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Structure and Reactivity Studies of 5-Methyl-1,5-dihydro-5-deazaisoalloxazinophane

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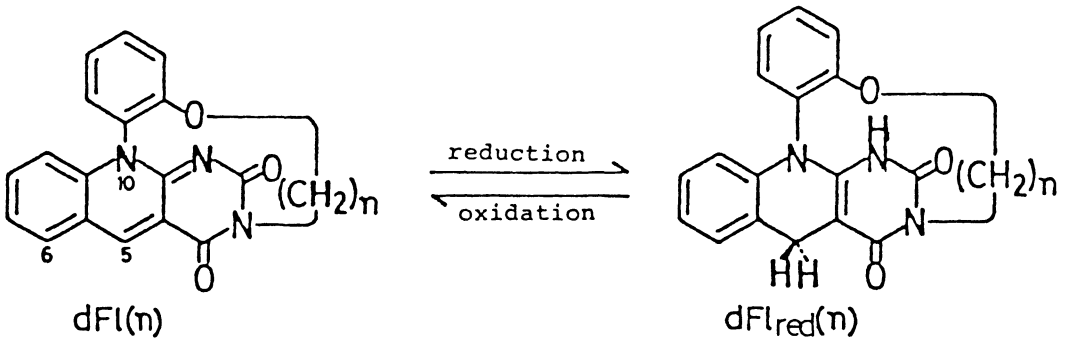
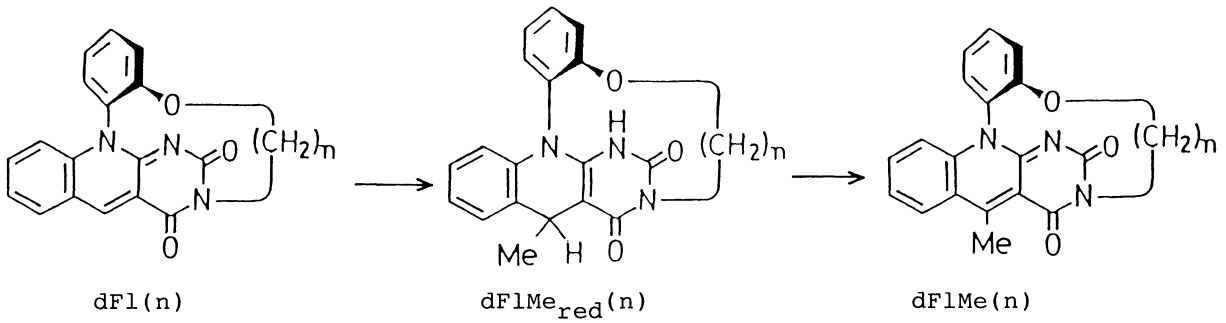
The X-ray structure analysis established that in the reaction of 5-deazaisoalloxazinophane and MeMgBr the methyl group is incorporated into the axial C(5) position. The axial selectivity is in line with the stereochemical course observed for the reduction of this compound. The product having only H_{eq} at C(5) is much less reactive than 1,5-dihydro-5-deazaisoalloxazinophane having both H_{eq} and H_{ax}.

In NAD(P)H, the two protons at C(4) of the 1,4-dihydronicotinamide moiety occupy diastereotopic positions. Discrimination between these two protons in enzyme-bound NAD(P)H is possible from their ^{1}H-NMR chemical shifts, but the difference becomes minimal in the free coenzymes.[1] In an NAD(P)H model system Rob et al.[2] and de Kok et al.[3] demonstrated that these protons show quite different chemical shifts when the nicotinamide skeleton is included in a ring structure. We synthesized 5-deazaisoalloxazinophanes dFl(n) (n=6-12) including the isoalloxazine skeleton in a ring structure and found that the reduced forms $dFl_{red}(n)$ give different chemical shifts for the two C(5) protons, H_{ax} and H_{eq}.[4] By using these cyclic NAD(P)H model compounds[2,3] and 5-deazaisoalloxazinophanes[4] it was shown that hydrogen exchange occurs exclusively at the axial position in their redox reactions.



