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SYNTHESIS OF NEW DEAZAFLAVINS WITH PLANAR CHIRALITY. REDOX-INDUCED "ROPE-SKIPPING" RACEMIZATION

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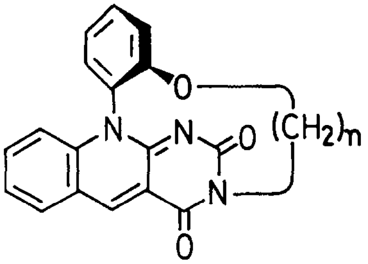
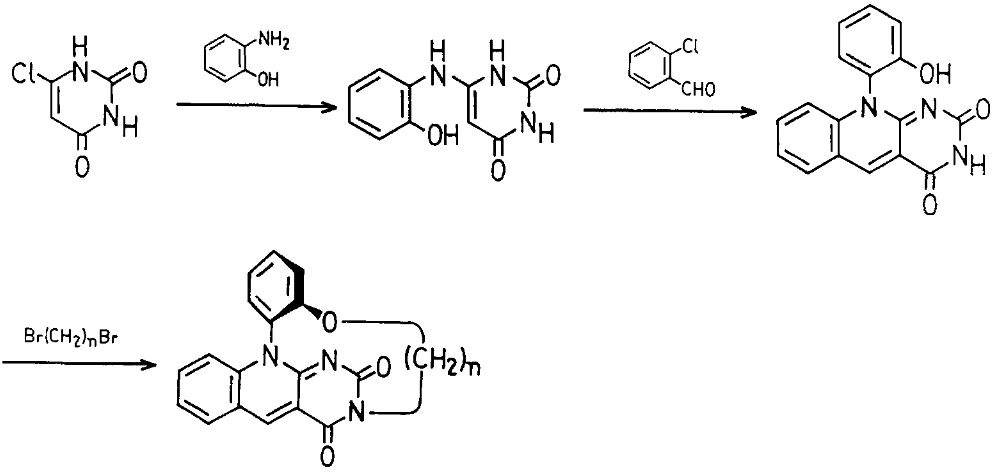
New 5-deazaflavins with planar chirality (dFl(n)) were synthesized in which N(3) and O(2'α) in the 10-(2'-hydroxy)phenyl group were linked by a $\left(CH_2\right)_n$ chain (n=8,10). (+)-dFl(n=8) showed a large chiral discrimination in fluorescence quenching by (R)- and (S)-1,1'-bi-2-naphthol. (+)-dFl(n=10), which was optically stable at ambient conditions, racemized only when it was converted to the reduced form. This is the first example for redox-induced rope-skipping racemization.

Flavin and NAD(P)$^+$ coenzymes are versatile redox "catalysts" in many biological systems. In the past, model studies of these redox coenzymes have been of interest and in fact, asymmetric reduction of substrates with carbonyl groups by optically active NADH model compounds has been widely investigated.1) In contrast, asymmetric hydrogen transfer to and from flavins has been an escaped attention and there exists only a few precedents.2-4) In the course of our studies on chiral flavins, we noticed that flavins with "planar chirality" have never been reported. We considered that planar chirality would be expeditiously attained by including a flavin skeleton in a cyclic structure. The survey of the past literatures indicates that in 1983 Zipplies et al.5) have reported on the synthesis of [4]metacyclo[3](6,10)isoalloxazinophane which is only one published paper on a flavinophane.6) However, neither optical resolution nor racemization is mentioned in their paper. Here we synthesized new 5-deazaflavinophanes (dFl(n): n denotes the number of the methylene units in the bridge) with planar chirality and succeeded in the optical resolution by a liquid chromatographic (LC) method using an optically-active sorbent. Interestingly, we have found that the oxidized forms of dFl (n=8,10) cannot be racemized at ambient conditions while the reduced form of dFl(n=10) readily racemizes via a "rope-skipping" process.

dFl(n):



dFl(n=8) and dFl(n=10) were synthesized from 6-chlorouracil according to Yoneda's method[7] and identified by IR, ^{1}H-NMR, mass spectrum, and elemental analysis. Inspection of the CPK molecular models suggests that the smallest number to form a phane structure would be eight. Under high-dilution conditions we could synthesize dFl(n=8) and dFl(n=10) in 10.5% and 10.2% yields, respectively, from 10-(2'-hydroxy)phenyl-5-deazaisoalloxazine and $Br(CH_2)_nBr$.



The enantiomers were optically resolved by a LC method using chiral packing column (Sumipax OA-2000). This method resulted in a satisfactory separation of the enantiomers: optical purities are 99.6% and 97.5% for (+)- and (-)-dFl(n=8) and 99.6% and 97.9% for (+)- and (-)-dFl(n=10), respectively. Specific rotation for the (+)-enantiomers was measured in methanol: $[\alpha]_D^{25}$ = +301° for (+)-dFl(n=8) and +234° for (+)-dFl(n=10).

