The Anomeric Equilibrium of Glucose in Acidic and Basic Media

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The anomeric effect has been studied by many research groups. Those people have shown that anomeric equilibria of saccharides are dominated not only by the electric dipolar repulsion of the anomeric effect but also by other factors such as steric interactions, solvation, and so on. Our recent experiments by proton NMR in acidic and basic media suggested that hydrogen bonding is very important in the equilibria of glucose.

Generally speaking, D-glucose has more β-anomer than 2-O-methyl-D-glucose, and both of them had more α-anomer in acidic media and more β-anomer in basic media (Table and Fig. 2). The difference of the equilibrated ratios between glucose and 2-O-methyl-D-glucose might be attributable to the microenvironmental difference of dielectric constants due to the 2-O-substitution. The equilibrated ratios of these compounds were almost constant in various basic media, except in d5-pyridine, and also in various acidic media, however, in spite of very different dielectric constants of basic media and also of acidic media. Hence, those facts cannot be rationalized by the electric dipolar repulsion between the anomeric hydroxyl and neighboring hydroxyl or methoxyl group. Only intermolecular cyclic and intramolecular hydrogen bondings can elucidate those facts. On the other hand, there are the chemical shift difference of these compounds in various solvents as shown in the Table. However, these differences cannot be attributable to hydrogen bonding, since all solvents used here can make hydrogen bonding and there is a possibility of hydrogen bonding of the basic type in the Fig. 1 in all these solvents except pyridine.

In basic media, the β-anomeric hydroxyl group of D-glucopyranose would be a better hydrogen bonding donor than the α-group against a base molecule in a media. The hydrogen-bonded base molecule would be also a hydrogen bonding donor against the ethereal ring oxygen of the β-anomer of D-glucopyranose, as shown in Fig. 1. This intermolecular double hydrogen bonding makes a stable six membered ring with trans ring junction, and stabilizes the β-anomer under this condition. Although D-glucopyranose and 2-O-methyl-D-glucopyranose may be partially undergoing isomerization or epimerization under such conditions, we might neglect these possibilities. It is because both sugars did not show any other anomeric proton signals except for the two that were expected from the original anomers.

In acidic media, the α-anomeric hydroxyl of the D-glucopyranose would be a hydrogen bonding acceptor or donor against the protonated or unprotonated 2-

### Table: The Proton NMR Data of D-Glucose and 2-O-Methyl-D-Glucose in Acidic and Basic Media

<table>
<thead>
<tr>
<th>Solvent (dielectric constant)</th>
<th>D-Glucose</th>
<th>2-O-Methyl-D-Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>J₁,2(%)</td>
</tr>
<tr>
<td>HCOOH (58.5)</td>
<td>α</td>
<td>5.50</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>4.93</td>
</tr>
<tr>
<td>2.5N DCl</td>
<td>α</td>
<td>5.28</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>4.68</td>
</tr>
<tr>
<td>D₂O (78.3)</td>
<td>α</td>
<td>5.22</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>4.65</td>
</tr>
<tr>
<td>1N NaOH</td>
<td>α</td>
<td>5.10</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>4.49</td>
</tr>
<tr>
<td>Et₄N (3.6)</td>
<td>α</td>
<td>5.09</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>4.45</td>
</tr>
<tr>
<td>d₅-Pyridine (12.3)</td>
<td>α</td>
<td>5.72</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>5.15</td>
</tr>
</tbody>
</table>


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b Chemical shifts (ppm) of anomeric protons from internal DSS.

c Coupling constants (Hz) between anomeric and 2-protons.

d Equilibrated ratios.
FIG. 1. The Predominant Structure of 2-O-Methyl-D-
Glucose in Acidic, Neutral and Basic Media.

The predominant structure of 2-O-methyl-D-
glucose in acidic, neutral, and basic media is shown. In acidic media, the β-anomer is predominant, while in neutral and basic media, the α-anomer is predominant.

FIG. 2. Partial Proton NMR Spectra at 100 MHz of 2-
O-Methyl-D-glucose in HCOOH (a), D₂O (b) and
Diethylamine (c).

The partial proton NMR spectra of 2-O-methyl-D-glucose in different media are shown. The spectra reveal the presence of two anomers, α and β, with different chemical shifts in each medium.

In acidic media, the spectrum shows a sharp peak at 5.3 ppm due to the presence of the 2-oxidomethyl group. In neutral and basic media, the spectrum shows a peak at 4.8 ppm due to the presence of the 2-hydroxyl group.

methoxyl or 2-hydroxyl of the D-glucopyranoses. The 1,2-
eq-eq-bonds approaching of cyclohexane has steeper
energy increase than that of the 1,2-eq-ax-ones. Hence,
the bonds approaching due to the formation of the
intramolecular hydrogen bonding between the α-anomeric
hydroxyl and the 2-methoxyl of 2-O-methyl-D-
glucopyranose should be easier than that between the β-
anomeric hydroxyl and the 2-methoxyl. In D-
glucopyranose, the situation is similar. Thus, the
intramolecular hydrogen bonding seems to increase the α-
anomer abundance in acidic media.

In neutral heavy water or D₅-pyridine, there is no good
hydrogen bonding acceptor-donor such as hydroxyl anion
or diethylamine. Hence, the intramolecular hydrogen
bonding may form between the anomeric hydroxyl and the
2-methoxyl or the 2-hydroxyl of the D-glucopyranose
in analogy with the acidic case.

EXPERIMENTAL

Proton NMR spectra. Spectra were measured at 24°C
with a JEOL PS-100 spectrometer at 100 MHz. Spectral data
were obtained at a concentration of 10% Sodium 3-
(trimethylsilyl)-propanesulfonate (DSS) was used as an
internal standard. The measurements of anomeric com-
position at equilibrium were made over prolonged periods
(10 ~ 40 hr) until no further change was evident.

Material. D-Glucose, diethylamine, and 99% formic acid
(all were the reagent grade) were obtained from Wako
Pure Chemicals, Tokyo. 2-O-Methyl-D-glucose was syn-
thesized by the method of Deferrari et al.15 Heavy water,
sodium deuteroxide in heavy water, deuterium chloride in
heavy water, and D₅-pyridine were obtained from Merck,
West Germany. All commercially obtained chemicals were
used without further purification.

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