REACTIVITY OF HYDROXYL GROUPS OF 1,6 : 2,3- AND 1,6 : 3,4--DIANHYDRO-β-D-HEXOPYRANOSES IN METHYLATION WITH IODOMETHANE*

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Relative rate constants for reaction of 1,6 : 2,3- and 1,6 : 3,4-dianhydro-β-D-hexopyranoses with iodomethane in acetonitrile in the presence of silver oxide were measured. Their values, ranging from 1 to 8·6, were interpreted on the basis of polar and steric effects and intramolecular hydrogen bonds.

Since 1,6 : 2,3- and 1,6 : 3,4-dianhydro-β-D-hexopyranoses *I*–*VIII* contain only one free hydroxyl group, they are potentially suitable as starting compounds for selective syntheses of oligosaccharides. The hydroxyl group in these derivatives is easily acylated or alkylated with usual reagents[1]. The assumed reactivity differences might also appear in glycosylations, affecting the stereoselectivity and yield of the reaction[2]. It was therefore of interest to study the reactivity of complete series of dianhydrohexoses *I*–*VIII* in the methylation reaction under conditions similiar to usual glycosylations and to ascertain factors affecting the alkylation of hydroxyl in α-position to the oxirane ring. The reaction was carried out with iodomethane in acetonitrile in the presence of silver oxide. Under these conditions the compounds *I*–*VIII* were sufficiently stable and no epoxide migration occurred[1,3]. It was reasonable to assume that the reaction takes place on the surface of silver oxide by a mechanism similar to S_N2 substitution. Because of considerable excess of iodomethane in the reaction mixture, the reaction was pseudomonomolecular. The relative methylation rate constants were determined from the time dependence of concentration changes of the starting compounds *I*–*VIII* and the arising 2- or 4-O-methyl derivatives, as monitored by gas–liquid chromatography, and are given in Table I.

The reactivity of saccharide hydroxyl groups in the methylation is usually interpreted in terms of polar factors, affecting the nucleophilicity of hydroxyl oxygen atoms, and of steric factors. The role of hydrogen bonds in vicinal hydroxy com-

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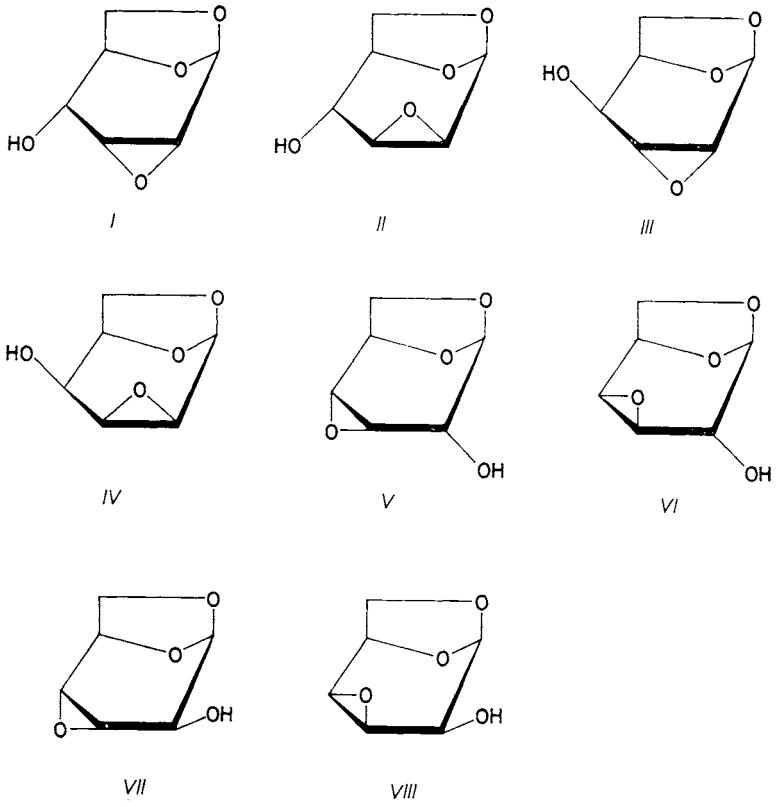
pounds is not clear and no decisive effect on the diol grouping of 4,6-dideoxyhexopyranosides has been observed[4,5]. Nevertheless, for the series of dianhydro derivatives *I* – *VIII* the hypothesis that intramolecular hydrogen bonds increase the nucleophilicity of the hydroxyl oxygen atoms – and thus their reactivity – seems to be useful for interpreting the results. The existence of intramolecular hydrogen bonds



