Mild and Efficient Flavin-Catalyzed H_2O_2 Oxidation of Tertiary Amines to Amine *N*-Oxides

Katarina Bergstad[†] and Jan-E. Bäckvall*[,†,‡]

Department of Organic Chemistry, University of Uppsala, Box 531, SE-751 21 Uppsala, Sweden, and Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

Received May 15, 1998

A mild and highly effective H_2O_2 oxidation of tertiary amines has been developed by the use of flavin catalysis. Eight aliphatic amines were oxidized to their corresponding *N*-oxides in fast and selective reactions. For all substrates a considerable rate enhancement was observed compared to the noncatalyzed reactions. The product *N*-oxides were isolated in good yields using this mild oxidation system based on the environmentally attractive oxidant H_2O_2. As the catalyst, an N^1,N^5-dialkylated flavin was used as an analogue of the biologically important flavin redox cofactor. The catalytic cycle proposed for the flavin catalysis accounts for the observation that, in addition to the hydrogen peroxide oxidant, molecular oxygen is required for the initiation of the process.

Introduction

Oxidation reactions with environmentally acceptable oxidants such as molecular oxygen[1−19] and hydrogen peroxide[1,7,8,15,20−37] have been intensively studied during recent years. These oxidants are highly attractive since they are cheap and produce no toxic waste products in contrast to many commonly employed inorganic electron-accepting agents. Aqueous hydrogen peroxide is easy to handle and has a high percentage of available oxygen compared to most other oxidizing compounds except dioxygen.

Although hydrogen peroxide has a high oxidation potential (1.76 V), there is generally a high activation barrier for its reaction with organic substrates.[38] As a consequence, a number of catalytic procedures for H_2O_2 oxidation have been developed in which the activation barrier is significantly lowered. Examples of catalytic reactions are transition metal-catalyzed[22−27] and polyoxometalate-catalyzed[15,30−34] oxidations of different organic substrates by H_2O_2. Only to a limited extent have bio- or biomimetic catalysts been employed in such processes.[7,20,28,29,35−37]

Amine *N*-oxides are widely employed oxidants which can be prepared by H_2O_2 oxidation of tertiary amines in a slow reaction.[39,40] Recently, catalytic H_2O_2 oxidations

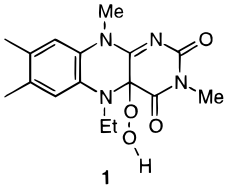
[†] University of Uppsala.
[‡] University of Stockholm. Correspondence to this address. E-mail: jeb@organ.su.se.

