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Unusual Temperature Dependence of Enantioselectivity in Asymmetric Reductions by Chiral NADH Models

Ryota Saito,*,† Shoichiro Naruse,† Koji Takano,† Keiko Fukuda,† Akira Katoh,† and Yoshihisa Inoue*,‡,§

Department of Materials and Life Science, Seikei University, 3-3-1 Kichijoji-kitamachi, Musashino 180-8633, Japan, Entropy Control Project, ICORP, JST, Kamishinden, Toyonaka 560-0085, Japan, and Department of Applied Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan

rsaito@st.seikei.ac.jp

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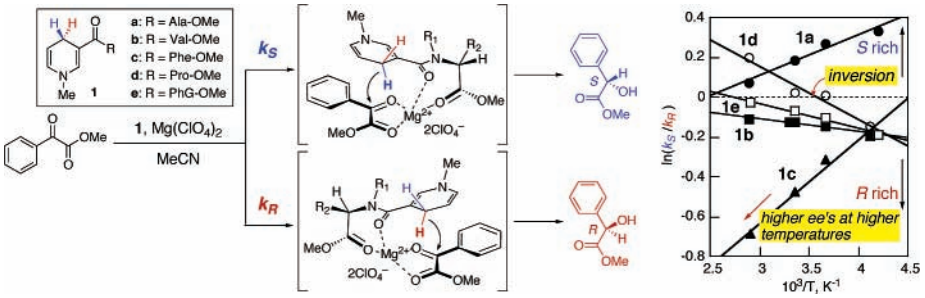
ABSTRACT



Unusual stereoselectivity changes, i.e., enhancement and inversion of enantioselectivity with increasing temperature, were observed in the asymmetric reduction of methyl benzoylformate with chiral 1,4-dihydropyridines possessing amino acid residues as ligating chiral auxiliaries. The differential activation parameters, $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$, obtained from the Eyring plots demonstrate that the entropy term controls the enantiodifferentiating step, accounting for the observed unique temperature dependencies.

1,4-Dihydropyridines are known to be the active part of the reduced form of the nicotinamide adenine dinucleotide (NADH), which plays a vital role in many biological reductions through the transfer of a hydride or two electrons plus one proton to a substrate bound to an enzyme in living systems.[1] Since the first demonstration of the stereoselective reduction of ethyl benzoylformate with an NADH model possessing a chiral carboxamide at C3,[2] a variety of 1,4-dihydropyridine derivatives have been synthesized and examined as chiral reducing agents for activated carbonyl compounds (such as α-ketoesters) to mimic the highly stereoselective bioreductions and consequently apply them to synthetic organic chemistry.[3−13]

These studies demonstrated that a magnesium ion plays a major role in the reduction of activated ketones with NADH models through the formation of a transient "ternary" complex with an NADH model and a substrate (Figure 1)[4,5] and that the enantiomeric excess of the reduction product can be enhanced by blocking one of the two enantiotopic hydrogens at C4 or by locking the dihydropyridine conformation by bridging its C2 and C3,[10,11] C3 and C5,[3] or N1 and C3[12] positions. Earlier studies also revealed that the simple alteration of an *achiral* moiety of the chiral 1,4-dihydropyridines, possessing a natural amino acid or amino alcohol residue, can switch the chiral sense of the product.[3,8] Similarly, a 1,3-cyclic NADH model and the corresponding

† Seikei University.
‡ Entropy Control Project.
§ Osaka University.

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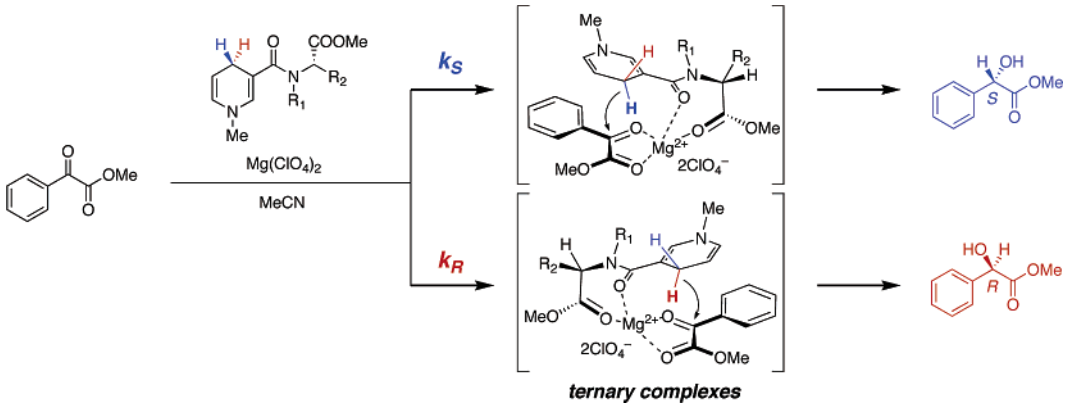


