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Diastereoface-Differentiating Reactions in a New Type of Enzyme Bound 5-Deazaflavin Model

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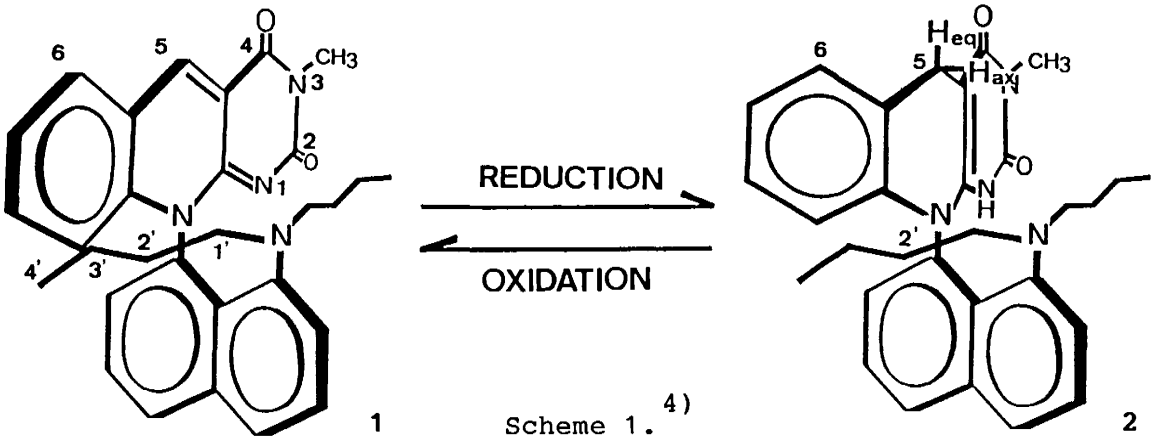
In a new type of enzyme bound 5-deazaflavin model (**1**), hydrogen incorporation occurred exclusively at the pseudo-equatorial position at C(5) in the reduced product. In hydrocyanation of **1**, cyano group occupied both the equatorial and the axial positions depending on the experimental conditions employed. Consideration of bent conformations of the reduced or addition products explains these results.

Recently, we developed 5-deazaflavin (**1**) with both axial and planar chirality as a new type of enzyme bound 5-deazaflavin model.[1] In **1**, the N, N-dibutylamino group ("alkyl chain wall") will cover one face of 5-deazaflavin molecule and effectively inhibit the substrate access, which may lead to high degree of diastereoface-differentiating reactions[2,3] characteristic of enzymatic systems. The present paper reports stereochemical reactivity of this new model compound through the studies of diastereoface-differentiating reactions.

In ^{1}H-NMR spectrum of **1**, geminally coupled peaks were given for the C(2') methylene protons in a rather higher magnetic field, whereas the peaks were coalesced in a usual magnetic field in **2**, which was given in the reduction of **1** with $NaBH_4$. This clearly indicates that the benzene ring of



1 Scheme 1.[4] **2**

5-deazaflavin locates nearly over the protons at C(2') in **1**, in contrast, resides apart from those in **2**. Furthermore, the peaks for the two protons at C(5) in **2** appear as a double doublet (Fig. 1(a)) and different NOESY spectra[3] were observed between each doublet and the peaks for the proton at C(6); a stronger N.O.E. was observed for the doublet in the lower magnetic field than that for in the higher field. These results suggest that the central ring of **2** adopts a fixed boat or half-boat form and the proton in the lower magnetic field occupies (pseudo)equatorial position and that in the higher field, (pseudo)axial position, consequently, the molecule **2** adopts a bent conformation shown in Scheme 1.

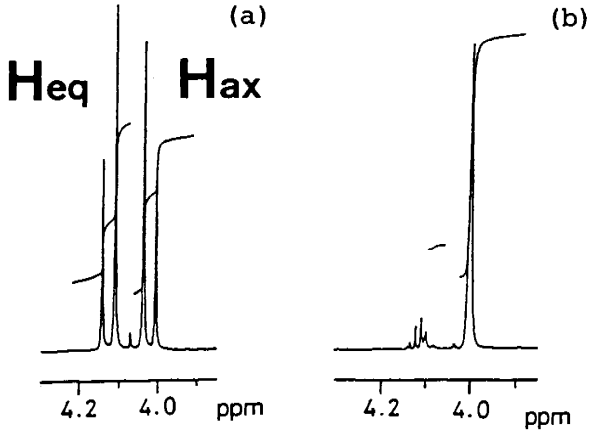


Fig. 1.

^{1}H-NMR spectra (600 MHz) at C(5) in $CDCl_3$ at 25 °C in **2**(a), and in monodeuteriated **2** with a system of $Na_2S_2O_4$, D_2O (b).

Table 1. Reduction of **1** and deuteriated positions at C(5) in the products

Run	Reducing reagent(Isotope purity/%)	D(equatorial)/%	D(axial)/%
1	$Na_2S_2O_4$, D_2O (100)	96	4
2	BNAH-4,4-d_2 (96)	99	1
3	$NaBD_4$ (98)	76	24

Three kinds of the reducing system for **1** were employed for incorporation of a deuterium atom into **2** (Table 1); [1] $Na_2S_2O_4$, D_2O, [2] 4,4-dideuterio-1-benzyl-1,4-dihydronicotinamide (BNAH-4,4-d_2), and [3] $NaBD_4$, which may give a mixture of diastereomers (**Hax,Deq** and **Dax,Heq** at C(5) in **2**) easily detectable by ^{1}H-NMR spectroscopy.