(1) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443.
(2) Hosokawa, T.; Nakahira, T.; Takano, M.; Murahashi, S.-I. *J. Mol. Catal.* **1992**, *74*, 489.
(3) Simándi, L. I. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer: Dordrecht, The Netherlands, 1992.
(4) Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160.
(5) Bergstad, K.; Grennberg, H.; Bäckvall, J.-E. *Organometallics* **1998**, *17*, 45.
(6) Byström, S. E.; Larsson, E. M.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 5674.
(7) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
(8) Arts, S. J. H. F.; Mombarg, E. J. M.; van Bekkum, H.; Sheldon, R. A. *Synthesis* **1997**, 597.
(9) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661.
(10) Lenz, R.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3291.
(11) Neumann, R. *J. Org. Chem.* **1989**, *54*, 4607.
(12) Neumann, R.; Levin, M. *J. Org. Chem.* **1991**, *56*, 5707.
(13) Neumann, R.; Dahan, M. *Nature* **1997**, *388*, 353.
(14) Grate, J. H.; Hamm, D. R.; Mahajan, S. In *Polyoxometalates: From Platonic Solids to Anti-Retroviral Activity*; Pope, M. T., Müller, A., Eds.; Kluwer: Dordrecht, The Netherlands, 1994; p 281.
(15) Hill, C. L.; Prosser-McCartha, C. M. *Coord. Chem. Rev.* **1995**, *143*, 407.
(16) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.
(17) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357.
(18) Rönn, M.; Andersson, P. G.; Bäckvall, J.-E. *Tetrahedron Lett.* **1997**, *38*, 3603.
(19) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.
(20) Meunier, B.; Sorokin, A. *Acc. Chem. Res.* **1997**, *30*, 470.
(21) Strukul, G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer: Dordrecht, The Netherlands, 1992.
(22) Herrmann, W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1638.
(23) Romão, C. C.; Kühn, F. E.; Herrmann, W. A. *Chem. Rev.* **1997**, *97*, 3197.
(24) Al-Ajlouni, A. M.; Espenson, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 9243.
(25) Zauche, T. H.; Espenson, J. H. *Inorg. Chem.* **1997**, *36*, 5257.
(26) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189.
(27) Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386.
(28) Thellend, A.; Battioni, P.; Sanderson, W.; Mansuy, D. *Synthesis* **1997**, 1387.
(29) Andersson, M.; Willetts, A.; Allenmark, S. *J. Org. Chem.* **1997**, *62*, 8455.
(30) Khenkin, A. M.; Hill, C. L. *J. Am. Chem. Soc.* **1993**, *115*, 8178.
(31) Duncan, D. C.; Chambers, R. C.; Hecht, E.; Hill, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 681.
(32) Neumann, R.; Gara, M. *J. Am. Chem. Soc.* **1994**, *116*, 5509.
(33) Neumann, R.; Gara, M. *J. Am. Chem. Soc.* **1995**, *117*, 5066.
(34) Ishii, Y.; Ogawa, M. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1990; Vol. 3, p 121.
(35) Shinkai, S.; Yamaguchi, T.; Manabe, O.; Toda, F. *J. Chem. Soc., Chem. Commun.* **1988**, 1399.
(36) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 8.
(37) Murahashi, S.-I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5002.
(38) Curci, R.; Edwards, J. O. In *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Strukul, G., Ed.; Kluwer: Dordrecht, The Netherlands, 1992; p 45.
(39) Cope, A. C.; Ciganek, E. *Org. Synth. Coll. Vol.* **1963**, *IV*, 612.
(40) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth. Coll. Vol.* **1988**, *VI*, 342.

S0022-3263(98)00926-8 CCC: $15.00
Published on Web 08/26/1998

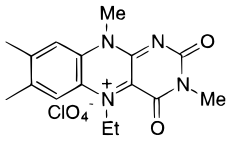
of aromatic N-heterocyclic compounds to their corresponding *N*-oxides employing a biomimetic manganese porphyrin[28] or methyltrioxorhenium(VII)[41,42] as catalyst were reported. Other oxidants employed in the oxidation of tertiary amines include peracids,[43] magnesium monoperphthalate,[44] 2-sulfonyloxaziridines,[45] α-azohydroperoxides[46] and dioxiranes.[47] Amine *N*-oxides are used as stoichiometric oxidants, for example in osmium-catalyzed dihydroxylation of olefins,[40,48,49] in ruthenium-catalyzed oxidation of alcohols[50,51] and in a mild procedure for conversion of halides to aldehydes.[52−54]

In connection with a project on the development of new O_2 or H_2O_2 oxidations of organic substrates,[4,5,55−57] one objective was to use an amine *N*-oxide as an in situ generated oxidant. We therefore needed to develop a mild and efficient oxidation of tertiary amines, preferentially by the use of an environmentally friendly oxidant such as hydrogen peroxide. Obviously, a direct oxidation of the amine by H_2O_2 is too slow, and a catalytic N-oxidation was therefore called for. Although a fast oxidation of tertiary amines to amine *N*-oxides by the stoichiometric flavin hydroperoxide **1** has been described,[58,59] no catalytic reaction employing a flavin as a catalyst has been realized. In fact, only a few examples of flavin-catalyzed H_2O_2 oxidations of organic substrates are known.[35−37,60] In one of these reactions secondary amines were oxidized to imine oxides, however at a moderate rate and with less than 10 turnovers.[37]

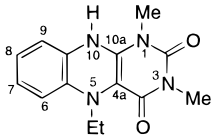


1

The few previously described catalytic flavin systems for oxidation of organic substrates employ a perchlorate salt of an isoalloxazine (e.g. **2**) as a model of the biologically important flavin redox cofactor.[35−37] These cationic isoalloxazines are known to give an intermediate flavin hydroperoxide like **1**, an active oxygen donor, upon reaction with hydrogen peroxide.[61]

