Carbohydrate Research, 184 (1988) 244–246
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Effects of methyl, ethyl, and carboxymethyl *O*-substitution on the anomeric equilibrium of D-glucopyranose

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(Received May 10th, 1988; accepted for publication, May 25th, 1988)

One of the characteristic features that distinguishes reducing sugars from other organic compounds is that sugars exist in solution as a mixture of several tautomeric forms. In a comprehensive review, Angyal[1] observed that very few systematic studies had been conducted on substituted sugars. He also noted that, in some instances, n.m.r. chemical shifts had been reported for both of the pyranose anomers, but that no information was given on the anomeric composition[1]. Data on the anomeric equilibria in solutions of two series each of D-glucopyranose and methyl D-glucopyranoside substituted at O-2, -3, and -6 are available from studies on the monomer composition of cellulose ethers[2–4]. The monomer compositions were determined from a quantitative analysis of the ^{13}C-n.m.r. spectra of the monosaccharide mixtures obtained by hydrolysis or methanolysis of the polymers. In the spectra, the resonances of individual monosaccharide species, including anomers, were resolved, assigned, and quantitated. However, only the monomer mole fractions given by the sums of both anomers of the corresponding *O*-substituted D-glucopyranoses or methyl D-glucopyranosides were of interest in the work published. The anomeric compositions are the subject of this report. The earlier reports[2–4] shoud be consulted for the experimental details, as no new experiments were needed in order to obtain the data reported here.

RESULTS AND DISCUSSION

Recently published ^{13}C-n.m.r. spectra of D-glucose labeled with ^{13}C at C-1 have revealed the presence of six tautomeric forms[5]. However, as is well known[1], the two pyranose forms preponderate, amounting[5] to 99.7% at 27°. No tautomeric forms other than the pyranose were detected in the ^{13}C-n.m.r. spectra (at natural abundance of ^{13}C) of the monosaccharide mixtures resulting from the hydrolysis of *O*-(carboxymethyl)cellulose[2] and *O*-methylcellulose[3], or the methanolysis of *O*-methylcellulose[3] and *O*-ethylcellulose[4]. Therefore, the present discussion is limited

0008-6215/88/$ 03.50

TABLE I

EFFECTS OF *O*-METHYLATION AND *O*-(CARBOXYMETHYL)ATION ON THE ANOMERIC EQUILIBRIUM OF D-GLUCOPYRANOSE IN ACIDIFIED D_2O

Position substituted	*Proportions of anomers (mol % ±3)*			
	Methylated derivatives		*(Carboxymethyl)ated derivatives*	
	α	β	α	β
None	36	64	36	64
2	56	44	44	56
3	41	59	41	59
6	44	56	36	64
2,3	57	43	48	52
2,6	58	42	44	56
3,6	46	54	43	57
2,3,6	60	40	51	49

TABLE II

EFFECTS OF *O*-METHYLATION AND *O*-ETHYLATION ON THE ANOMERIC EQUILIBRIUM OF METHYL D-GLUCOPYRANOSIDE IN METHANOLIC HCl

Position substituted	*Proportions of anomers (mol % ±3)*			
	Methylated derivatives		*Ethylated derivatives*	
	α	β	α	β
None	77	23	77	23
2	73	27	73	27
3	80	20	81	19
6	76	24	76	24
2,3	71	29	75	25
2,6	74	26	73	27
3,6	85	15	81	19
2,3,6	75	25	73	27

to the effects of methyl and carboxymethyl *O*-substitution on the α/β equilibrium of D-glucopyranose in acidified (pH 1–2) aqueous solution and the effects of methyl and ethyl *O*-substitution on the α/β equilibrium of methyl D-glucopyranoside under methanolysis conditions (refluxing methanolic HCl). The results are summarized in Tables I and II, respectively.

The results in Table I for the anomeric composition of D-glucopyranose and its 2- and 3-*O*-methyl derivatives are in good agreement with the corresponding values in the literature[1,5–7]. The most conspicuous effect observed in the data in Table I is the dramatic increase in the proportion of the α anomer upon methylation

at O-2. The effect of methylation at O-3 and -6, although also leading to some increase in the level of the α anomer, is much smaller. The effect of double and triple substitution is similar to that of single substitution; additivity of substituent effects, if any, is apparently masked by experimental error.

The effects of *O*-substitution on anomeric equilibria have been discussed in terms of non-bonded 1,2-interactions between groups *gauche* to each other and the repulsive interaction (known as the anomeric effect) between the electric dipoles associated with the oxygen atoms on[1,7,8] C-1 and -5. Particularly important seem to be the influences of solvation and local dielectric constant on the magnitude of the anomeric effect. Angyal[1,8] suggested that the α anomer is favored in less polar environments due to an enhancement in the anomeric effect. The effect of methylation at O-2, and to a lesser extent at O-3 and O-6, would be to lessen hydration thereby lowering the polarity and the dielectric constant of the immediate environment of the D-glucopyranose molecule, while increasing the electron density on vicinal atoms *via* inductive effects. Both effects should lead to an enhancement in the magnitude of the anomeric effect and to an increase in the proportion of the α anomer. Based on such arguments, it would be expected that further substitution of one of the methyl hydrogen atoms by the hydrophilic carboxyl group should at least diminish, if not totally obliterate, the phenomenon. This is indeed observed (see Table I) in comparing the effect of *O*-methyl with that of *O*-carboxymethyl substitution.

For methyl D-glucopyranoside (see Table II), the α anomer is preponderant, amounting to 77% (*versus* 36% for D-glucopyranose). Two factors, both leading to an enhancement of the anomeric effect, seem to be responsible for this phenomenon. The electron-releasing methyl group contributes to a larger electric dipole at O-1, thereby destabilizing the β anomer. In addition, the less-polar solvent (methanol *versus* water) also contributes to the higher proportion of the α anomer[8]. Methyl or ethyl *O*-substitutions at other positions on the D-glucose molecule have an indirect and, therefore, much smaller effect on the anomeric equilibrium. Indeed, noteworthy in this regard is the virtual absence of differences between the effects of such methyl and ethyl substitutions (see Table II).

REFERENCES

1 S. J. ANGYAL, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 15–68.
2 J. REUBEN AND H. T. CONNER, *Carbohydr. Res.*, 115 (1983) 1–13.
3 J. REUBEN, *Carbohydr. Res.*, 157 (1986) 201–213.
4 J. REUBEN, *Carbohydr. Res.*, 161 (1987) 23–30.
5 S. R. MAPLE AND A. ALLERHAND, *J. Am. Chem. Soc.*, 109 (1987) 3168–3169.
6 H. SUGIYAMA AND T. USUI, *Agric. Biol. Chem.*, 44 (1980) 3001–3002.
7 W. MACKIE AND A. S. PERLIN, *Can. J. Chem.*, 44 (1966) 2039–2049.
8 S. J. ANGYAL, *Angew. Chem., Int. Ed. Engl.*, 8 (1969) 157–166.