Flavin Mimics possessing Remarkably High Oxidizing Power: 6,8-Diazaflavins

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6,8-Diazaflavin (**1**) and 6,8-diaza-7-methylthioflavin (**2**) show remarkably high oxidizing activity towards thiols and nitroalkanes; 6,8-diazaflavins [(**1**) and (**2**)] are 10^6—10^8 times more reactive in the oxidation of thiols compared with 3,10-dimethylisoalloxazine.

The use of flavin mimics possessing high oxidizing power shows promise in model studies of oxidation reactions mediated by flavin coenzymes in biological systems. Recently, we have found[1] that 3,10-dimethyl-8-azaisoalloxazine [8-azaflavin, (**3**)] shows unusually high activity for the oxidation of thiols and nitroalkanes, and it can be used as a catalyst for disulphide and aldehyde syntheses under aqueous and aerobic conditions.

We report herein the much higher oxidizing power of 6,8-diazaflavins [(**1**) and (**2**)] towards thiols and nitroalkanes under aqueous and anaerobic conditions (Scheme 1). Diazaflavins (**1**) and (**2**) were prepared by condensation of 4-amino-5-methylamino- or 4-amino-5-methylamino-2-methylthio-pyrimidine[2] with *N*-methylalloxane.†

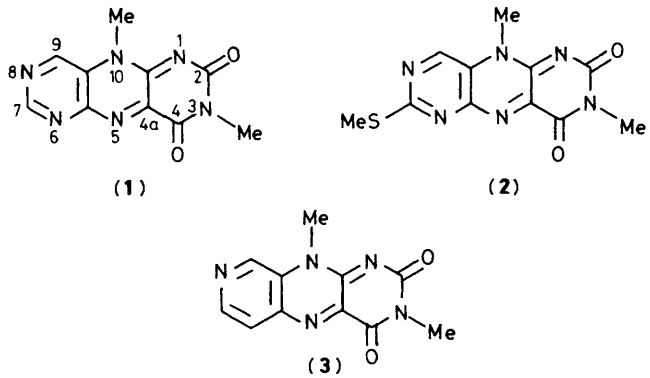
In contrast with the monoazaflavin (**3**), the diazaflavins [(**1**) and (**2**)] were found to form adducts with MeOH, EtOH, H_2O, and H_2O_2 [$\lambda_{max.}$ 330 for hydrated (**1**) and 343 nm for hydrated (**2**)]. From the absorption spectra of (**1**) and (**2**) at various pH values (2.5—11.0) the pK_a values of the pseudo bases are found to be 8.6 for (**1**) and 9.1 for (**2**), respectively.‡ The possible hydration sites are the 4a- or/and 9-positions of the diazaflavins. The possibility of 4a-adduct formation, however, is eliminated by spectroscopic examination of the reaction of reduced (**1**) with O_2 in MeCN. Namely, (**1**) was quantitatively regenerated by the action of O_2 on the reduced form of (**1**). An isosbestic point is observed during this reaction; thus no intermediate is formed, whereas (**1**) forms an adduct with H_2O_2 in MeCN. Therefore, the hydration sites must be the 9-positions of (**1**) and (**2**). This type of covalent hydration is well known for pteridine derivatives.[3] Hydrolyses of the diazaflavins (**1**) and (**2**) were slower than that of (**3**) owing to hydration effects; the rate constants are 3.33×10^{-2} min^{-1} for (**1**), 2.25×10^{-2} min^{-1} for (**2**), and 2.24×10^{-1} min^{-1} for (**3**) at pH 11.0 at 25 °C.

