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Carbonyl Orientation Determines Regio- and Enantioselectivity in 1,2-/1,4-Reduction of an NAD Model Compound

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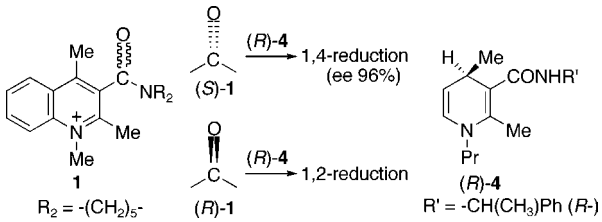
ABSTRACT



An optically active, axially chiral NAD model compound(1) with a quinoline ring system was reduced by the chiral NADH model compound (4), affording a mixture of 1,2- and 1,4-dihydroquinolines. The carbonyl orientation governs the molecular arrangement in the transition state of the reaction and determines the regio- and enantioselectivity of the product.

Stereoselective reductions using chiral NADH model compounds are some of the most extensively studied reactions related to biomimetic molecular transformations.[1] Although a large amount of work deals with asymmetric reduction by chiral NADH model compounds, face-selective reduction of (chiral) NAD models has been somehow limited.[2−8] This reaction often affords mixtures of 1,2-, 1,4-, and 1,6-isomers. In general, hydride reductants such as sodium borohydride afford 1,2- or 1,6- isomers, while sodium hydrosulfite or NADH model compounds give 1,4-isomers predominantly,[9,10] although some exceptions have been reported.[8]

It is known that the carboxamide group at the 3-position of the nicotinamide ring in enzyme-bound NADH is about 30° out of the plane of the nicotinamide ring.[11] In model systems, the carbonyl orientation also plays an important role for the selectivity of the reaction face.[3−5,8,12] In this communication, we report the first example of the regio- and stereoselective reduction of an NAD model compound controlled by the carbonyl orientation, using 3-piperidinylcarbonyl-1,2,4-trimethylquinolinium ion (**1**) as an NAD model compound with axial chirality on the carbonyl group.

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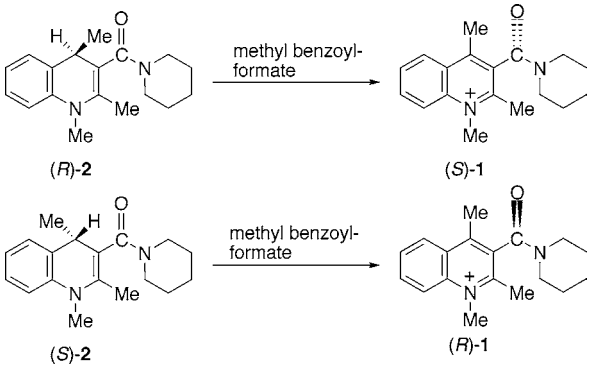
Scheme 1



Optically active **1** (ee > 95%) was prepared by the oxidation of enantiomerically pure parent NADH model compound **2**[13,14] with methyl benzoylformate (Scheme 1). In this reaction, (*R*)-**2** affords (*S*)-**1**, while (*S*)-**2** affords (*R*)-**1** in a stereospecific manner.[13] Due to the carbonyl rotation, it was very difficult to isolate **1** in enantiomerically pure form; however, ee > 95% was confirmed by HPLC analysis for both enantiomers of **1** obtained in ~100 mg scale.

Thus, **1** was then reacted with the chiral NADH model compound, (*R*)- and (*S*)-**4** (Me_2PNPH, 2,4-dimethyl-3-(*N*-α-methylbenzylcarbamoyl)-1-propyl-1,4-dihydropyridine),[15] in acetonitrile at room temperature in the dark for 36 h, at which time the reaction was judged to be complete by ^{1}H NMR. Products of the reaction were analyzed by ^{1}H NMR and HPLC (Figures S1 and S2, Supporting Information), affording the 1,4-/1,2-isomer ratio (**2**/**3**) and enantiomer ratio in **2** ((*R*)-**2**/(*S*)-**2**), respectively. Results are summarized in Table 1.[16,17]

