# Remarkably High Reactivity of an 8-Azaflavin for the Oxidation of Nitroalkanes in Aqueous Solution

**Yumihiko Yano,* Masashi Ohshima, and Susumu Sutoh**

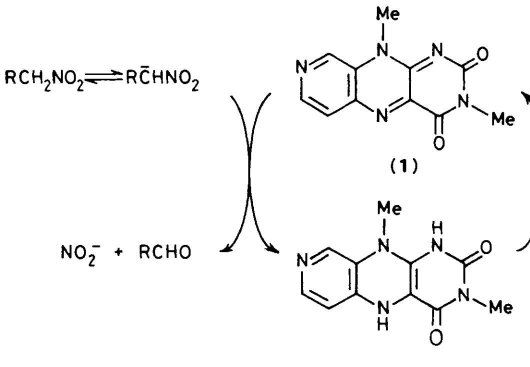
*Department of Chemistry, Gunma University, Kiryu, Gunma 376, Japan*

8-Azaflavin (**1**) oxidizes nitroalkanes to the corresponding carbonyl compounds in aqueous solution, and it can be used as a catalyst for aldehyde syntheses; yields of 2200—2700% based on (**1**) are obtained under aerobic conditions.

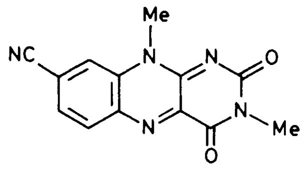
Flavins possessing a high oxidizing power would have potential as oxidation–reduction catalysts under aerobic conditions. For this purpose, it is of primary importance to have a reactive flavin model compound. Recently, we have found[1] that 3,10-dimethyl-8-azaisoalloxazine (**1**) shows a remarkably high oxidizing activity towards thiols; $10^4$—$10^6$ times more reactive than 3,10-dimethylisoalloxazine.

We now wish to report facile oxidation of nitroalkanes by (**1**), and aldehyde syntheses from primary nitroalkanes under aerobic conditions as shown in Scheme 1.

D-Amino acid oxidase oxidizes the nitroethane anion to give acetaldehyde and the nitrite ion.[2] In nonenzymatic systems, however, only two examples of such an oxidising capability are known: (i) the 8-cyanoflavin (**2**)[3] and (ii) micelle or polymer



Scheme 1



(2)

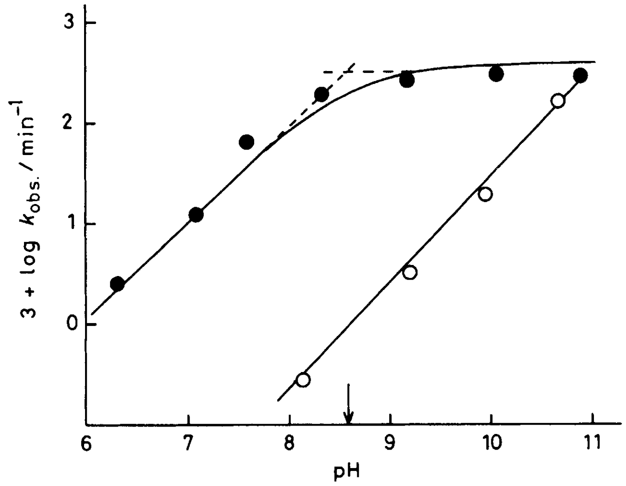


**Figure 1.** pH-Dependence on rates: ●; $EtNO_2$ oxidation, [(**1**)] 5 × $10^{-5}$ M, [$EtNO_2$] 1 × $10^{-2}$ M, [buffer] 0.1 M (μ 0.3), 25 °C, rate = $k_{\rm obs.}$[(**1**)] = $k_2K_a$[(**1**)][$EtNO_2$]$_0$/$K_a$ + [$H^+$], $K_a$ (dissociation constant of $EtNO_2$) is $10^{-8.6}$; ○; hydrolysis rates of (**1**); [(**1**)] 5 × $10^{-5}$ M, 25 °C.