I, 1,6 : 2,3-dianhydro-β-D-allopyranose
II, 1,6 : 2,3-dianyhdro-β-D-mannopyranose
III, 1,6 : 2,3-dianhydro-β-D-gulopyranose
IV, 1,6 : 2,3-dianhydro-β-D-talopyranose
V, 1,6 : 3,4-dianhydro-β-D-allopyranose
VI, 1,6 : 3,4-dianhydro-β-D-galactopyranose
VII, 1,6 : 3,4-dianhydro-β-D-altropyranose
VIII, 1,6 : 3,4-dianhydro-β-D-talopyranose

in compounds *I* – *VIII* has been proved already earlier by IR spectra in tetrachloromethane and their relative strength as well as population has been determined[6]

(Table I). On the other hand, a decrease in reactivity of hydroxyl groups on the C-2 carbon atom due to a −I effect of the acetal grouping can be expected.

Accordingly, the hydroxyl group on C-4 in 1,6 : 2,3-dianhydro-β-D-allopyranose (*I*) appeared to be the most reactive. Its reactivity is enhanced by a strong hydrogen bond to the oxirane oxygen atom and is not influenced by the −I effect of the acetal group. The dianhydro derivatives *II*, *V*, *VII*, and *VIII* are less reactive. In compounds *V*, *VII*, and *VIII* the effect of the intramolecular hydrogen bond is compensated by the −I effect of the acetal group which reduces the reactivity of their hydroxyl group on C-2. Although the −I effect does not operate in compound *II*, the relative decrease in reactivity as compared with *I* may be caused by a weaker and less populated hydrogen bond (Table I). The hydroxyl groups in *III* and *VI* are still less reactive. The low reactivity of the latter compound is due both to the −I effect of the acetal group and a relatively weaker, less populated, intramolecular hydrogen bond. Compound *III*, without any unfavourable −I effect, is the only one of all the dianhydrohexoses that (for steric reasons) cannot form an intramolecular hydrogen bond (see *IIIa*). It is also possible that the transition state in the methylation is destabilized by unfavourable steric interactions with the atoms H-5 and H-6endo.

Compound *IV* is the least reactive of the whole series. At the first glance, this fact is surprising because, similarly to the isomer *III*, no unfavourable −I effect of the

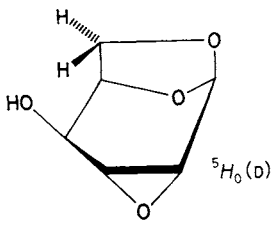
TABLE I

Methylation of 1,6 : 2,3- and 1,6 : 3,4-dianhydro-β-D-hexopyranoses

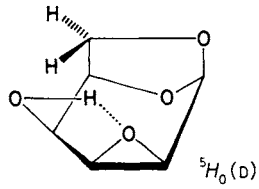
Compound	k_{rel}[a]	ν(O—H) cm^{-1}	Population of the intramolecular hydrogen bod, %
I	8·2	3 570	100[b]
V	5·4	3 569	100[b,c]
II	5·0	3 582	87[d]
VII	4·0	3 565	100[b,c]
VIII	3·7	3 569	100[b,c]
VI	2·2	3 585	75[c,e]
III	1·8	3 628	0[f,g]
IV	1·0	3 592	76[e,h]

