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1-D-Glucopyranosyl-1,4-dihydronicotinamides as Chiral NADH Model and Their Asymmetric Reactions with Prochiral Substrates

Naomichi BABA, Taketoshi MAKINO, Jun'ich ODA, and Yuzo INOUYE

In a series of asymmetric NADH model reactions, we have reported[1] that 1,4-dihydronicotinamide sugar pyranosides and their acetylated forms display marked difference in reactivity and stereochemical outcome of the reduction when 3,3,5-trimethyl-2-cyclohexenylidenepyrrolidinium perchlorate is used as a prochiral substrate. In order to know whether such a difference is characteristic of the substrate itself or not, we examined other prochiral substrates such as trifluoroacetophenone (**1**), α-methylbenzylidenemalononitrile (**2**) and ethyl benzoylformate (**3**).
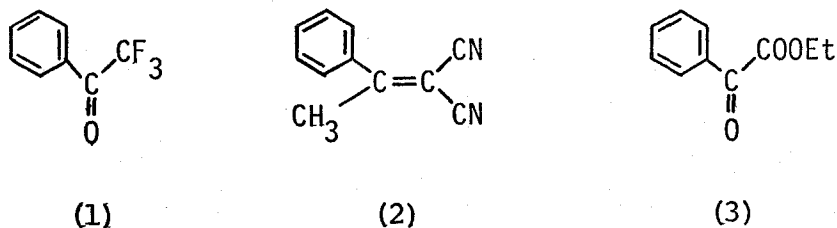

(1)   (2)   (3)

Fig. 1.

As was described in the preceding paper,[2] all the 1,4-dihydronicotinamide sugar pyranosides examined were superior in reactivity toward the α,β-unsaturated iminium salt to their acetylated forms except in the case with α-D-glucopyranoside which afforded comparable yields with both forms. The exceptional results were supposedly attributed to the remarkable hygroscopicity and instability of the OH-form of α-anomer.

Similarly, the tabulated data show that the chemical yield with OH forms of the α-anomer did not exceed that with its OAc-form for the present substrates (**1**)–(**3**). The cause of the difference from the β-anomer has remained obscure, because the reactivity is not always reflected in chemical yields, and kinetic means should be preferred for this purpose.

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Table   Asymmetric Reduction of the Substrates (1)–(3) with OAc- and OH-forms of
1,4-Dihydronicotinamide α- and β-D-glucopyranosides

run[a]	D-glucopyr-anoside	substrate	solvent[b]	chemical yield (%)	$[\alpha]_D^{25}$/°	optical yield (%)	configur-ation
1	β-OAc	1	DMF	50	−0.77	5[d]	S'
2	β-OH	1	DMF	73	+1.20	8	R
3	α-OAc	1	DMF	45	0	0	—
4	α-OH	1	DMF	42	+0.56	4	S
5	β-OAc	2	DMF	48	−1.64[c]	9[e]	S
6	β-OH	2	DMF	63	−1.88[c]	11	S
7	α-OAc	2	DMF	88	−0.19[c]	1	S
8	α-OH	2	DMF	88	−0.66[c]	4	S
9	β-OAc	3	EtOH	45	+3.28	3[f]	S
10	β-OH	3	EtOH	31	+4.68	4	S
11	α-OAc	3	EtOH	37	+24.40	19	S
12	α-OH	3	EtOH	38	+24.84	20	S
13	β-OAc	1	DMF	1.5	—	—	—
14	β-OH	1	DMF	46.8	—	—	—
15	β-OAc	1	NMAA	10.7	—	—	—
16	β-OH	1	NMAA	30.1	—	—	—
17	β-OAc	1	DMSO	7.4	—	—	—
18	β-OH	1	DMSO	53.6	—	—	—
19	β-OAc	1	EG	5.0	—	—	—
20	β-OH	1	EG	15.0	—	—	—

a) Reaction temperature applied was 140°C for runs 1–8 and 13–20, and 62°C for runs 9–12.
Reaction period was 1 hr for runs 5–8 and 13–20, 48 hr for runs 1–4 and 68 hr for runs 9–12.
b) DMF; N,N-dimethylformamide, NMAA: N-metnhylacetamide, EG: ethyleneglycol. c) Optical
rotations at 456 nm.   d) Based on the maximum rotation of (S)-phenyltrifluoromethylcarbonol,
$[\alpha]_D$ 14.76° (benzene) calculated from the data in reference (5).   e) Based on the maximum
rotation of (S)-(α-methylbenzyl)malononitrile, $[\alpha]_{564}^{25}$ −17.52° (95% ethanol) calculated from the
data in reference (6).   f) Based on the reported maximum rotation of (S)-(+)-ethyl mandelate,
$[\alpha]_D^{25}$ 126.2° (chloroform) in reference (7).   g) In runs 13–20, attention was focused only on the
relative reactivity without taking up the sterochemistry here.