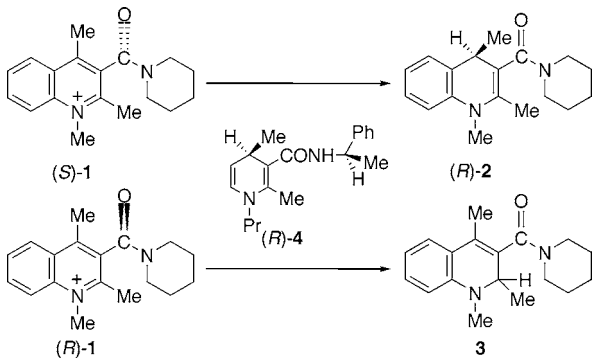
Table 1. Reduction of **1** with **4**

		product ratio[b]	
configuration of **1**[a]	configuration of **4**	**2**:**3**	(*R*)-**2**:(*S*)-**2**
R	R	31:69	71:29
R	S	78:22	2:98
S	R	83:17	98:2
S	S	28:72	34:66

[a] Enantiomeric purity of the starting materials was >95%. [b] Errors were estimated within 5% from the standard deviations derived from at least three independent experiments.

In Table 1, the product ratio of **2**/**3** reveals the regioselectivity of the 1,4-/1,2-reduction, whereas the enantiomer ratio in **2** ((*R*)-**2**/(*S*)-**2**) reflects the stereo- (face) selectivity of the 1,4-reduction. Since the enantiomers of **3** could not be separated by HPLC in all conditions tested, the face selectivity for the 1,2-reduction could not be determined. In the reaction of (*S*)-**1** with (*R*)-**4**, 1,4-reduction occurs predominantly, and (*R*)-**2** was obtained in a 98/2 enantiomeric ratio. On the other hand, 1,2-reduction is the main reaction when (*R*)-**1** is employed with the same reducing agent. The only difference in these two reactions is the orientation of the carbonyl group in starting material **1**; thus, the carbonyl dipole controls the regio- and stereoselectivity of the reaction (Scheme 2).

Scheme 2



To understand the selectivity of this reaction, all possible molecular arrangements in the transition state should be considered (Figure 1). There are three major factors to be accounted for the reaction of **1** with **4**: (i) syn/anti arrangement of the carbonyl group in **1** with respect to the reaction face, (ii) cis/trans arrangement between two carboxamide groups in **1** and **4**, and (iii) parallel/antiparallel arrangement with respect to the ring nitrogen orientation between **1** and **4** in the $\pi-\pi$ stacking interaction.

These parameteters differentiate eight ($=2^3$) possible molecular arrangements as shown in Figure 1, where only *re*-face reactions are depicted.

Both theoretical[18−21] and experimental[8,12,13,22,23] results have demonstrated that syn orientation where the carbonyl oxygen points to the transferring hydrogen has lower energy than an anti-orientated transition state. One reason for this stabilization is considered to be the electrostatic attraction between the amide oxygen and the partially positively charged hydride acceptor.[19,21] Partial enolization by the intramolecular hydrogen atom transfer in the radical cation of NADH model compounds might be additional support of the carbonyl effect.[24,25] These electronic effects of the

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(16) Reduction of **1** with sodium hydrosulfite afforded exclusively **2** (with low enantioselectivity), whereas sodium borohydride gave **3** as a sole product.
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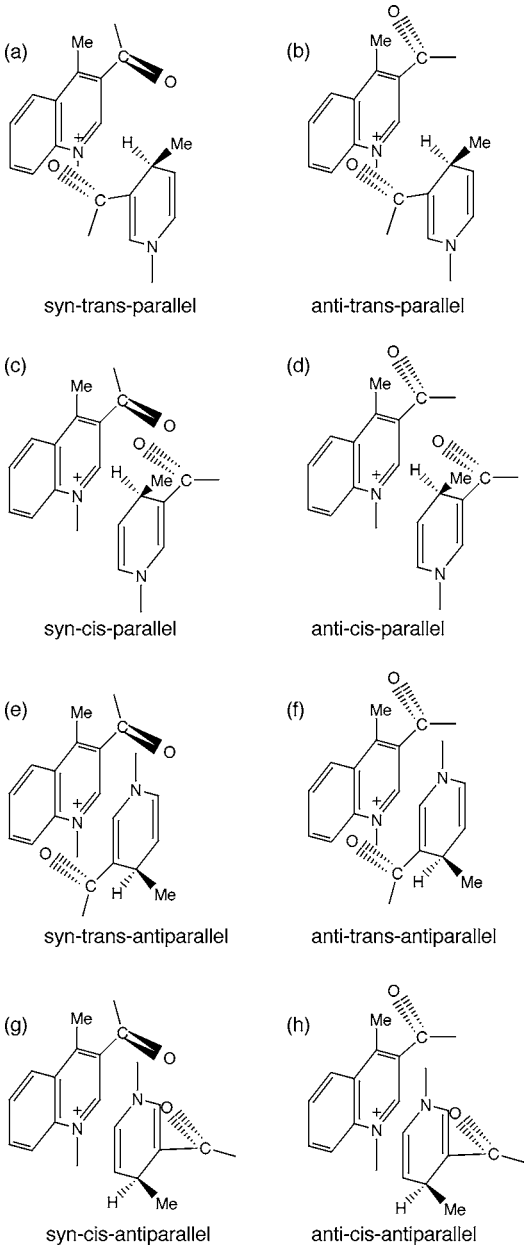

