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Highly reactive and stereospecific reaction of quinoline-type NADH model compounds with methyl benzoylformate

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Abstract

NADH model compounds with a dihydroquinoline ring can reduce methyl benzoylformate with very high reactivity and stereospecificity. Chiral column HPLC is effective in the separation and analysis of enantiomers of NADH and NAD model compounds, respectively.

Keywords: NADH model; NAD model; axial chirality; HPLC; optical resolution.

The elucidation of the origin of A/B face specificity of the nicotinamide coenzyme in dehydrogenase is an exciting field in biological chemistry.[1,2] In one interesting explanation of this specificity, it has been demonstrated that the orientation of the carbamoyl oxygen in the nicotinamide coenzyme governs the reactivity of the hydrogen atom in the hydride transfer reaction.[3] We and other chemists have attempted to account for this reactivity through calculation or model studies.[4–8] Vekemans et al. have synthesized 1,2,4,*N*,*N*-pentamethyl-1,4-dihydronicotinamide as a simple NADH model and studied its reaction with methyl benzoylformate.[7] However, this model compound is too reactive at room temperature to exert satisfactory stereospecificity. Here we describe preliminary studies using novel quinoline-type NADH model compounds with simple structures: 3-*N*,*N*-dimethylcarbamoyl-1,2,4-trimethyl-1,4-dihydroquinoline (**1a**) and 3-piperidinylcarbonyl-1,2,4-trimethyl-1,4-dihydroquinoline (**1b**) (Fig. 1). These compounds undergo highly stereospecific reaction at room temperature.

NAD model compounds, 3-*N*,*N*-dialkylcarbamoyl-1,2,4-trimethylquinolinium iodide (**2**) were prepared from 2,4-dimethylquinoline-3-carboxylic acid[4] by the procedure shown in Scheme 1 (WSC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt: 1-hydroxy-1*H*-benzotriazole). Chiral HPLC analysis (column: Daicel Chiralcel OD®, eluent: *n*-hexane/*i*-PrOH=7/3 with 0.1% diethylamine) revealed that these compounds have axial chirality with respect to the carbamoyl orientation, and the enantiomer pairs exist with considerable stability. The racemic compounds **3a** and **3b** could be preparatively separated by

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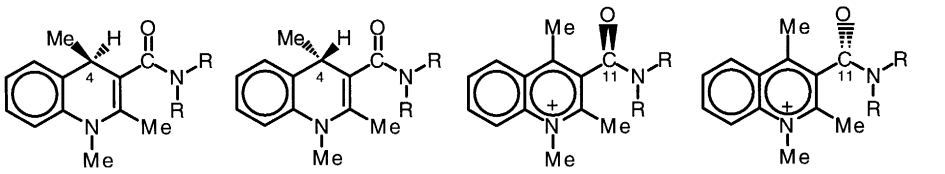
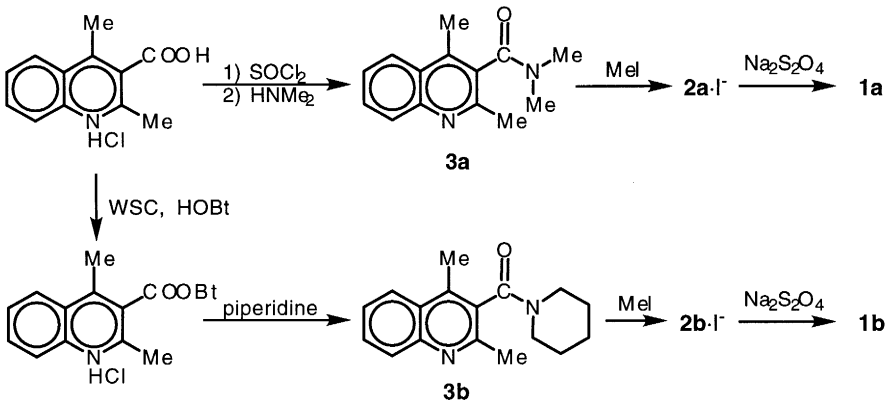


Fig. 1. Structures of NAD and NADH model compounds

HPLC into their enantiomers, but no preparative separation was achieved for the racemic pairs **2a** and **2b**.



