A Note on the Difference in Reactivity of Dihydronicotinamide β-D-glucopyranoside and Its Acetylated Form

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In a previous communication,1) we reported that β-D-glucopyranosyl-1,4-dihydronicotinamide was more reactive in the reduction of 3,3,5-trimethyl-2-cyclohexenylidenepyrrrolidinium perchlorate than its acetylated form as was indicated by the difference in yield. The stereochemical aspect of the reduction was described in detail elsewhere,2) but the cause of the observed difference in reactivity has remained obscure.

We wish, at this time, to add some other comments on the origin of the reactivity of the reductants in the present NADH model system.

Hydroxy- and acetylxy-forms of several sugar pyranosides were prepared and submitted to the reduction of the substrate iminium salt (1) under the same conditions. The results are summarized in Table I.

Table I. Reduction of 3, 3, 5-Trimethyl-2-cyclohexenylidenepyrrrolidinium perchlorate (1) with various sugar pyranosides

<table>
<thead>
<tr>
<th>run</th>
<th>1,4-dihydronicotinamide</th>
<th>solvent</th>
<th>chemical yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>β-D-glucopyranosyl</td>
<td>OAc DMF</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>β-D-glucopyranosyl</td>
<td>OH DMF</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>β-D-xylopyranosyl</td>
<td>OAc DMF</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>β-D-xylopyranosyl</td>
<td>OH DMF</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>β-D-mannopyranosyl</td>
<td>OAc DMF</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>β-D-mannopyranosyl</td>
<td>OH DMF</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>β-D-galactopyranosyl</td>
<td>OAc DMF</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>β-D-galactopyranosyl</td>
<td>OH DMF</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>β-D-lactopyranosyl</td>
<td>OAc DMF</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>β-D-lactopyranosyl</td>
<td>OH DMF</td>
<td>26</td>
</tr>
<tr>
<td>11</td>
<td>simple model (2)</td>
<td>OAc DMF</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>simple model (2)</td>
<td>OH DMF</td>
<td>34</td>
</tr>
<tr>
<td>13</td>
<td>β-D-glucopyranosyl</td>
<td>OAc N-methylacetamide</td>
<td>27</td>
</tr>
<tr>
<td>14</td>
<td>β-D-glucopyranosyl</td>
<td>OH N-methylacetamide</td>
<td>45</td>
</tr>
<tr>
<td>15</td>
<td>β-D-glucopyranosyl</td>
<td>OAc ethylene glycol</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>β-D-glucopyranosyl</td>
<td>OH ethylene glycol</td>
<td>16</td>
</tr>
</tbody>
</table>

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Reactivity of Dihydronicotinamide D-glucopyranosides

tions. The results obtained (Table I) showed that the more reactive were unexceptionally the OH-forms, as revealed by the reduction yields. This trend was observed for the reductions in polar protic media (runs 13–16) as well as for those in a polar aprotic solvents, DMF (runs 1–12).

Then, the more simplified synthetic models for dihydronicotinamide sugar pyranosides (2)-OAc and (2)-OH were examined, and here again the latter afforded

the higher yield than the former (runs 11 and 12).

Thus, the results unambiguously show that the reactivity is dependent on whether the hydroxyl group(s) in the substituent at N₁ (pyridine nitrogen atom) of dihydronicotinamide is acetylated or not. Since the effective reduction of the substrate (1) requires considerably higher temperature (140°C), which is inevitably accompanied by undesirable side reactions, the observed chemical yields can not always be taken as a reliable measure of reactivity. We employed 2,6-dichlorophenolindophenol as an alternative substrate of choice for a more quantitative measure of reactivity. The substrate has been used by Wallenfels³ as a sensitive indicator for reactivity of various NADH model compounds. Under the same conditions as described by the author, a pseudo-first order rate constant was found for the present reduction of the substrate with the OH- and the OAc-forms of 1,4-dihydronicotinamide β-D-gluco-pyranoside.

As shown in Table II, all the OH-forms were twice as reactive as their acetylated counterparts in aqueous media. Sigman and Creighton⁴ have reported that in

<table>
<thead>
<tr>
<th>run</th>
<th>1,4-dihydronicotinamide</th>
<th>( k_{obsd} ) ((1./\text{mol.min.}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>β-D-glucopyranosyl OAc</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
<td>β-D-xylopyranosyl OAc</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>9.1</td>
</tr>
<tr>
<td>5</td>
<td>simple model (2) OAc</td>
<td>57.1</td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>103.3</td>
</tr>
</tbody>
</table>

* Salt free 2,6-dichlorophenolindophenol was used as a substrate by Wallenfels but the slight modification may not interfere the reasonable comparison of reactivity in phosphate buffer (pH 7.0).
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Aprotic solvent, hydroxyl group attached close to the pyridine nitrogen of dihydronicotinamide activates the NADH model toward 1-methylacridinium chloride, by some unidentified electronic interactions, but the effect was lost in aqueous solvent. In our system, however, such a mechanism can not be a major factor of the reactivity difference between the OH- and the OAc-forms because the difference was observed in aqueous media as well (Table II).

On the other hand, Wallenfels and Gellrich found that Log $k_{obsd.}$ obtained in the reaction with 2,6-dichlorophenolindophenol correlate linearly with the redox potential of various N$_1$-substituted nicotinamides and the wavelength at maximum absorption in UV spectra of 4-cyano-1,4-dihydronicotinamides, and these authors suggested that the relative reactivity could be interpreted in terms of electronic properties of the N$_1$-substituents, i.e., the more electron-rewiing the substituent is, the less reactive the dihydronicotinamide.