The reactivity of (**1**) and (**2**) in the oxidations of thiols and nitroalkanes over the pH range where no hydration occurs was investigated. The rate constants were determined by following the decrease in the absorption at 440 nm for (**1**) and 494 nm for (**2**) under anaerobic conditions. Both reactions followed first-order kinetics for more than two half-lives, and the rates were found to be second-order with respect to [$HS(CH_2)_2OH$], and first-order with respect to [$EtNO_2$]. Formation of reduced diazaflavins was confirmed by quantitative regeneration of the oxidized diazaflavins by introduction of O_2. The oxidation products, disulphides from thiols and carbonyl compounds from nitroalkanes, were detected by t.l.c. for the former and formation of 2,4-dinitrophenylhydrazone derivatives for the latter. The kinetic results, together with the data for (**3**), are presented in Table 1. The results show that (**1**) is more reactive than (**3**) by a factor of 410 for $HS(CH_2)_2OH$ and a factor of 39 for $EtNO_2$

Table 1. Pseudo-first order rate constants for oxidation by (**1**)—(**3**).[a]

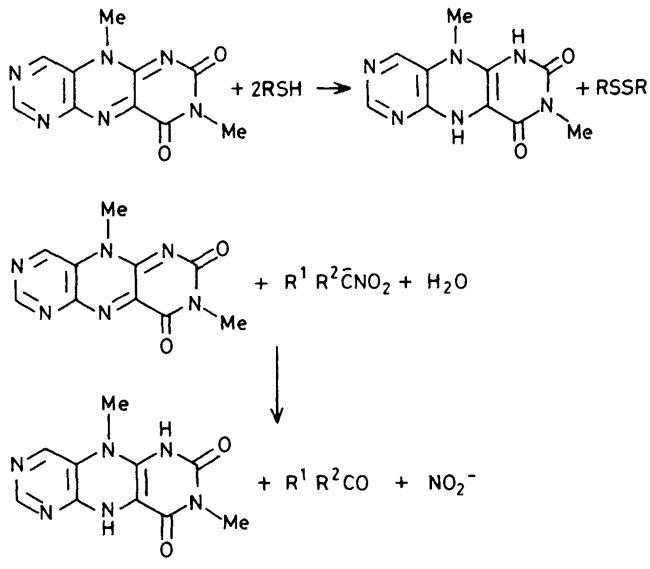
Substrates	$k_{obs.}$/min^{-1} (**1**)	(**2**)	(**3**)	Relative rate [(**1**)/(**3**)]
$HS(CH_2)_2OH$[b]	5.80	4.20	1.42×10^{-2}	410
$HS(CH_2)_4SH$[c]	16.2	12.3	0.142	110
$EtNO_2$[d]	0.372	0.252	9.50×10^{-3}	39
Pr^iNO_2[d]	9.40×10^{-2}	6.00×10^{-3}	1.69×10^{-3}	56

[a] [Flavins] 5×10^{-5} M under N_2 at 25 °C. [b] [$HS(CH_2)_2OH$] 1×10^{-3} M, pH 6.60 (0.1 M phosphate, μ 0.3 M). [c] [$HS(CH_2)_4SH$] 5×10^{-4} M, pH 3.90 (0.1 M acetate, μ 0.3 M). [d] [$R^1R^2CHNO_2$] 1×10^{-2} M, pH 7.10 (0.1 M phosphate, μ 0.3 M).



† Selected spectral data; (**1**), m.p. 245—248 °C (decomp.), M^+ 244, $\lambda_{max.}$(Bu^{t}OH), 444 (ε 5 800 dm^3 mol^{-1} cm^{-1}) and 322 nm (ε 4 100). (**2**), m.p. 275—280 °C (decomp.), M^+ 290, $\lambda_{max.}$ (Bu^{t}OH), 495 (ε 5 800) and 337 nm (ε 2 480). Satisfactory elemental analyses were obtained.

‡ The spectral changes were reversible with pH changes, and the pH dependences of the absorptions at 437 nm for (**1**) and 494 nm for (**2**) gave typical titration curves.



Scheme 1

oxidation. This indicates that (**1**) is more reactive than the non-azaflavin 3,10-dimethylisoalloxazine by a factor of 10^6—10^8 for the thiol oxidation.[1] It should be noted that conventional flavin models are unable to oxidize nitroalkanes in aqueous solution.[4] Furthermore, the 7-methylthio group of (**2**) has little effect on the oxidizing activity, implying that various 6,8-diazaflavins containing functional groups at the 7-position are of potential interest as higher oxidation-active flavin mimics owing to their synthetic availability. To date (**1**) is the most active flavin mimic known for oxidation of thiols and nitroalkanes.

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