As an extension of this study, we were interested in stereochemistry and reactivities of 5-methyl-5-deazaisoalloxazinophanes dFlMe(n). Attachment of the C(5) methyl group has important consequences to answer the following questions: (1) in the reaction of dFl(n) with MeMgBr to yield $dFlMe_{red}(n)$, is the methyl group also incorporated into the axial C(5) position? (2) how is hydrogen transferred from $dFlMe_{red}(n)$ and to dFlMe(n)? and (3) how is the reactivity of $dFlMe_{red}(n)$ in comparison to $dFl_{red}(n)$? With these questions in mind, we determined the structure of $dFlMe_{red}(8)$ by an X-ray crystallographic method and compared the reactivities of $dFlMe_{red}(8)$ with $dFl_{red}(8)$.



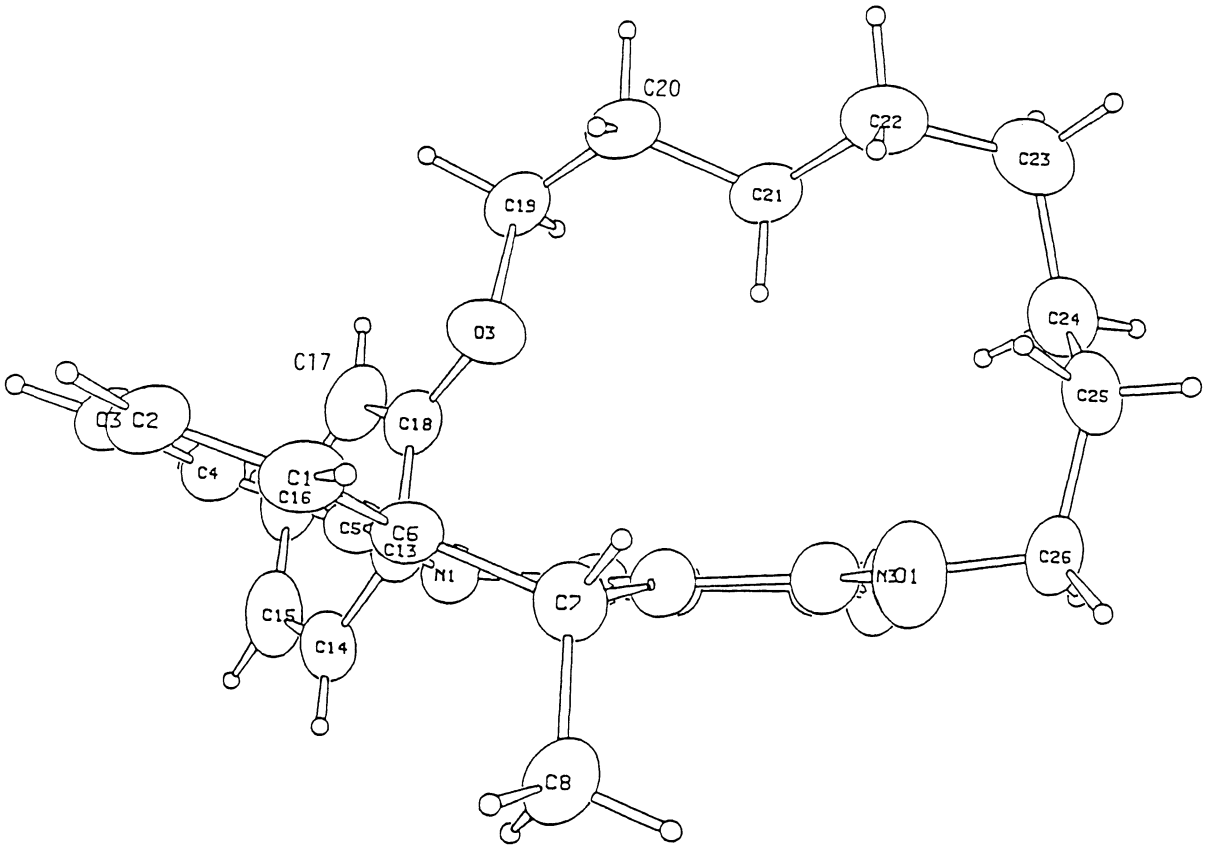


Fig. 1. Crystal structure of $dFlMe_{red}(8)$.