[a] k_{rel} denotes the relative methylation rate, based on the rate of *IV*, $k = 1{\cdot}66 \cdot 10^{-5}\ s^{-1}$, $c(CH_3I) = 10{\cdot}7\ mol\ l^{-1}$; [b] strong hydrogen bond; [c] −I effect of the acetal functionality; [d] weaker hydrogen bond; [e] weak hydrogen bond; [f] no intramolecular hydrogen bond; [g] possible steric interaction with H-5 and H-6endo in the transition state; [h] possible interaction with H-5 and H-6endo in the transition state or unfavourable polar interaction of 3 oxygen atoms above the plane of the pyranose ring.

acetal group operates; on the contrary, the nucleophilicity of the hydroxyl should be somewhat enhanced by the weak intramolecular hydrogen bond. An explanation may be found in an unfavourable steric situation in the transition state. The site of highest electron density in the intramolecularly hydrogen-bonded hydroxyl points to the atoms H-5 and H-6endo making thus the hydroxyl less accessible (see *IVa*). In the reaction of the free hydroxyl, unfavourable interactions with the oxirane ring and the H-6endo atom could also be significant.



III a



IV a

The relative rate of methylation of hydroxyl groups is known[7-9] to depend on reaction conditions and further on whether the hydroxyl reacts free or hydrogen-bonded or after previous dissociation to the alkoxide ion. Therefore, we can expect that methylation rates in an aprotic solvent in the presence of silver oxide will differ from those in a strongly alkaline aqueous medium; in the latter case the rate can depend on the concentration of alkoxide ions which is a function of acidity of the given hydroxyl. We tried to verify this assumption on the selected pair of compounds *I* and *V*. On transition from acetonitrile (catalysis with Ag^+ ions) to aqueous dioxane (catalysis with NaOH) the reactivity ratio $k_I : k_V$ is practically reversed, shifting from 1·53 : 1 to 1 : 1·38. This may be due to higher acidity of the hydroxyl on C-2 in compound *V* (caused by the −I effect of the neighbouring acetal group) than of the hydroxyl on C-4 in compound *I*.

EXPERIMENTAL

Gas–liquid chromatography was performed on a Chrom 3 (Laboratorní přístroje, Prague) instrument; compounds *I*—*III*, *V*, *VII*, and *VIII* were separated from their methyl ethers on a column packed with 5%OV-210 on Gas-Chrom Q (80—100 mesh), derivatives *IV* and *VI* were separated from the methyl ethers using 4% OV-225 on Chromosorb W-AW (60—80 mesh). The chromatography was performed at 137°C (T_i 160°C), carrier gas nitrogen (flow rate 22 ml . . min^{-1}), flame-ionization detector.

Methylation with Iodomethane in Acetonitrile, Catalyzed by Silver Oxide

The dianhydro derivative *I*— *VIII* were prepared according to the literature[3,10-15]. The catalyst (Ag_2O) was prepared as described[16], dried in vacuo at room temperature and kept for a short

time (maximum 3 days) under exclusion of moisture in the dark. The methylation was performed at 22°C in a 5 ml glass autoclave, closed with a silicone septum for withdrawal of samples by a microsyringe.

The dianhydro derivatives *I*—*VIII* (20 mg; 0·14 mmol), silver oxide (50 mg; 0·22 mmol), and a 4 Å molecular sieve (100 mg) were stirred in acetonitrile (1 ml) for 10 min. Iodomethane (2 ml; 4·56 g; 32 mmol) was injected through the septum and the mixture was stirred. Samples for gas–liquid chromatography (2—2·5 μl) were withdrawn in 10—60 min intervals, the stirring being interrupted for 10—15 s. In all cases 10 samples were taken during 5—6·5 h.

Methylation with Iodomethane, Catalyzed by Sodium Hydroxide in Aqueous Dioxane

Dianhydro derivative *I* or *V* (50 mg; 0·35 mmol) and powdered sodium hydroxide (100 mg; 0·4 mmol) were dissolved in a 5 : 1 mixture of dioxane–water (6 ml). Iodomethane (5 ml; 80·3 mmol) was then added and the mixture was stirred (800 rpm). The samples for gas–liquid chromatography were withdrawn from the dioxane layer after interrupting the stirring for a short time. Seven samples were taken in all cases.

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