Scheme 1.

The 1,4-reductions of compounds **2a** and **2b** were performed in 80–90% yield by sodium hydrosulfite in an aqueous sodium bicarbonate/dichloromethane biphasic mixture (Scheme 1).[9] The corresponding pyridine compounds resisted this reduction, although a similar reduction had been reported earlier.[7,10]

The separations of enantiomers **1a** and **1b** were successfully performed by HPLC (column: Daicel Chiralcel OD® (2 cmϕ×25 cm), eluent: *n*-hexane/*i*-PrOH=20/1 for **1a**; 9/1 for **1b**).

In our earlier studies, the chiral separation of the 3–*N*,*N*–dialkylcarbamoyl-1,2,4-trimethyl-1,4-dihydroquinoline systems modified at the 4-position had been performed by recrystallization from a diastereomer mixture of the crystalline precursor using a chiral auxiliary in the side chain.[4] The present compounds are the first quinoline-type NADH models in which *enantiomer pairs* are well resolved. The absolute configurations of these NADH model compounds were assigned by the comparison of their CD spectra (Fig. 2) with those of previous compounds.[7,11]

The asymmetric reduction of methyl benzoylformate with these chiral NADH model compounds was performed. When an equimolar amount of methyl benzoylformate was added to an acetonitrile-d_3 solution of **1** and 1 equiv. of magnesium perchlorate, the reaction was completed within 5 min as evidenced by ^{1}H NMR measurement. The reaction proceeds only in the presence of magnesium ion. Judging from GC analysis of the product (column: CP-cyclodextrin-B-236-M-19 (Chrompack®), 25 m×0.25 mm i.d.), methyl mandelate (80–93% isolated yield) was obtained in excellent stereospecificity (Table 1), and the configuration of the product was identical with previous studies.[4,7,9] (*R*)-**1** Affords (*R*)-mandelate and vice versa. The moderate reactivity of the quinoline ring system generated a stable ternary complex in the transition state even in room temperature reactions.

The NAD model compounds obtained from these reactions are also stereospecific. The determination of absolute configurations of these compounds was not straightforward because CD measurements are not

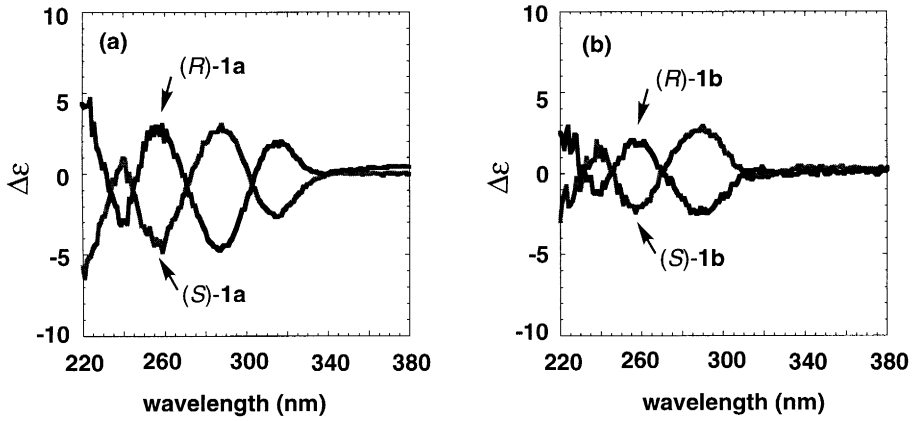


Fig. 2. CD spectra of **1a** (a) and **1b** (b) in EtOH

Table 1
Asymmetric reduction of methyl benzoylformate with NADH models (**1**)