Table 1. Second-order rate constants (k_2) for the oxidation of $dFl_{red}(8)$ and $dFlMe_{red}(8)$[a)]

Oxidizing agent	$10^3 \cdot k_2/M^{-1}s^{-1}$	
	$dFlMe_{red}(8)$	$dFl_{red}(8)$
Dichlorodicyanobenzoquinone	38.3	3.3×10^4
Chloranil	0.018	36.7

a) 30 °C, anaerobic, acetonitrile, [$dFl_{red}(8)$ of $dFlMe_{red}(8)$] = 2.50×10^{-5} M, [oxidizing agent] = 1.00×10^{-3} M.

$dFlMe_{red}(8)$ was prepared by the reaction of dFl(8) and MeMgBr.[5)] Figure 1 indicates the structure of $dFlMe_{red}(8)$ determined by the X-ray crystallographic analysis.[6)] It is seen from Fig. 1 that the central ring adopts a boat-shaped conformation and the incorporated methyl group (C8 in Fig. 1) occupies the axial position. It is known that the $(CH_2)_8$ strap in $dFl_{red}(8)$ is too short for the 1,5-dihydro-5-deazaisoalloxazine ring to be inverted.[4,7)] Therefore, this structure supports the view that the methyl group attacks the isoalloxazine ring from the axial side. The result is in line with our previous finding that in the reduction of dFl(n) hydrogen is exclusively incorporated into the axial position.[4)] The axial selectivity for the nucleophilic attack would be accounted for by the stereoelectronic effect.[2,4)]

The ^{1}H-NMR spectrum of $dFlMe_{red}(8)$ in $CDCl_3$ is also consistent with this structure. It is known that $dFl_{red}(8)$ gives a pair of doublet at 3.92 and 4.06 ppm for the two C(5) protons.[4)] On the basis of the NOE studies, H_{ax} and H_{eq} were assigned to the higher and the lower magnetic field, respectively.[4)] The shift of H_{eq} to the lower magnetic field is caused by the deshielding effect of the neighboring phenyl and carbonyl groups. The C(5) proton of $dFlMe_{red}(8)$ gave a singlet peak at 4.28 ppm. This chemical shift is lower by 0.22 ppm than that for H_{eq} of $dFl_{red}(8)$ and therefore commensurate with H_{eq}.

In the oxidation of $dFl_{red}(n)$ to dFl(n) hydrogen is exclusively eliminated from the axial position: in the oxidation by N-methylacridinium iodide, for example, H_{ax} is 8.2 times more reactive than H_{eq}.[4)] In the present study, we found that $dFlMe_{red}(8)$ is remarkably deactivated: as shown in Table 1, $dFlMe_{red}(8)$ is (2-8) 10^3 times less reactive than $dFl_{red}(8)$. This is primarily related to the stereochemical reason that $dFlMe_{red}(8)$ only has less reactive H_{eq}. In addition, H_{eq} in $dFlMe_{red}(8)$ is surrounded by bulky groups such as 3-C=O, 5-Me, and 6-H. Thus, H_{eq} behaves as a less reactive "buried hydride equivalent".

1-Alkyl-3-carbamoyl-1,4-dihydroquinoline derivatives have been used as a

convenient, acid-stable NAD(P)H model compounds.[8-10] Since the basic skeleton is wholly included in the structure of 1,5-dihydro-5-deazaisoalloxazines, they show the reactivities similar to 1,5-dihydro-5-deazaisoalloxazines. Recently, Romoff et al.[10] found that substitution of the 4-hydrogen in 1-benzyl-3-carbamoyl-1,4-dihydroquinoline by a methyl group lowers rate constants for hydride transfer by a factor of over 2000. However, they did not address any rationale for this unusual deactivation. Although the structure of this compound is not determined, we believe that the deactivation is accounted for by the boat-shaped conformation and the equatorial C(4) hydrogen.

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5) dFl(8) was treated with MeMgBr in the presence of CuI in tetrahydrofuran at room temperature: mp 242-245 °C, yield 58%.
6) Recrystallized from chloroform-methanol. Crystal data. $C_{26}H_{29}N_3O_3$, F. W. 431.54, monoclinic, space group P21/c, a=13.433, b=18.361, c=11.441 Å, α=90.00, β=127.12, γ=90.00, Dc=1.28 g cm^{-3} for Z=4, R=0.04619.
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