On the other hand, with the β-anomer of the glucopyranoside, the OH-form
afforded a considerably higher chemical yield than its OAc-counterpart, as can be
seen from runs 1–2 and 5–6 except for the case with (3).[3]   Particularly for the sub-
strate (1), the OAc- and OH-forms afforded remarkably different chemical yields
even in highly polar protic solvent such as N-methylacetamide, ethylene glycol
and in highly solubilizing solvent such as dimethylsulfoxide for both of the pyran-
oside.

Thus, the difference in reactivity between the two forms originally observed for
the iminium salt was found to emerge also in the present system involving different
substrates, and the mechanism should be similar to that proposed in the preceding
paper.[2]

In view of the stereochemical aspect of the present reduction system, the result
seems to be different from those observed in the asymmetric reduction of an iminium

salt.[1] For this prochiral substrate, the OH- and OAc-forms of sugar pyranosides afforded divergent optical yields and, in some cases, even a reversal of optical rotation was observed. Interestingly, however, for the present substrates (2) and (3), the OAc- and OH-forms of both anomers afforded a comparable enantiomeric excess with the same direction of optical rotation (Chart 1). On the other hand, in view of anomerization in the OH- and OAc-forms respectively, the change of e.e. is significantly enough (Chart 2). Thus, for the substrate (2), both the β-anomers afforded higher e.e. than the α-anomers, whereas with substrate (3), the reversed situation prevailed.
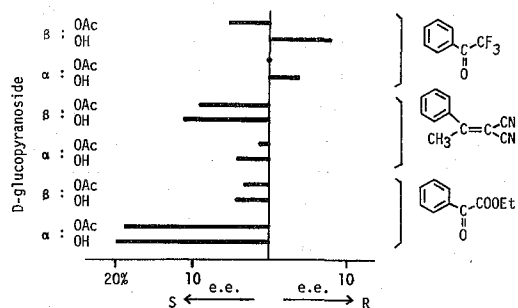

Chart 1. Graphic Representation of the Stereochemical Results Shown in Runs 1–10 in Table.
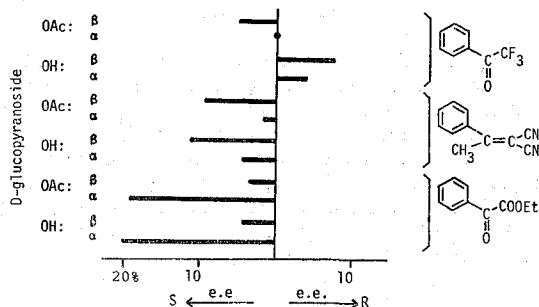

Chart 2. Graphic Representation of the Stereochemical Results Shown in Runs 1–10 in Table

Accordingly, the present study suggests that so far as the present NADH model system is concerned, it seems very likely that the mechanism of asymmetric induction in the substrates (2) and (3) by the chiral centers during the course of the simultaneous hydrogen transfer is different from that being operative in case with 3,3,5-trimethyl-2-cyclohexenylidenepyrrolidinium perchlorate.

MATERIAL AND METHOD

Trifluoroacetophenone was prepared according to the method by Dishart and Livine[8] and purified through sodium hydrogen sulfite adduct. α-Methylbenzylidenemalononitrile was prepared according to Mowry.[9] Optical rotations were

measured with a Perkin-Elmer 241 polarimeter and preparative v.p.c. was performed on a Varian Aerograph Model 920 with aluminum column (3 m) packed with 15 % Apiezone at 175°C or 210°C.

For asymmetric reduction of ethyl benzoylformate, equimolar amount of magnesium perchlorate was used as catalyst.[10]

Isolation procedures for the reduction products are as follows: Phenyltrifluoromethylcarbinol was extracted several times with ether from the reaction mixture after quenching with water. The ether solution was dried over anhydrous sodium sulfate and the carbinol was isolated by preparative v.p.c. The reaction mixture of α-methylbenzylidenemalononitrile was quenched with 4N-ethanolic hydrogen chloride after addition of benzene. The product was extracted with ether three times after addition of water. The ether solution was decolorized with charcoal and concentrated, and the pure malononitrile was isolated by preparative v.p.c. Ethyl mandelate was extracted four times with methylene chloride from the reaction mixture after quenching with water. The solution was dried over anhydrous sodium sulfate and concentrated. The concentrate was chromatographed by preparative t.l.c developing with benzene and pure mandelate was extracted with chloroform from the t.l.c plate.

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(3) The values in runs 9 and 10 do not represent true chemical yield because of the partial insolubility of the glucopyranosides in ethanol which was used here as the solvent of choice.
(4) Stereochemical outcome (runs 1–4) involving configurational reversal of the reduction products for the substrate (1) with the both forms of the β-D-glucopyranoside is inconsistent with the trend observed for the other substrate.
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