Figure 1. Molecular arrangements in the transition state of the reaction of **1** with **4**. Only *re*-face reaction is depicted.

carbonyl group are important for both NAD (hydride acceptor) and NADH (hydride donor) model compounds. In such a double-carbonyl system, a cis arrangement where two carbonyl groups are sterically hindered seems to be avoided especially in the parallel orientation (Figures 1c and 1d). Although several reactions with neutral substrates adopt cis arrangements,[26,27] it is reasonable to expect that the trans arrangement for two carbonyl groups in the transition state has lower energy than the cis arrangement for the present system. There are several examples discussing the parallel/antiparallel arrangement with respect to the orientation of the heterocyclic ring in $\pi-\pi$ stacking interaction.[3−5] The puckered structure of a dihydropyridine ring in the transition state[7,20] may stabilize the parallel arrangement. The nitrogen lone pair of NADH model compounds, oriented to the same face to the transferring axial hydrogen atom at the 4-position (i.e., reaction face), would interact with the positively charged quinolinium nitrogen, making the parallel orientation preferred. A theoretical investigation into endo/exo arrangements in 1,4-reduction also supports that an endo or a $\pi-\pi$ overlapped transition state is more stable than an exo arrangement.[19] Taking the relevance of this stacking interaction into account, it is reasonable to assume that 1,2-reduction in the present reaction proceeds through antiparallel arrangement, where a stacking interaction is preserved.

Considering the reaction of (*S*)-**1** with (*R*)-**4**, the molecular configuration in the transition state is expected to be a syn-trans-parallel arrangement (*mirror image* of Figure 1a). This is considered to be the most stable transition state arrangement, on the basis of the above criteria. The strong (*R*)-preference in product **2** is the result of a strict syn face preference in the transition state, leading to 1,4-reduction.

On the other hand, the major product was **3** in the reaction of (*R*)-**1** with (*R*)-**4**. Although we do not know the face selectivity in **3** at present, as mentioned above, we can speculate on the molecular arrangement in the transition state of this reaction. Assuming that 1,2-reduction proceeds with an antiparallel arrangement as discussed above, the only possible arrangement in the transition state leading to 1,2-reduction would be syn-trans-antiparallel (Figure 1e). Thus, we estimate the stereochemistry of **3** obtained in the reaction of (*R*)-**1** with (*R*)-**4** to be predominantly (*S*)-configuration (syn attack). In this reaction, interestingly, the face selectivity for 1,4-reduction also decreased significantly. The molecular arrangement for 1,4-reduction would be anti-trans-parallel for the (*R*)-product (*mirror image* of Figure 1b) and syn-cis-parallel for the (*S*)-product (Figure 1c). The observed small preference for the (*R*)-product indicates that trans preference for the arrangement of two carboxamide groups would be the dominant factor over the syn/anti orientation of the carbonyl group in **1**.

In summary, the carbonyl orientation of NAD model compound **1** plays an important role for determination of the regio- and enantioselectivity of the reaction. The relative importance of the controlling factors of molecular arrangement in the transition state of the reaction is estimated to be as follows: cis/trans arrangement for the carboxamide groups > syn/anti orientation of carbonyl oxygen > parallel/antiparallel arrangement of heteroaromatic rings, with the syn-trans-parallel arrangement as the most preferred one. These results provide not only a new understanding of the reactivity of NAD model compounds toward 1,2-/1,4-

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reduction but also a possibility for the undefined role of the carboxamide group of the NAD coenzyme itself.

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Supporting Information Available: Experimental procedure and ^{1}H NMR and HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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