**Table 1.** Rate constants and relative rates for various nitroalkanes at 25 °C under anaerobic conditions.[a]

| Nitroalkanes | $k_{\rm obs.}$/min$^{-1}$ | Relative rate |
|---|---|---|
| $EtNO_2$ | $8.57 \times 10^{-2}$ | 21 |
| $Pr^nNO_2$ | $7.00 \times 10^{-2}$ | 17 |
| $Bu^nNO_2$ | $4.57 \times 10^{-2}$ | 11 |
| n-$C_8H_{17}NO_2$ | $3.17 \times 10^{-2}$ | 8 |
| $Pr^iNO_2$ | $4.04 \times 10^{-3}$ | 1 |
| $\overline{CH_2[CH_2]_3CH}NO_2$ | [b] | — |
| Hydrolysis of (**1**) | $6.56 \times 10^{-4}$ | 0.16 |

[a] [(**1**)] 5 × $10^{-5}$ M, [$RNO_2$] 1 × $10^{-2}$ M in aqueous MeCN (pH 9.5 buffer : MeCN = 1 : 1). [b] Not determined owing to hydrolysis of (**1**).

bound flavins.[4] Thus, the reactivity of (**1**) for $EtNO_2$ oxidation was at first estimated by kinetics. Pseudo-first-order rate constants ($k_{\rm obs.}$) were determined by following the decrease of the absorption of (**1**) at 440 nm under anaerobic conditions. The final spectra showed the formation of reduced (**1**), which was also confirmed by the introduction of $O_2$ to regenerate (**1**) quantitatively. Acetaldehyde was detected as its 2,4-dinitrophenylhydrazone derivative.

The pH–log $k_{\rm obs.}$ profiles for $EtNO_2$ oxidation and hydrolysis of (**1**) are shown in Figure 1. The second-order rate constant ($k_2$) of [(**1**) + $Me\bar{C}HNO_2$] was determined to be 39.8 $dm^3 mol^{-1} min^{-1}$, which is larger than that for (**2**) by two orders of magnitude, whereas the hydrolysis rate of (**1**) ($k_{\rm HO^-}$ = 2 × $10^2$ $dm^3 mol^{-1} min^{-1}$) is only several times faster than that of (**2**).[3] This indicates that an 8-aza moiety is much more electron-withdrawing than an 8-cyano group. To the best of our knowledge, (**1**) is the most oxidation-active flavin model among the flavins so far prepared.

Meanwhile the hydrolysis mechanism of (**2**) is well established to proceed through $HO^-$ attack at the 10a-position of the isoalloxazine nucleus.[3] Therefore, the higher reactivity of (**1**) for the oxidation than for the hydrolysis compared with (**2**) shows that the reaction site for the oxidation must be such a position as N(5) which is much more affected by electronic effects from the 8-position compared with the 10a-position. In fact, enzymatic oxidation of $EtNO_2$ is known to occur at the N(5)-position.[2]

The rate constants for various nitroalkanes (listed in Table 1) indicate that secondary nitroalkanes are less reactive than primary ones probably owing to bulkiness, and the decomposition of (**1**) through hydrolysis is negligible for the reaction with primary nitroalkanes. Thus, the possibility of (**1**) acting as a catalyst in air was examined, employing primary nitroalkanes. A typical run is as follows: a mixture of (**1**) (2.3 mg, 0.1 mmol) and nitroalkanes (10 mmol) in 50 ml of aqueous MeCN (0.1 M buffer : MeCN = 1 : 1) was stirred in air at 40—50 °C. The pH of the solution was maintained at *ca.* 8 during the reaction by adding alkaline solution (2 M NaOH). Propanal, butanal, and octanal were produced in 2200, 2700, and 2500% yields based on (**1**) after 5 h. Spectroscopic examinations of the reaction mixture showed that considerable amounts of (**1**) (50% for $Pr^nNO_2$ and 80—85% for $Bu^nNO_2$ oxidations) change to a product ($\lambda_{\rm max.}$ 380 nm) which has not yet been identified, but which is not a hydrolysis product of (**1**). This may be the reason for the saturation level of aldehydes obtained with respect to the course of the reaction. Nevertheless it is noteworthy that primary nitroalkanes can be converted into the corresponding aldehydes in fair yields by using a flavin mimic under aqueous and aerobic conditions.

We thank Professor S. Watanabe for encouragement.

*Received, 16th January 1984; Com. 063*

## References

1 Y. Yano, I. Yatsu, E., Ohya, and M. Ohshima, *Chem. Lett.*, 1983, 775.
2 D. T. Porter, J. G. Voet, and H. J. Bright, *J. Biol. Chem.*, 1972, **247**, 1951; 1973, **248**, 4400.
3 I. Yokoe and T. C. Bruice, *J. Am. Chem. Soc.*, 1974, **96**, 540; T. C. Bruice, T. W. Chan, J. P. Taulene, I. Yokoe, D. E. Elliott, R. F. Williams, and M. Novak, *ibid.*, 1977, **99**, 6713.
4 S. Shinkai, in 'Flavins and Flavoproteins,' ed. K. Yagi and T. Yamano, University Park Press, Baltimore, 1980, p. 45.