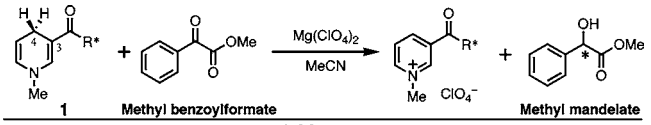
Figure 1. Schematic illustration of the proposed ternary complexes (or the transition states) involved in the asymmetric reduction of α-ketoesters with chiral 1,4-dihydronicotinamides.

open-chain analogue afford (*R*)- and (*S*)-products, respectively, upon reduction of methyl benzoylformate.[12] Clearly, the conformational changes, caused by varying the achiral moiety or disconnecting the bridge, are suspected to be responsible for such switching of the product's chirality. However, its origin and the factors and mechanism controlling this intriguing and potentially useful phenomenon remain unanswered. We wish now to report the results of our examinations of the temperature effect on the enantiodifferentiating reduction of methyl benzoylformate with simple NADH models, **1a**−**d**, containing amino acid residues as chiral auxiliaries (Table 1). This study will reveal the origin of the chirality inversion and the role of entropy in this biomimetic enantiodifferentiating process and will propose the possibility of enantioselectivity manipulation by reaction temperature.

1,4-Dihydronicotinamides (**1**) possessing an amino acid residue (i.e., methyl esters of L-alanine, L-valine, L-phenylalanine, L-proline, and (*S*)-phenylglycine) were synthesized by reduction of the corresponding pyridinium salts, which were synthesized by reacting nicotinyl chloride hydrochloride with the corresponding amino acid methyl esters in the presence of triethylamine and the subsequent N-methylation with iodomethane.[12]

We performed the asymmetric reduction of methyl benzoylformate (0.2 mmol) with **1a**−**d** (0.2 mmol) under an argon atmosphere in the presence of anhydrous magnesium perchlorate (0.2 mmol)[12,13] in dehydrated acetonitrile (4.0 mL) over a temperature range of −35 to 72 °C. Gas chromatographic (GC) analysis of the reaction mixture after workup showed that only the reduction of the ketoester proceeded to give chiral methyl mandelate in moderate to excellent chemical yields, which were not completely

Table 1. Results and Activation Parameters for the Asymmetric Reduction of Methyl Benzoylformate with the Enantiopure NADH Models **1a**−**e** in Acetonitrile in the Presence of Magnesium Ions at Various Temperatures



Model	R*	temp. (°C)	yield (%)	ee (%)[a]	config.	$\Delta\Delta H^{\ddagger}_{S-R}$[b]	$\Delta\Delta S^{\ddagger}_{S-R}$[b]
1a	(-Ala-OMe)	−35	39	+16.5	*S*-(+)	−0.40	−1.07
		0	>99	+13.4	*S*-(+)		
		25	>99	+9.0	*S*-(+)		
		72	>99	+3.6	*S*-(+)		
1b	(-Val-OMe)	−30	59	−9.4	*R*-(−)	+0.13	+0.16
		0	48	−7.4	*R*-(−)		
		25	79	−6.4	*R*-(−)		
		72	81	−5.6	*R*-(−)		
1c	(-Phe-OMe)	−30	51	−9.8	*R*-(−)	−0.83	−3.75
		0	90	−15.7	*R*-(−)		
		25	>99	−23.3	*R*-(−)		
		70	>99	−33.2	*R*-(−)		
1d	(-Pro-OMe)	−30	85	−7.2	*R*-(−)	+0.53	+1.89
		0	39	+0.3	*S*-(+)		
		25	94	+1.2	*S*-(+)		
		72	51	+9.8	*S*-(+)		
1e	(-PhG-OMe)	−35	90	−9.4	*R*-(−)	+0.25	+0.67
		0	>99	−5.2	*R*-(−)		
		25	>99	−3.5	*R*-(−)		
		70	>99	−1.5	*R*-(−)		

[a] The positive sign of the ee indicates the predominant formation of the *S*-(+)-isomer. [b] From eqs 1 and 2. $\Delta\Delta H^{\ddagger}_{S-R}$ given in kcal mol^{-1}; $\Delta\Delta S^{\ddagger}_{S-R}$ given in cal mol^{-1}.