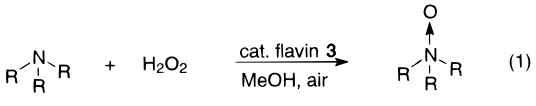


2



3

Interestingly, N^1,N^5-dialkylated 5,10-dihydroalloxazines such as **3** are suggested to give a hydroperoxide similar to **1** upon reaction with molecular oxygen.[62] We considered these alloxazine derivatives a highly attractive group to study as models for flavins in catalytic oxidations. In this paper we report on the first, to the best of our knowledge, efficient catalysis by an N^1,N^5-dialkyl blocked flavin analogue **3** applied on the oxidation of tertiary amines by H_2O_2. Turnover numbers up to 182 were obtained with this flavin analogue as a biomimetic catalyst (eq 1).



(1)

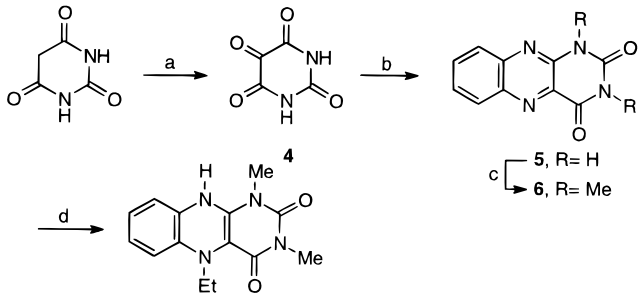
Results and Discussion

Synthesis of the Flavin Catalyst 3. The catalyst **3** was synthesized in a four-step procedure according to Scheme 1. The tricyclic alloxazine skeleton was built up via oxidation of barbituric acid, followed by condensation between the alloxan (**4**) thus formed and *o*-phenylenediamine. After methylation of the two sp^3-nitrogens in **5**, the desired 5,10-dihydroalloxazine **3** was obtained by a one-pot 1,4-hydrogenation/reductive alkylation procedure.[62] A hard electrophile like acetaldehyde preferentially adds to the N^5-carbon in a reductive alkylation of the 5,10-dihydroalloxazine, as has been described by Hemmerich et al previously.[63] Reduction by sodium dithionite, a widely employed method for the reduction of isoalloxazines,[64] was tried in the presence of sodium cyanoborohydride[65] but resulted in an overreduced product. The catalyst **3** is like most models of dihydroflavins very sensitive toward molecular oxygen.[62,64] Consequently, it was found to be crucial to carry out the workup under a strictly inert atmosphere for a successful preparation. The flavin analogue **3** was obtained as a yellow solid, which was characterized by spectroscopic means. In contrast, workup in air resulted in a brown powder with different spectroscopic properties.

Flavin-Catalyzed H_2O_2 Oxidation of Tertiary Amines. Reaction of *N*-methylmorpholine (**7**) with H_2O_2 in the presence of air and 2.5 mol % of the flavin **3** resulted in a rapid conversion of the amine to its corresponding *N*-oxide **8**. After about 1 h, more than 80% conversion had been obtained (Table 1, entry 1). Several

