Asymmetric Oxidation by New Cyclic Flavins with Planar Chirality (Chiral Flavinophanes)

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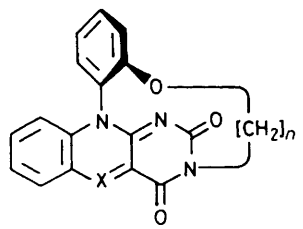
Cyclic flavins with planar chirality (chiral flavinophanes) can oxidise thiols (*ca.* 43% enantiomeric excess) and NADH model compounds (*ca.* 60% enantiomeric excess) in an asymmetric manner.

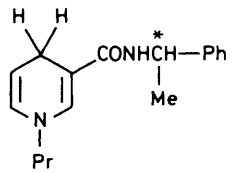
Flavins and NAD(P)$^+$ coenzymes are versatile redox 'catalysts' in many biological systems. In the past decade, asymmetric reduction of substrates with carbonyl groups by optically active NADH model compounds has been widely investigated.[1,2] In contrast, very few precedents exist for asymmetric redox reactions mediated by flavins. To the best of our knowledge, there are only two examples of flavins with a chiral substituent: one possesses an asymmetric carbon substituent at N(3)[3] and the other has one at N(10).[4] Unfortunately, the optical yields attained in these chiral flavins were relatively low (less than 31% enantiomeric excess). We therefore tried the synthesis of new flavins with



(1)

X = N or CH

n = 7, 8, or 12



(2)

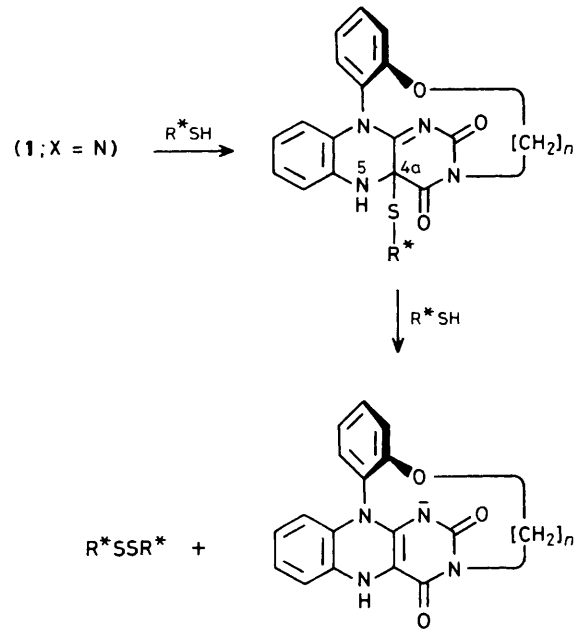
Table 1. Second-order rate constants (k_2/mol^{-1} dm^3 s^{-1}) for the reaction of (**1**; X = N or CH) with (**2**).[a]

Flavin (+)-(**1**)			k_2 for (**2**)		
X	n	[Mg(ClO$_4$)$_2$] /mM	(*R*)-(**2**)	(*S*)-(**2**)	$k_{2,R}/k_{2,S}$
N	7	100	0.55	0.66	0.83
N	8	100	0.24	0.12	2.0
N	12	100	0.14	0.035	4.0
CH	7	1.0	2.63	1.24	2.1
CH	8	1.0	1.38	0.59	2.3
CH	12	1.0	0.72	0.18	4.0

[a] 30 °C, N_2, [(**1**)] = 5.00 × 10^{-5} M, [(**2**)] = 4.00 × 10^{-4} M. We also carried out the reactions with (+)-(**1**; X = N) at [Mg(ClO$_4$)$_2$] = 2.0 × 10^{-3} M and with (+)-(**1**; X = CH) at [Mg(ClO$_4$)$_2$] = 0.100 M but the enantiomeric selectivities were lower than those recorded in Table 1 ($k_{2,R}/k_{2,S}$ <2.1).

'larger' chiral frames of reference such as axial chirality and planar chirality.[5,6] We here report the asymmetric oxidation of optically active thiols and 1,4-dihydronicotinamides (**2**) by flavins and 5-deazaflavins (**1**)† with planar chirality.[7] We have found that 43—60% enantiomeric excess is attainable in these reactions. This indicates that planar chirality provides a potential approach to asymmetric reactions mediated by flavins.