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optimized. The enantiomeric excess (ee) of the product was determined by chiral HPLC analysis.[12] Control experiments revealed that the enantiomeric methyl mandelate does not racemize under the employed reaction conditions even at 72 °C.

The temperature effects on the product's ee are illustrated in Figure 2, where the natural logarithm of the relative rate

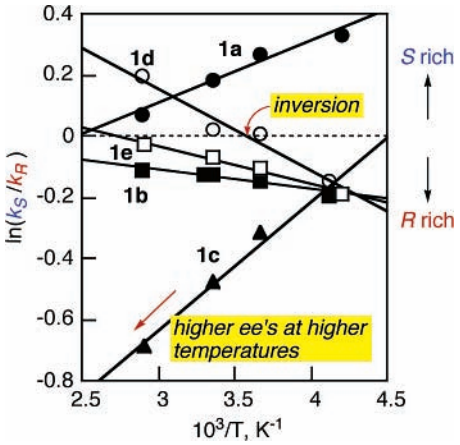

Figure 2. Temperature dependence of the enantioselectivity in the asymmetric reduction of methyl benzoylformate with **1a** (closed circle; r (correlation coefficient) = 0.983), **1b** (closed square; r = 0.973), **1c** (closed triangle; r = 0.989), **1d** (open circle; r = 0.980), and **1e** (open square; r = 0.990).

constant for the formation of (*S*)-(+)- and (*R*)-(−)-methyl mandelate, i.e., the $\ln(k_S/k_R)$ value calculated by eq 1,[14] is plotted as a function of the reciprocal temperature to give a good straight line in each case. When the reduction was conducted with **1a** (R = Ala-OMe), (*S*)-methyl mandelate was predominantly obtained, whereas the reduction with **1b** (Val-OMe) and **1e** (PhG-OMe) gave the (*R*)-enantiomer (at least in the temperature range employed). This clearly demonstrates that the achiral substituent at the stereogenic center significantly affects the stereochemical outcome of the asymmetric reduction and can cause the inversion of the product's chirality, as revealed by simply replacing the methyl in **1a** with isopropyl (**1b**) or phenyl (**1e**) which leads to the inversion of the product's chirality. It is also noteworthy that the product's ee is improved not by lowering but by raising the temperature, as can be seen with **1c** (Phe-OMe) in the temperature range employed. Of particular interest is the discovery that the major enantiomer produced with **1d** (Pro-OMe) is switched from (*R*)- to (*S*)-methyl mandelate at around 0 °C, and thereafter, the ee continues to increase as the temperature is further elevated. It should be emphasized that the enantiodifferentiation mechanism is unchanged over the whole temperature range in the present system because, in each case, all the plots fit to a single straight line over the temperature range.[15]

$$\ln(k_S/k_R) = \ln[(100 + \%\ ee)/(100 - \%\ ee)] \quad (1)$$

$$\ln(k_S/k_R) = \Delta\Delta S^{\ddagger}_{S-R}/R - \Delta\Delta H^{\ddagger}_{S-R}/RT \quad (2)$$

As can be seen from the differential Eyring equation (eq 2),[14−16] the enantioselectivity in an asymmetric reaction is determined in general by a balance of the enthalpy and entropy terms. The unique temperature dependence profiles obtained with **1c** and **1d** (and anticipated for the other NADH models) imply that not only the enthalpic but also the entropic contributions are significant in the enantiodifferentiating reduction step of this reaction, as was the case with the other photochemical and catalytic asymmetric reactions reported previously.[14−17]

To understand the nature of the present temperature effect, the differential activation enthalpy ($\Delta\Delta H^{\ddagger}_{S-R} = \Delta\Delta H^{\ddagger}_S - \Delta\Delta H^{\ddagger}_R$) and entropy ($\Delta\Delta S^{\ddagger}_{S-R} = \Delta\Delta S^{\ddagger}_S - \Delta\Delta S^{\ddagger}_R$) values were calculated by applying eq 2 to the plots in Figure 2. As shown in Table 1, the $\Delta\Delta S^{\ddagger}_{S-R}$ values are not equal to zero. Especially, the $\Delta\Delta S^{\ddagger}_{S-R}$ values for **1c** (−3.75 cal/mol) and **1d** (+1.89 cal/mol) are comparably large to those observed in the enantiodifferentiating photoisomerization of cyclooctene.[17] These large $\Delta\Delta S^{\ddagger}_{S-R}$ values are thought to be due to large activation volume variations caused by the broader movement sphere of the benzyl group (for **1c**) and the flipping action of the pyrrolidine ring (for **1d**). Moreover, the $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ values were found to have the same sign. These factors are jointly responsible for the unique temperature-dependent ee changes, i.e., the switching of the product's chirality at certain temperatures and the ee enhancement at higher temperatures.[14,17]