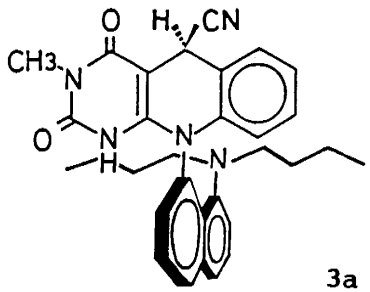
As Fig. 1(b) shows, the deuterium uptake generally occurred at the (pseudo)equatorial position. Although the approach of the reductants was possible predominantly to the "open face" of **1**, the degree of the selectivity observed was variable depending upon the bulkiness of the actual deuterium donors. In fact, with smaller reagents, such as BD_4^-, the selectivity decreased to some extent.

To compare the reactivity of the two protons at C(5) in **2**, the monodeuteriated **2** (**Hax,Deq** at C(5)) was reoxidized by 3-methyl-10-tolylflavin in acetonitrile at room temperature. Judging from ^{1}H-NMR, the

reoxidized product contained 48% deuterium atom at C(5). This result indicates that the reactivity of the axial proton was remarkably decreased in **2**, compared with that observed in the cyclic models.[2a,3] This is probably because in **2**, the "Hax" resides in a shielded position by the "alkyl chain wall" (Scheme 1).

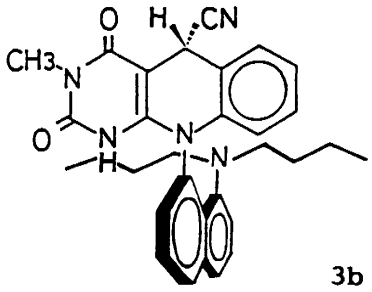
Hydrocyanation to **1** with potassium cyanide and trimethylammonium chloride in DMF is a key step for the optical resolution of **1**.[1,5] In this reaction, it was found that two diastereomers **3a** and **3b** (Scheme 2) were formed in a ratio of 32 : 68 respectively[6] (Table 2. Run 1). Interestingly enough, cyanide ion was incorporated at C(5) mainly from the "covered face", in contrast to the results observed in the hydrogen uptakes.

Diethylaluminium cyanide[7] was also employed for hydrocyanation of **1** and the ratios of these diastereomers were investigated and are shown in Table 2. As Table 2 shows, the ratio of the diastereomers varied with the experimental conditions employed, and there is a tendency of the increase in the ratio of **3b** in the time course of this reaction.



3a

Scheme 2.



3b

Table 2. Hydrocyanation of **1** into **3ab** [a]

Run	Reagents	Solvent	Temp/°C	Time/min	Yield/%	Diastereomer ratio[b] **3a / 3b**
1	KCN, Me_3NHCl[c]	DMF	65	4320	10	32 / 68
2	Et_2AlCN[d]	Benzene	25	3.5	100	47 / 53
3	Et_2AlCN[d]	Benzene	25	1080	100	30 / 70

a) All the reactions were carried out under N_2.
b) determined by HPLC analysis.
c) [**1**] = 5.0×10^{-2}M, [Me_3NHCl] = 2.5×10^{-1}M, [KCN] = 2.5×10^{-1}M.
d) [**1**] = 2.0×10^{-2}M, [Et_2AlCN] = 1.0×10^{-1}M.

These results might be explained by a consideration that the attack of the cyanide ion essentially takes place from the "open face" of **1** to give the thermodynamically less stable diastereomer **3a** or its aluminium enolate, which was transformed into more stable **3b** or its enolate through a reversible process. Consideration of a bent conformation similar to the reduced product for these diastereomers could best account for the results.

In such a conformation, the cyano group of **3a** and its enolate occupies (pseudo)equatorial position. These compounds are less stable than those concerning **3b**, due to both the dipole-dipole interaction or the peri interaction between the cyano group and the carbonyl oxygen at C(4) or the hydrogen at C(6) respectively, whereas the more stable diastesreomer **3b** and its enolate are free from such repulsions.

The present study reveals that besides covering one face of the 5-deazaflavin molecule, the "alkyl chain wall" could serve to fix the "bent conformation" of the products, which also affects diastereoface-differentiation, leading to quite unique stereochemical reactivity of this new model compound.

References

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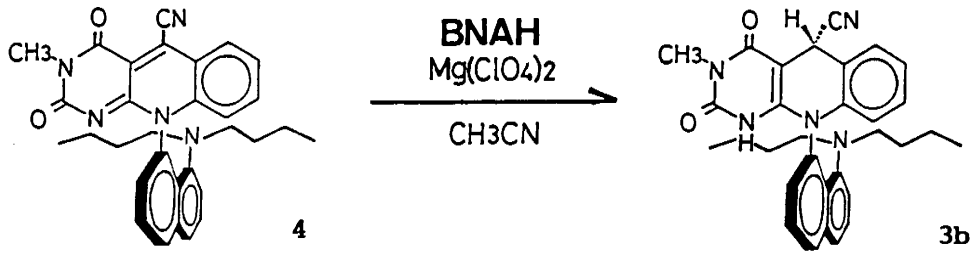
4) For convenience, only one enantiomer is shown in this paper.
5) Both **3a** and **3b** were subjected to the same reaction condition to give the mixture of **3a**, **3b**, and **1** in the similar ratio shown in Table 2 (run 1). This result leads to the conclusion that hydrocyanation of **1** in this condition is a reversible process.
6) After the unfruitful N.O.E. experiments in ^{1}H-NMR, the stereochemistry of the diastereomers was determined by the following chemical transformation. The compound (**4**), the oxidized form of **3a** and **3b**, was reduced with 1-benzyl-1,4-dihydronicotinamide (BNAH) to afford **3b** in 99% yield, which was identical with the major product (68 ratio product) in this reaction. From this result, **3a** was assigned to the minor product (32 ratio product).



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