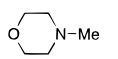
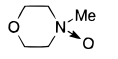
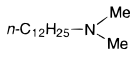
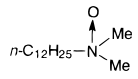
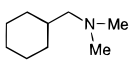
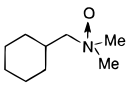
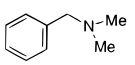
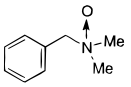
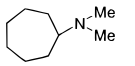
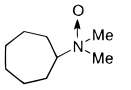
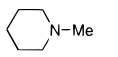
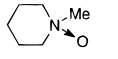
(41) Copéret, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.
(42) The MTO catalyst has also been used for H_2O_2 oxidation of tertiary amines: Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 1326.
(43) Mosher, H. S.; Turner, L.; Carlsmith, A. *Org. Synth. Coll. Vol.* **1963**, *IV*, 828.
(44) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.
(45) Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856.
(46) Baumstark, A. L.; Dotrong, M.; Vasquez, P. C. *Tetrahedron Lett.* **1987**, *28*, 1963.
(47) Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 15877.
(48) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.
(49) Ahrgren, L.; Sutin, L. *Org. Proc. Res. Dev.* **1997**, *1*, 425.
(50) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(51) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(52) Franzen, V.; Otto, S. *Chem. Ber.* **1961**, *94*, 1360.
(53) Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3287.
(54) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825.
(55) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U. *J. Chem. Soc., Chem. Commun.* **1991**, 473.
(56) Grennberg, H.; Faizon, S.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 263.
(57) Wang, G.-Z.; Andreasson, U.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1994**, 1037.
(58) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4017.
(59) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 6498.
(60) In one case the flavin system has been used to induce a radical chain reaction: Mager, H. I. X.; Tu, S.-C. *Tetrahedron* **1994**, *50*, 6759.
(61) Bruice, T. C. *Acc. Chem. Res.* **1980**, *13*, 256.
(62) Mager, H. I. X.; Berends, W. *Tetrahedron* **1976**, *32*, 2303.
(63) Ghisla, S.; Hemmerich, P. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1564.
(64) Ghisla, S.; Hartmann, U.; Hemmerich, P.; Müller, F. *Justus Liebigs Ann. Chem.* **1973**, 1388.
(65) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 8, p 25.

Scheme 1. Synthesis of the Flavin Catalyst 3[a]



[a](a) CrO_3, HOAc/H_2O; (b) *o*-phenylenediamine, H_3BO_3, HOAc; (c) MeI, K_2CO_3, DMF; (d) H_2, Pd/C, CH_3COH, HCl, EtOH/H_2O.

Table 1. Oxidation of Tertiary Amines Employing the Flavin–Hydrogen Peroxide System as Oxidant[a]

entry	amine	time (>85% conv.)	product	rate enhancement cat. : non-cat.[b]
1	 **7**	1 h[c]	 **8**	61:1 (6344:1)[d]
2	 **9**	27 min	 **10**	49:1 (5096:1)[d]
3	 **11**	25 min	 **12**	51:1 (5304:1)[d]
4	 **13**	50 min	 **14**	83:1 (8632:1)[d]
5	 **15**	31 min	 **16**	67:1 (6968:1)[d]
6	 **17**	32 min	 **18**	27:1 (2808:1)[d]
7	 **19**	55 min	 **20**	39:1 (4056:1)[d]
8[e]	 **21**	54 min	 **22**	27:1 (2507:1)[d]

[a] The reactions were performed using 2.5 mol % flavin in MeOH-d_4 as described in the Experimental Section. [b] Calculated by division of the initial rates for catalyzed and noncatalyzed reactions, respectively. [c] 80% conversion. [d] Estimated ratio of the reactivities of catalytic flavin hydroperoxide and H_2O_2 (see text). [e] 2.8 mol % flavin was used.

other amines having different kinds of R groups attached to the tertiary nitrogen atom were also oxidized in fast reactions by the catalytic flavin-hydrogen peroxide system (Table 1). Interestingly, although H_2O_2 is thought to be the active oxidant (vide infra), molecular oxygen (air) was necessary for generation of an active catalyst.[66] The product amine *N*-oxides are in many cases synthetically useful compounds or important intermediates for further transformations.[67,68] *N*-Methylmorpholine *N*-oxide (**8**) is a commonly employed oxidant for the reoxidation of transition metals such as osmium and ruthenium (vide supra). Larger *N*-oxides such as **10** are often prepared by H_2O_2 oxidation on an industrial scale as they are useful surfactants.[68] However, these large-scale direct oxidations by hydrogen peroxide may require elevated temperatures and also prolonged reaction times. These disadvantages could possibly be overcome by the use of a catalytic system such as the one described here. *N*,*N*-Dimethylamine *N*-oxides, e.g. **14**, are important intermediates in the synthetically useful preparation of olefins via the well-known Cope elimination.[39,69] Interestingly, the catalytic oxidation of amine **13** occurs with a rate comparable to most other substrates (Table 1). The noncatalyzed reaction was found to be particularly slow and required 2 days for completion, which has also been observed by Cope.[39] In the Meisenheimer rearrangement, allylic or benzylic amine *N*-oxides serve as substrates in a transformation into O-alkylated *N*,*N*-disubstituted hydroxylamines.[70] The *N*-oxide **16** would be a suitable substrate for this reaction.

