively weak hydrogen bond acceptor[19] and an intramolecular hydrogen bond can exist in this medium[20].

The strength of the hydrogen bridge, and hence also the change in nucleophilicity of the oxygen of the bound hydroxyl group caused by it, is proportional to the magnitude of the frequency shift of its vibration band, so that the reactivity of the bound hydroxyl group during methylation may be correlated to a certain extent with the value $\Delta\nu$. However, no less important role is played by the population of the hydrogen bond which is only approximately correlative with ε (ref.[21]). Consequently, the reactivity of the hydroxyl group bound even by a strong hydrogen bond need not be affected seriously by this bond if the bound form is for some reason (for example steric) unfavourable and therefore its concentration low. In systems with several hydroxyl groups the situation is more complex. The frequency ν(OH) decreases (in comparison with $\nu(\mathrm{OH})_{\mathrm{free}}$) not only in groupings where this hydroxyl group

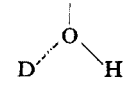


SCHEME 3

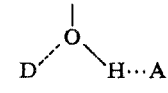
functions as a donor (type *1*), but also when its oxygen atom is an acceptor for the hydrogen bond (type *2*). If the hydrogen atom is simultaneously involved as a donor and oxygen as an acceptor (type *3*), the decrease in ν(OH) frequency is substantially higher[22]. However, the situation is different with the nucleophilicity change (and hence also with the reactivity) of the corresponding hydroxyl group thus caused. While in the hydrogen bond of type *1* the nucleophilicity of the oxygen atom increases in comparison with the isolated hydroxyl group, in the case of type *2*, on the contrary, it decreases. In type *3* it may be supposed that the reactivity is between these extremes, depending on the relative strength of the donor and the acceptor[23]. In polysubstituted derivatives, as for example sugars, it is therefore necessary to take into consideration the possibility of the formation of this double bridge (type *3*) during the correlations of the reactivity of the hydroxyl group and its $\Delta\nu$ value.



type *1*



type *2*



type *3*

The values of vibrations of ν(OH) of the substances discussed are listed in Table IV. For the sake of comparison we also give the ν(OH) values of compounds *IX–XVI*, *i.e.* for the systems of one donor and one acceptor on the tetrahydropyran skeleton which might be considered as fundamental models of hydrogen bonds in compounds *I* and *V*. For derivatives with L-*lyxo* configuration (Table IV), the strength of the intramolecular hydrogen bond $O_{(3)}$—H → $O_{(2)}$ does not practically change when the hydroxyl group on $C_{(2)}$ is substituted for a methoxyl group. However, this substitution corresponds to an approximately three-fold decrease in reactivity of the hydroxyl group on $C_{(3)}$ ($k_{VI-VIII}/k_{V-VII} = 0{\cdot}2-0{\cdot}4$). As the change of hydrogen bond, as well as of the inductive effect (see below) and of the conformation[1] is negligible when —OH is substituted for —OCH_3, we must attribute this decrease in the reaction rate to the different steric effect of the methoxyl and the hydroxyl group on the methylation rate of the neighbouring hydroxyl. The same hindrance by the neighbouring methoxyl group should, of course, also manifest itself in the etherification of the hydroxyl group at $C_{(2)}$ in derivative *VII*, where on the contrary, a 1·3 to 2·0 fold increase in the rate constant ($k_{VII-VIII}/k_{V-VI}$) was observed. In contrast to the preceding case the hydroxyl group on $C_{(2)}$ displays a 10 cm^{-1} lower value of the vibration of the intramolecular hydrogen bond directed to the ring-oxygen in glycoside *V* than in 3-O-methyl derivative *VII*. This difference in the hydrogen bond strength cannot be attributed to the change in the molecular geometry; the magnitude of $J_{1,2}$ in compounds *V* and *VII*, as well as in *I* and *III* is the same[1,24]. Equally it is not due to the difference of the I-effect of the OH and the OCH_3 groups either, as may be judged

TABLE IV

Frequencies (cm^{-1}, accuracy $\pm 2\ cm^{-1}$) of Vibrational Bands of Hydroxyl Groups in Infrared Spectra of Compounds Studied, in Tetrachloromethane

Compound	free OH	$O_{(2)}H \rightarrow O_{(1)}CH_3$	$O_{(2)}H \rightarrow O_r$	$O_{(3)}H \rightarrow O_{(2)}$	$\Delta\nu$ [a] cm^{-1}	Ref.
I	3 629[b]	3 574	—	3 597	55;32	[d]
II	3 629[b]	—	—	3 601	28	[d]
III	—	3 581[c]	—	—	48	[d]
V	3 625	—	3 581	3 581	44	[d]
VI	3 629	—	—	3 579	50	[d]
VII	—	—	—	—	38	[d]
IX	—	3 585	3 591	—	44	[d]
X	3 630	—	3 604	—	26	[d]
XI	—	3 584	—	—	45	[d]
XII	3 629	—	3 596	—	33	[d]
XIII	3 625	3 588	—	—	37	27
XIV	—	—	—	3 583	46	28
XV	—	—	—	3 608	21	28
XVI	—	—	3 590	—	39	27
			(3 604)		(25)	29

[a] The shift $\Delta\nu$ is the difference of the frequencies of the bands of the bound and free hydroxyl group. Unless the band of the free hydroxyl group was present in the spectrum, the value 3 629 cm^{-1} was used instead of it. [b] Trace. [c] In the spectrum also a trace of 3600 cm^{-1} frequency was observed, corresponding probably to the bridge $O_{(2)}H \rightarrow O_{(3)}CH_3$. [d] The given data were measured in connection with this investigation.