Ohno et al. previously proved the significant contribution made by the entropy term in the asymmetric reduction with simple NADH models.[18] However, they employed inherently chiral 4-substituted NADH models possessing a methyl at C4, and the asymmetric reduction of benzoquinones was conducted in the absence of the magnesium ion. Our present study provides the first example of the entropy-controlled asymmetric reduction with NADH models, which do not carry a stereogenic center at the C4 but form a ternary complex with the substrate organized by the magnesium ion, thus constituting one of the simplest biomimetic asymmetric reduction systems using 1,4-dihydronicotinamides. Moreover, the present study provides the first example of chirality inversion instigated by the reaction temperature in a biomimetic reduction. Product-chirality switching phenomena caused by temperature have recently been reported for chiral photochemical reactions[14,16,19] and less frequently for thermal reactions, such as desymmetrization with chiral organotin catalysts[15] and the enzymatic kinetic resolution of racemic secondary alcohols,[20] but the same phenomenon has never been observed in a biomimetic reduction.

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For a global view of the present asymmetric reduction system, we examined whether the enthalpy−entropy compensation relationship holds. In Figure 3, the obtained

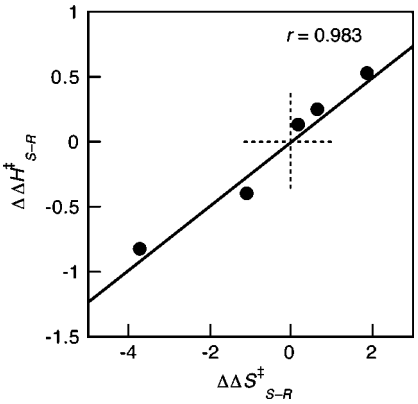

Figure 3. Enthalpy−entropy compensation plot for the differential activation parameters obtained in the asymmetric reduction of methyl benzoylformate with 1,4-dihydropyridines (**1a**−**e**).

$\Delta\Delta S^{\ddagger}_{S-R}$ values are plotted against the $\Delta\Delta H^{\ddagger}_{S-R}$ values. Interestingly, all of the data points fit well to a single straight line with a correlation coefficient of 0.983. The slope of this line gives an isokinetic, or isoenantiodifferentiating, temperature of −27 °C. These results confirm that the enantiodifferentiating mechanism is not altered by changing the chiral auxiliary, even though a chirality switching by temperature variation is observed.

According to mechanistic investigations of the enantiodifferentiating photoreactions, the chirality inversion phenomenon is associated with the intervention of a conformationally flexible excited-state complex (exciplex), where several weak interactions are involved to retain the structural integrity of the diastereomeric exciplex structure.[14,19] In the present system, the ternary complex composed of the NADH model, the magnesium ion, and the substrate is in a very similar situation, involving weak ligation of multiple carbonyls to the magnesium ion. As a consequence of the conformational flexibility of the ternary complex, arising from the weak interactions, the enantiodifferentiating hydride transfer is thought to be sensitive to the temperature changes.

In conclusion, we have shown that the product chirality can be inverted by simply changing the reaction temperature and further that the product's ee increases with increasing temperature. These apparently unusual phenomena were analyzed by the differential Eyring equation (eq 2) to show the crucial contributions of the same-sign enthalpic and entropic terms, which are balanced depending on the reaction temperature. Thus, the product's chirality is determined by the enthalpy term at low temperatures. As the temperature increases, the relative contribution of the enthalpy to the differential activation free energy, or the product's ee, decreases as it reaches the critical racemic point, where $\Delta\Delta S^{\ddagger}_{S-R}/R = \Delta\Delta H^{\ddagger}_{S-R}/RT$ in eq 2, and thereafter, the product's chirality is dominated by the entropy term to give the product with the opposite ee increasing with increasing temperature. Judging from the similar phenomena found already for several asymmetric reactions in the ground and excited states, we may conclude that the origin of such dramatic switching behavior is the difference in conformational flexibility of the diastereomeric transition states involved. We may further propose a new general strategy for controlling chiral reactions utilizing conformational flexibility and other entropy-related factors, which is an alternative approach to the conventional strategy of constructing a rather rigid, structured framework around the reaction center.

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Supporting Information Available: Experimental procedures and spectroscopic data for the NADH models. This material is available free of charge via the Internet at http://pubs.acs.org.

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