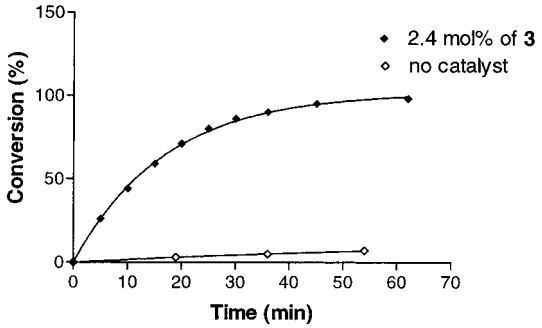


Figure 1. Rate of conversion for catalyzed and noncatalyzed H_2O_2 oxidation of *N*,*N*-dimethyldodecylamine (**9**) to its corresponding *N*-oxide.

Heteroaromatic compounds are normally not oxidized by hydrogen peroxide[67] but require stronger oxidants such as peracids. The flavin hydroperoxide **1** is described to be between H_2O_2 and mCPBA in reactivity as oxygen donor.[71] An interesting substrate to try to oxidize with the catalytic system employing a flavin analogue would therefore be pyridine. However, attempted oxidation of pyridine with our system failed, and apparently the oxidizing power of the intermediate hydroperoxide is too low for this heteroaromatic substrate.

To estimate the rate enhancement for the catalytic reaction, the noncatalyzed oxidation of tertiary amines with hydrogen peroxide was studied in control experiments. For most substrates less than 20% conversion had been obtained after 2–7 h reaction time. This is to be compared with more than 85% conversion within 1 h for all reactions performed in the presence of the flavin catalyst (Table 1). In Figure 1, the conversion versus reaction time is plotted for catalyzed and noncatalyzed oxidation of amine **9** as an example of the observed difference in rate. For all aliphatic amines studied, a

(66) When the reaction was performed under argon, the solubility of the catalyst was low, and no conversion could be seen. However, upon inlet of molecular oxygen the catalyst immediately dissolved, and a rapid oxidation of the amine was observed.

(67) Albini, A. *Synthesis* **1993**, 263.
(68) Sauer, J. D. *Surfactant Sci. Ser.* **1990**, *34*, 275.
(69) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.
(70) Meisenheimer, J. *Ber. Dtsch. Chem. Ges.* **1919**, *52B*, 1667.
(71) Bruice, T. C. *Isr. J. Chem.* **1984**, *24*, 54.

substantial rate enhancement was obtained in the presence of catalyst **3** (Table 1).

In the experiments reported in Table 1 an excess of hydrogen peroxide (2.6 equiv) was employed to get a better accuracy in the determination of the initial rate of the noncatalyzed reactions, which are known to be slow.[39,40] The rate of the noncatalyzed reaction is proportional to the H_2O_2 concentration. The flavin-catalyzed reaction, on the other hand, is not dependent on the H_2O_2 concentration (except at very low concentrations), which is consistent with a mechanism involving the catalyst in the rate-limiting step of the catalytic cycle (vide infra).[72] Therefore, the rate enhancement factors in Table 1 should roughly be 2.6 times larger when 1 equiv of H_2O_2 is used. To demonstrate this point we have run one experiment with 0.5 equiv of H_2O_2. *The rate enhancement for oxidation of amine **13** could thus be increased from 83 (Table 1, entry 4) to as much as 355 simply by the use of a lower peroxide concentration.*[73] The possibility of using low concentrations of the oxidant (e.g. via slow addition) makes our mild oxidation system highly attractive for oxidation of tertiary amines in the presence of other functionalities that may be sensitive to hydrogen peroxide.