Along this line, we measured and compared the redox potential of the OH-form of β-D-glucopyranoside (−0.308 V) and the wavelength at maximum absorption of 4-cyano-1,4-dihydronicotinamide β-glucopyranoside (328 nm) with those reported by Wallenfels and Diekmann for the OAc-counterpart (−0.267 V, 318 nm). The magnitude of the difference in these physical properties seems to reflect roughly the difference in reactivity between these two forms in reference to the linear relation cited above. In the consequence, the difference in reactivity most probably originates in that the better electron-rewiing acetoxy group (σ$_{inductive}$ 0.39) lowers the reductive potential toward the substrate more than does the free hydroxyl group (σ$_{inductive}$ 0.25). However, there is not excluded an alternative possibility that a change of chemical potential between the two forms due to the different solubility in the reduction media may in part be responsible for the difference in yield.

**MATERIAL AND METHOD**

Preparation of 3,3,5-trimethyl-2-cyclohexenylidenepyrrolidinium perchlorate and 1,4-dihydronicotinamide sugar pyranosides were described in our previous paper. 2,6-Dichlorophenolindophenol sodium salt dihydrate (95 % purity) was commercially supplied.

N$_1$-(2′-Acetoxy-2′-phenylethyl)-1,4-dihydronicotinamide ((2)-OAc): To a mixture of ethanol (125 ml) and phenacyl bromide (25 g) was added dropwise an ethanol solution of sodium borohydride (25 g in 130 ml) at 0–5°C during 30 min. Immediately after the addition, water (60 ml) and conc. hydrochloric acid were added to adjust the pH of the mixture at 3. The ethanol was evaporated under reduced pressure and the residue was extracted with methylene chloride. The organic phase was dried over anhydrous sodium sulfate and concentrated to give 25.1 g (quantitative) of β-bromophenacyl alcohol. Pmr(CDCl$_3$)δ(ppm): 2.70(1H, br, s, OH), 4.78–5.10(1H, m, CH), 7.33(5H, s, phenyl). To the mixture of β-bromophenacyl alcohol (20 g) thus obtained and acetic anhydride (72 ml), was added dropwise 70 % perchloric acid (400 mg) with vigorous stirring at room temperature. After stirring for 30 min., the reaction mixture was poured into ice-water to decompose unreacted
acetic anhydride and then extracted with methylene chloride. The extract was
dried over sodium sulfate and concentrated under reduced pressure to give O-acetyl-
β-phenacyl alcohol (23.7 g, 98 %). The compound was identified by pmr (CDCl₃).
δ(PPM): 2.10(3H, s, CH₃), 3.60(2H, d, J=7.0 Hz, CH₂), 5.95(1H, t, J=7.0 Hz, CH), 7.33(5H, s, phenyl). This O-acetyl-β-phenacyl alcohol (11.6 g) and nicotin-
amide (5.8 g) were gently refluxed in dry acetonitrile (80 ml) for 25 hr. After
the period, the solvent was evaporated and the residue was dissolved in water. The
aqueous solution was extracted with ethyl acetate to remove unreacted material and
then concentrated, leaving a hygroscopic light brown oil (12.4 g, 83 %). The
salt, N₁-(2'-acetoxy-2'-phenylethyl)nicotinamide bromide, was subjected to reduc-
tion without further purification. A solution of sodium hydrogen carbonate (135 g)
in water (2250 ml) was saturated with carbon dioxide and to this aqueous solution
was added the quaternary salt dissolved in a small amount of water. After sodium
hydrosulfite (90 g) was added to this mixture, a brilliant yellow color immediately
appeared and there was a vigorous effervescence. The solution was left overnight
in the dark, during which time a precipitate separated. On filtration and washing
with water, N₁-(2'-acetoxy-2'-phenylethyl)-1,4-dihydronicotinamide (4.3 g, 44.3 %)
was isolated as a light yellow solid. Mp. 137–138°C. Anal. Calcd. for C₁₆H₁₈O₃N₂:
C, 67.11; H, 6.34; N, 9.7. Found: C, 67.13; H, 6.25; N, 9.88. UV(ethanol), λmax:
348 nm (ε, 7500). Pmr(CDCl₃)δ(PPM): 2.06(3H, s, CH₃), 3.15(2H, dd, two pro-
tons at 4 position in pyridine nucleus), 4.50–4.90(4H, m), 5.42(2H, br, s, NH₂),
5.75(1H, br, d, J=8.0 Hz), 7.15(1H, br, s), 7.27 (5H, s, phenyl).

N₁-(2'-Hydroxy-2'-phenylethyl)-1,4-dihydronicotinamide ((2)-OH): (2)-OAc ob-
tained above was deacetylated by ammonia in dry methanol⁵ to give the title com-
POUND as a yellow hygroscopic powder, mp. 155–157°C. Anal. Calcd. for C₁₄H₁₆O₂N₂:
C, 68.83; H, 6.60; N, 11.74. Found: C, 68.94; H, 6.74; N, 11.59. UV(ethanol),
λmax: 352 nm (ε, 7350). No pmr spectrum could be taken because of its poor
solubility in pmr solvents.

Rate measurements were performed by a Spectrophotometer SM-401, Union
Giken, according to the procedure described in reference (3c) and the redox poten-
tial was obtained by cyanide addition method according to the procedure described
in reference (3b).

REFERENCES