NADH Models	Methyl Manderate Config.	ee	**2** Config.	ee
(*R*)-**1a**	*R*	(71±5)%	*S*	>99%
(*S*)-**1a**	*S*	>99%	*R*	>99%
(*R*)-**1b**	*R*	>99%	*S*	>99%
(*S*)-**1b**	*S*	(98±1)%	*R*	>99%

applicable in these compounds.[7] In this study, configurations were determined by HPLC retention time. As above, the quinolinium racemates separated into two peaks by HPLC when the case eluent contains 0.1% diethylamine. When diastereomer pairs **4** (Fig. 3) which have known carbonyl configurations[12] were subjected to HPLC analysis with same column, the *R*-isomer eluted earlier than *S*-isomer in both cases. Thus, we assigned the configuration of the earlier eluted enantiomer of compound **2** as the *R*-isomer. This assignment is reasonable because a similar interaction is expected in quinoline and pyridine model compounds toward the HPLC column. Also, in light of the reaction mechanism of **1** with methyl benzoylformate,[7,11] this assignment should be correct.

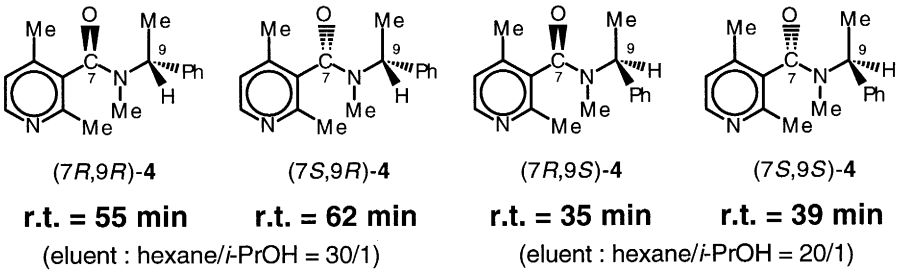


Fig. 3. Configuration and HPLC retention time of pyridine derivative

In this study, we synthesized quinoline-type NADH model compounds with simple structures that have high reactivity and selectivity. In addition, we have determined the enantiomer ratio of NAD model compounds with axial chirality by HPLC analysis in a precise and convenient manner. This procedure

would be easily applicable to the other NAD/NADH model compounds. Detailed studies of the reaction of **1** with other substrates as well as the reduction of **2** with several reducing agents are now under investigation.

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9. Selected data for **1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.20 (d, J=6.6 Hz, 3H, 4-Me), 1.99 (s, 3H, 2-Me), 3.02 (s, 6H, N-Me), 3.22 (s, 3H, N-Me), 3.56 (br., 1H, 4-H), 6.84 (br. d, 1H, J=7.8 Hz, ArH), 6.92 (m, 1H, ArH), 7.08 (dd, 1H, J=1.5, 7.8 Hz, ArH), 7.19 (m, 1H, ArH). ESI-MS: *m/z* 229 $[M-Me]^+$, 243 $[M-H]^+$, 245 $[M+H]^+$, 267 $[M+Na]^+$, 490 $[2M+H]^+$, 512 $[2M+Na]^+$, 755 $[3M+Na]^+$. For **1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.20 (d, J=6.6 Hz, 3H, 4-Me), 1.5–1.8 (m, 6H, -CH_2-), 2.00 (s, 3H, 2-Me), 3.20 (s, 3H, N-Me), 3.4–3.8 (m, 5H, –CH_2−+4-H), 6.80 (br. d, 1H, J=7.8 Hz, ArH), 6.90 (m, 1H, ArH), 7.05 (br. d, 1H, J=7.8 Hz, ArH), 7.20 (m, 1H, ArH). ESI-MS: *m/z* 269 $[M-Me]^+$, 283 $[M-H]^+$, 285 $[M+H]^+$, 307 $[M+Na]^+$, 570 $[2M+H]^+$, 592 $[2M+Na]^+$, 875 $[3M+Na]^+$.
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