To get an even better insight into how good catalyst the flavin is, the ratio of the reactivity of flavin hydroperoxide compared to hydrogen peroxide can be calculated. A rate enhancement of 61 (Table 1, entry 1) can be corrected for the fact that only 2.5 mol % flavin was used by division of 61 with 0.025 giving 2440. However, as an excess of H_2O_2 was used (2.6 equiv), the number 2440 should be multiplied by 2.6 to get an appropriate comparison of the reactivities of the two hydroperoxides. Thus, under the reaction conditions used in this study the flavin hydroperoxide is more than 6000 times more reactive than H_2O_2 toward amine **7**. In these calculations it has been assumed that there is a fast oxidation of flavin to its corresponding hydroperoxide, which is reasonable under conditions using a large excess of H_2O_2 compared to flavin. However, Murahashi has described formation of a cationic flavin complex as the rate-determining step in a catalytic cycle for a flavin such as **2**.[72] If this would be valid also for flavin **3** under the reaction conditions described here the calculated ratios between the reactivities of the two different hydroperoxides should be even higher than those reported in Table 1.[74]

The stability of a catalyst is of importance for the development of a good catalytic system. This feature was tested by addition of the substrate in several portions to the reaction mixture. The catalyst was found to be active even after a complete consumption of substrate, corresponding to 42 turnover numbers (TON) for the flavin catalyst. During the second addition a somewhat slower oxidation was observed (Figure 2) but the rate was still significantly higher than for the noncatalyzed reaction.

The amine *N*-oxides were also synthesized on a preparative scale by employing this efficient flavin catalytic system. Up to 85% isolated yield and turnover numbers of 73−85 on the flavin could easily be achieved (Table 2). By addition of hydrogen peroxide in portions to a reaction employing only 0.4 mol % catalyst, the TON could be raised to 182 (Table 2, entry 5). This, but also the TON of 73−85 (Table 2, entries 1−4), is much higher than what has generally been observed in the previously described catalytic flavin systems, where less than 20 TON have been reported for the majority of substrates.[35−37,75]

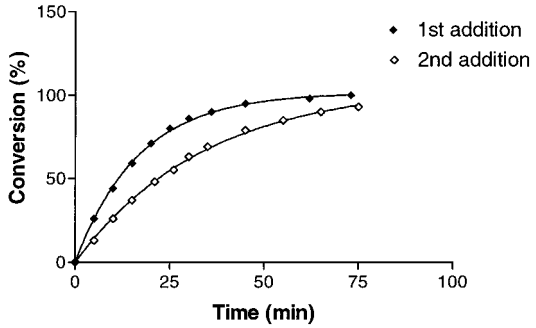


Figure 2. Rate of the reaction when *N*,*N*-dimethyldodecylamine (**9**) as substrate is added in several portions.

Suggested Catalytic Cycle For the Flavin Analogue 3. In the catalytic oxidations of amines the 5,10-dihydroalloxazine **3** most likely acts as a precursor of the active catalyst (Scheme 2). By reaction with molecular oxygen (step i) an intermediate flavin hydroperoxide **23** is formed.[62,76] Most likely the presence of an *N*-ethyl substituent in the 5-position of **23** is of importance for the success of the catalytic reaction. Earlier studies have shown that in the absence of an alkyl group in the corresponding position in N^{10}-alkylated flavins, a facile elimination of H_2O_2 occurs.[71] Moreover, previously described catalytic systems where this substituent is lacking have turned out to be inactive.[36,37]

The flavin hydroperoxide **23** would be able to transfer its electrophilic oxygen to an amine, in close analogy with what has been described by Bruice et al for the stoichiometric oxidation of tertiary amines by hydroperoxide **1** (steps ii and iii).[58,59] Elimination of a hydroxide ion from **24** would give the cationic alloxazine **25** (step iv), which on reaction with hydrogen peroxide can regenerate the hydroperoxide **23**.[37,61,77] In contrast to systems employing isoalloxazines (e.g. **2**) as flavin models, most likely there is no stable 4a-hydroxy intermediate **24** formed with this alloxazine system (Scheme 2).[62,63] In the present study of flavin-catalyzed amine oxidations both molecular oxygen and hydrogen peroxide have been shown to be essential for an oxidation to occur. This observation is explained by the catalytic cycle proposed (Scheme 2).

