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Author(s)	Baba, Naomichi; Makino, Taketoshi; Oda, Jun'ichi; Inouye, Yuzo
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A Note on the Difference in Reactivity of Dihydrionicotinamide β -D-glucopyranoside and Its Acetylated Form

Naomichi BABA, Taketoshi MAKINO, Jun'ichi ODA, and Yuzo INOUE

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In a previous communication,¹⁾ we reported that D-glucopyranosyl-1,4-dihydrionicotinamide was more reactive in the reduction of 3,3,5-trimethyl-2-cyclohexenylidenepyrrolidinium 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 acetoxy-forms of several sugar pyranosides were prepared and submitted to the reduction of the substrate iminium salt (1) under the same condi-

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

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

* 馬場直道, 牧野武利, 小田順一, 井上雄三: Laboratory of Plant Product Chemistry, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611.

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

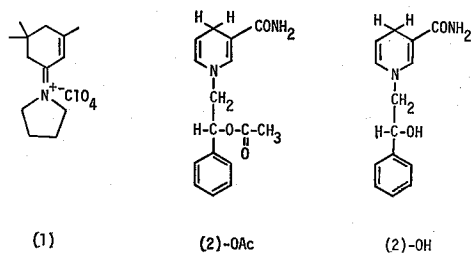


Fig. 1.

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 N_1 (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-dichlorophenol-indophenol 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-glucopyranoside.

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 II. Rate Constants for the Reduction of 2,6-Dichlorophenol-indophenol Sodium Salt Dihydrate*

run	1,4-dihydronicotinamide	k_{obsd} (1./mol.min.)
1	β -D-glucopyranosyl	OAc 4.2
2		OH 9.8
3	β -D-xylopyranosyl	OAc 3.3
4		OH 9.1
5	simple model (2)	OAc 57.1
6		OH 103.3

* 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).

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^{3a)} found that $\text{Log } k_{\text{obsd.}}$ 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-withdrawing 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 D-glucopyranoside (328 nm) with those reported by Wallenfels and Diekmann^{3b)} 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-withdrawer acetoxy group ($\sigma_{\text{inductive}}$, 0.39) lowers the reductive potential toward the substrate more than does the free hydroxyl group ($\sigma_{\text{inductive}}$, 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.⁵⁾

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⁾ 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 $0-5^\circ\text{C}$ 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. $\text{Pmr}(\text{CDCl}_3)\delta(\text{ppm})$: 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 (CDCl_3). δ (ppm): 2.10(3H, s, CH_3), 3.60(2H, d, $J=7.0$ Hz, CH_2), 5.95(1H, t, $J=7.0$ Hz, CH), 7.33(5H, s, phenyl). This *O*-acetyl- β -phenacyl alcohol (11.6 g) and nicotinamide (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, N_1 -(2'-acetoxy-2'-phenylethyl)nicotinamide bromide, was subjected to reduction 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, N_1 -(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 $\text{C}_{16}\text{H}_{18}\text{O}_3\text{N}_2$: C, 67.11; H, 6.34; N, 9.7. Found: C, 67.13; H, 6.25; N, 9.88. UV(ethanol), λ_{max} : 348 nm (ϵ , 7500). Pmr(CDCl_3) δ (ppm): 2.06(3H, s, CH_3), 3.15(2H, dd, two protons at 4 position in pyridine nucleus), 4.50–4.90(4H, m), 5.42(2H, br, s, NH_2), 5.75(1H, br, d, $J=8.0$ Hz), 7.15(1H, br, s), 7.27 (5H, s, phenyl).

N_1 -(2'-Hydroxy-2'-phenylethyl)-1,4-dihydronicotinamide ((2)-OH): (2)-OAc obtained above was deacetylated by ammonia in dry methanol²⁾ to give the title compound as a yellow hygroscopic powder, mp. 155–157°C. Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{N}_2$: C, 68.83; H, 6.60; N, 11.74. Found: C, 68.94; H, 6.74; N, 11.59. UV(ethanol), λ_{max} : 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 potential was obtained by cyanide addition method according to the procedure described in reference (3b).

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