First, we confirmed that these enantiomers do not racemize at ambient conditions (below 40 °C). The chiral discrimination ability of these enantiomers can be readily demonstrated by fluorescence quenching.[8] Photoexcitation of (+)-dFl at 420 nm in benzene gave a fluorescence around 470 nm. The fluorescence was quenched moderately by 1,1'-bi-2-naphthol (BN), and the

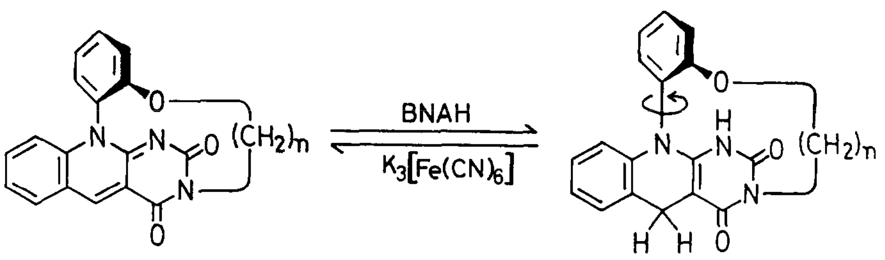
Table 1. Chromatographic analysis of reoxidized dFl(n)[a)]

Deazaflavin	Optical purity of used (+)-dFl(n)	Recovered dFl(n)	
		(+)-dFl(n)	(-)-dFl(n)
dFl(n=8)	99.6%	99.5%	0.5%
dFl(n=10)	99.6%	54.0%	46.0%

a) [BNAH]= 5.34 × 10^{-4} M, [dFl(n)] = 5.07 × 10^{-5} M, [$K_3Fe(CN)_6$] = 3.20 × 10^{-2} M, pH = 8.70, 30 °C. The reaction for BNAH + dFl(n) required 8.5 h.

quenching was similar to a typical exciplex type quenching. The Stern-Volmer plots gave a linear I_0/I vs. [BN] relationship (benzene, 30 °C, [dFl(n)] = 1.20 × 10^{-6} M, [BN] = (1-5) × 10^{-3} M). We estimated the Stern-Volmer constants (K_{sv}) by least-squares computation of these plots: (+)-dFl(n=8), K_{sv} = 18.4 M^{-1} for (R)-BN and 48.2 M^{-1} for (S)-BN; (+)-dFl(n=10), K_{sv} = 68.1 M^{-1} for (R)-BN and 79.0 M^{-1} for (S)-BN. The discrimination factor of 2.6 observed for (+)-dFl(n=8) is one of the largest values attained in chiral fluorescence quenching.[8)] The inferior discrimination ability of (+)-dFl(n=10) relative to (+)-dFl(n=8) is attributed probably to the flexibility of the $-(CH_2)_{10}-$ chain.

We reduced (+)-dFl by 1-benzyl-1,4-dihydronicotinamide(BNAH) in anaerobic aqueous solution (pH 8.70) at 30 °C. After completion of the reduction (+)-dFl_{red} was reoxidized by $K_3[Fe(CN)_6]$ and the aqueous solution was extracted with chloroform. (+)-dFl was recovered quantitatively in the chloroform layer, which was then subjected to the LC analysis using a chiral packing column (vide supra). As summarized in Table 1, (+)-dFl(n=8) is not racemized while (+)-dFl(n=10) has been racemized "completely" (within the experimental error). As the oxidized forms of (+)-dFl(n=8) and (+)-dFl(n=10) do not racemize under the identical conditions, this finding suggests that only the reduced form of (+)-dFl(n=10) can racemize in a "rope-skipping" manner.



It has been established that oxidized flavins are almost planar whereas reduced flavins are folded along the N(5)-N(10) axis like butterfly wings.[9] This is due to a redox-conjugated sp^2-sp^3 interconversion of these nitrogen atoms. In contrast, the structure of reduced 5-deazaflavins is rather unknown. Several lines of evidence suggest (although indirectly) that they may employ the folded structure. The fact that (+)-dFl(n=10) racemizes only when the planar oxidized form is converted to the reduced form is rationalized by an idea that the reduced form should employ the folded structure which could facilitate the "rope-skipping" racemization. The $-(CH_2)_8-$ chain in (+)-dFl (n=8) should be too short to "skip" even in the reduced form.

In conclusion, the present paper demonstrates the first example for deazaflavins with planar chirality and a novel racemization mode named "redox-induced rope-skipping racemization".

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