Oxidations of optically active thiols (L-cysteine, *N*-acetyl-L-cysteine, L-cysteine methyl ester, and 1,4-dithio-L-threitol) by (+)- and (−)-(**1**; X = N) to the corresponding disulphides were carried out anaerobically at 30 °C (water–methanol 1 : 2 v/v; pH 10.81 for L-cysteine, 9.55 for *N*-acetyl-L-cysteine and 1,4-dithio-L-threitol, and 9.01 for L-cysteine methyl ester;‡ [(**1**; X = N)] = 5.00 × 10^{-5} M, [1,4-dithio-L-threitol] = 7.20 × 10^{-4} M; the concentration for other thiols was 1.00 × 10^{-2} M). The pseudo-first-order rate constants (k_+ and k_-) were determined by monitoring the disappearance of the absorption band of these chiral flavins (445 nm). Three of the thiols showed almost no asymmetric discrimination (k_+/k_- = 1.0 ± 0.1) but the reaction between (**1**; X = N) and *N*-acetyl-L-cysteine occurred enantioselectively: k_+/k_- was 2.52 (k_+ = 5.50 × 10^{-5} s^{-1}, k_- = 2.18 × 10^{-5} s^{-1}) for (**1**; X = N, *n* = 7), 2.47 (k_+ = 5.07 × 10^{-5} s^{-1}, k_- = 2.05 × 10^{-5} s^{-1}) for (**1**; X = N, *n* = 8), and 3.05 (k_+ = 1.70 × 10^{-5} s^{-1}, k_- = 5.58 × 10^{-6} s^{-1}) for (**1**; X = N, *n* = 12). It is known that oxidation of thiols by flavin proceeds *via* covalent 4a-adducts [equation (1)].[8,9] The fact that a significant asymmetric discrimination was observed only for *N*-acetyl-L-cysteine suggests that the 4a-adduct intermediate with this thiol is the most crowded of the adducts from the thiols tested, and that some hydrogen-bonding interaction may exist between the neighbouring C(4)=O (or 5-NH) and the amide group in *N*-acetyl-L-cysteine.



(1)

The reactions of (+)-(**1**; X = N) or (+)-(**1**; X = CH) with (*R*)- and (*S*)-*N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide (**2**) were first carried out in an aqueous system at 30 °C but no asymmetric discrimination was observed ($k_{2,R}/k_{2,S}$ = 1.0 ± 0.1). We therefore employed acetonitrile as solvent, with an added metal cation to act as a bridge between flavin and 1,4-dihydronicotinamide at the hydrogen-transfer state.[1,2,4] The second-order rate constants (k_2) for the reaction in the presence of Mg^{2+} are summarised in Table 1. The k_2 values decrease with increasing ring size§ and the highest enantiomeric selectivity was observed for the less reactive (+)-(**1**; X = N, *n* = 12) and (+)-(**1**; X = CH, *n* = 12) ($k_{2,R}/k_{2,S}$ = 4.0). This rate difference corresponds to 60% enantiomeric excess [= $(k_{2,R} - k_{2,S})/(k_{2,R} + k_{2,S})$].

It is established that the intercoenzyme hydrogen transfer from flavins to NADH (and its model compounds) proceeds *via* a face-to-face orientation.[10,11] Examination of Corey-Pauling-Koltun models suggests that the polymethylene 'strap' in these flavinophanes effectively covers one side of the isoalloxazine plane and that (**1**; X = N, *n* = 12) and (**1**; X = CH, *n* = 12), having the longest polymethylene chains, provide the largest steric crowding. This explains why the highest enantiomeric selectivity was observed for (**1**; X = N, *n*

† Flavins and 5-deazaflavins (**1**) were synthesised by the reaction of 10-(2-hydroxyphenyl)isoalloxazine or 10-(2-hydroxyphenyl)-5-deazaisoalloxazine with Br[CH$_2$]$_n$Br.[6] They were optically resolved by a liquid chromatographic method using a chiral packing column (Sumipax OA-2000). The optical purities were higher than 99% except for (**1**; X = N, *n* = 12) (98.0%) and (**1**; X = CH, *n* = 12) (96.3%).

‡ The reaction pH was set near the pK_a of the thiol with 0.05 M-carbonate (pH 10.81) or 0.05 M-borate (other pH values) because the oxidation rate becomes maximal near the pK_a.[8,9]

§ Spectroscopic studies showed that (**1**; X = N, *n* = 7) and (**1**; X = CH, *n* = 7), with small ring size, are sterically distorted. This is why these compounds are more reactive than those with large ring size (*n* = 12). This problem will be discussed elsewhere.

= 12) and (**1**; X = CH, n = 12). On the other hand, oxidation of thiols proceeds *via* the 4a-adduct intermediate but not *via* face-to-face orientation.[8,9] Therefore, enantiomeric selectivity would be expected to be less affected by ring size in this case (k_+/k_- = 2.5—3.0).

In conclusion, the present study shows that planar chirality provides a potential approach to high optical yields in asymmetric intercoenzyme hydrogen transfer.

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