from the fact that, for example, the six-membered 1,3-diaxial bridge in 1,6-anhydro--4-O-methyl-β-D-glucopyranose and 1,6-anhydro-3,4-di-O-methyl-β-D-glucopyranose has the same value[25], 3560 cm^{-1}. Once the $O_{(2)}H \rightarrow O_{(5)}$ hydrogen bond in compound *V* existing, the orientation of the oxygen atom bound to $C_{(2)}$ is such that according to molecular models, it enables a simultaneous overlap of the directed *p*-orbital of this oxygen with the *s*-orbital of the hydrogen atom of $O_{(3)}H$, *i.e.* the formation of a double bridge $O_{(3)}H \rightarrow O_{(2)}—H \rightarrow O_{(5)}$. According to the above consideration, the reactivity of $O_{(2)}H$ in glycoside *V* (type *3*) should be decreased in comparison with the reactivity of the same hydroxyl group in compound *VII* (type *1*), in spite of the fact that in *V* the hydroxyl group $O_{(2)}H$ is bound by a stronger hydroxyl bond. The prevention of this double bridge by methylation on $C_{(3)}$ leads to an approximately seven-fold increase in reactivity of the hydroxyl group in position 2 (type *1* against type *3*), if including the above mentioned three to four-

-fold retarding steric effect of the neighbouring methoxyl group in the ratio $k_{VII-VII}$: : $k_{V-VI} \approx 1{\cdot}7$ observed.

The results obtained in experiments with derivatives of D-*xylo* configuration may be explained in a similar manner. The strengthening of the hydrogen bridge of the hydrogen group on the second carbon atom (3574 cm^{-1} in *I*, 3581 cm^{-1} in *III*) by the sterically possible hydrogen bond[22] coming from the hydroxyl group at $C_{(3)}$ (*i.e.* the formation of the double bridge $O_{(3)}$—H → $O_{(2)}$—H → $O_{(1)}CH_3$) leads to a decrease in nucleophilicity of the oxygen of this hydroxy group in glycoside *I*. The disappearance of this double bridge by methylation on $C_{(3)}$, *i.e.* in *III*, increases the reactivity on $C_{(2)}$ which is evidently compensated by the sterical deactivation with the vicinal methoxyl group on $C_{(3)}$ ($k_{III-IV}/k_{I-II} = 0{\cdot}9$) analogous to that in derivatives with L-*lyxo* configuration. The change in the reactivity of the hydroxyl group on $C_{(3)}$ ($k_{II-IV}/k_{I-III} = 0{\cdot}2-0{\cdot}5$) is also probably caused by steric deactivation by the neighbouring methoxyl group; the change of ν(OH), caused probably by the existence of a double bridge in *I*, may also contribute to it.

In comparison to the reactivity of the hydroxyl group on $C_{(3)}$ in diols *I* and *V*, the reactivity of the hydroxyl group on $C_{(2)}$ is affected in addition to the above discussed factors also by the inductive effect of the neighbouring hemiacetal group, and — in glycoside *V* — by the disadvantageous axial position, which cause it to assume the following values, $k_{I-II}/k_{I-III} = 2{\cdot}3$ to $3{\cdot}4$, and $k_{V-VI}/k_{V-VII} = 0{\cdot}8$ to $1{\cdot}0$.

From the above examples it is evident that the effect of intramolecular hydrogen bonds on the reactivity of the hydroxyl groups is especially pronounced in those cases where the neighbouring substitution abolishes the possibility of the existence of a double bridge decreasing the reactivity of the central hydroxyl group (type *3*) and enables the formation of a bridge which enhances the reaction. Concerning the substances with different configuration, however, the correlation of the values of the ratios of rate constants with the $\Delta\nu$ values of hydroxyl groups is no longer evident, even though the same hydroxyl groups are conceived, affected by the same polar and steric effects; see for example the values k_{I-III}/k_{V-VII} or $k_{II-IV}/k_{VI-VIII}$. For the last mentioned case a possible explanation can be sought in the fact that the bridge in compound *VI*, although strong (*cis, ea*) is very little abundant, as may be seen from the presence of a distinct band of free hydroxyl group at 3629 cm^{-1}. The reason for this might be the disadvantageous interaction of the electron pair or of the methyl group on $O_{(2)}$ with the electron pair of the ring oxygen in those positions of the methoxyl group which make an effective overlapping of the directed orbitals on $O_{(2)}$ and the hydroxyl group in the position 3 possible. For a similar reason the hydroxyl group on the second carbon atom of compound *VII* probably forms preferentially a bridge to the ring oxygen (3591 cm^{-1}) and not to the methoxyl in the position 3, in spite of the fact that the latter should by stronger (approx. at $\nu = 3579\ cm^{-1}$).

The results of methylation with methyl iodide and sodium hydroxide in dimethylformamide (Table I, col. *b*), although inaccurate in consequence of the losses of volatile

components during the elimination of high-boiling solvent, support the above mentioned idea on the effect of the intramolecular hydrogen bonds on the reactivity of the hydroxyl groups. Dimethylformamide as a strong acceptor of hydrogen bonds[18] cancels the activation and deactivation by hydrogen bonds which we observed in acetonitrile. The reaction rate is influenced mainly by the −I-effect of the hemiacetal group and by steric reasons, which results in the formation of a relatively larger amount of derivatives substituted in the position 2. This result is in agreement with that obtained during partial methylation of methyl α-D-mannopyranoside with methyl iodide and silver oxide in dimethylformamide[26]. In agreement with the ideas of English authors[20], a similar result may also be expected during methylations with methyl iodide and barium oxide in dimethylformamide, while when these reagents are used in acetonitrile the effect of intramolecular hydrogen bonds probably plays a role. A further checking of the above interpretation of experimental data could be obtained from the planned study of the remaining configurational and structural isomers of deoxy sugars.

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