Conclusion

Flavins are important cofactors in many biologically important redox reactions. Their redox chemistry can be taken advantage of in synthetic organic chemistry, as have been exemplified by the mild and highly efficient

(72) Murahashi et al. describe the formation of a cationic flavin complex as the rate-determining step in a detailed mechanistic study for the flavin-catalyzed oxidation of methyl phenyl sulfide. See ref 37.

(73) The reactions were performed using the same conditions as described for the kinetic study in the Experimental Section, except for the use of a lower amount of H_2O_2 (14 μL, 0.12 mmol). A larger volume of MeOH-d_4 (0.66 mL) was used to give the same total volume.

(74) Flavin hydroperoxides are described to be 10^4 times more reactive than H_2O_2 as oxygen donors: Bach, R. D.; Su, M.-D. *J. Am. Chem. Soc.* **1994**, *116*, 5392.

(75) In the flavin-catalyzed oxidation of dibutyl sulfide a TON of 99 has been reported. See ref 37.

(76) This is in analogy with what has been reported for the reaction of 1,5-dihydroflavins with $^3O_2$: Kemal, C.; Bruice, T. C. *Proc. Nat. Acad. Sci. U.S.A.* **1976**, 73, 995.

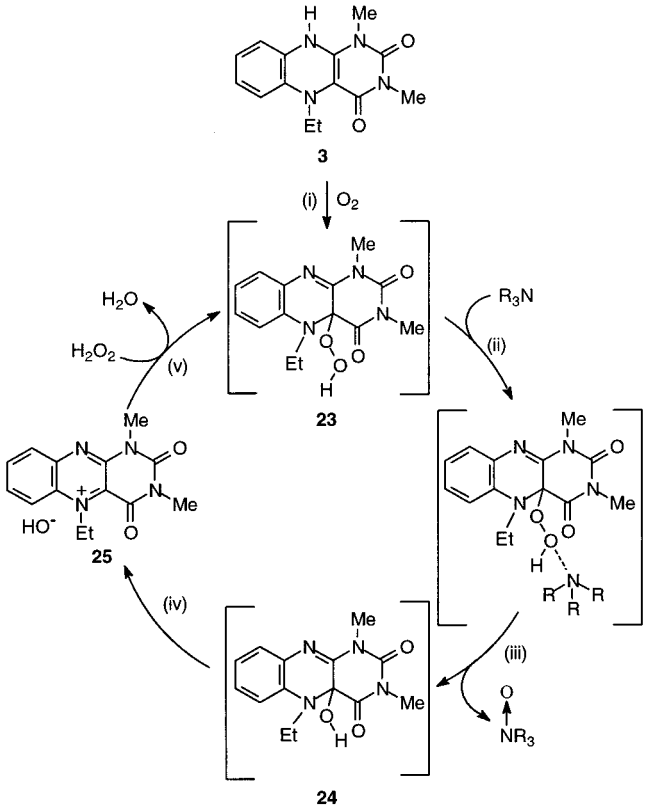
(77) Kemal, C.; Chan, T. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7273.

Table 2. Preparation of Amine *N*-Oxides from Tertiary Amines

entry	substrate	mol % of catal	reacn time (h)	yield (%)[a]	TON[b]
1	*N*-methylmorpholine (**7**)	1	8 h	75	75
2	*N*,*N*-dimethyldodecylamine (**9**)	1	2 h	85	85
3	*N*,*N*-dimethyl(cyclohexylmethyl)amine (**13**)	1	8 h	73	73
4	*N*,*N*-dimethylbenzylamine (**15**)	1	2 h	82	82
5[c]	*N*,*N*-dimethyldodecylamine (**9**)	0.4	4 h	73	182

[a] Isolated yields after purification. [b] A minor pathway for formation of amine *N*-oxide via a direct oxidation by H_2O_2 cannot be completely ruled out. [c] H_2O_2 (3.3 mmol) was added in three portions with 40 min intervals to a solution of substrate (3 mmol) and flavin **3** (3.2 mg) in 7.7 mL of MeOH, and the mixture was stirred for another 2 h 40 min.

Scheme 2. The catalytic cycle for flavin mediated oxidations of amines.



H_2O_2 oxidation of tertiary amines described in this paper. The present study represents the first example where an N^1,N^5-dialkyl blocked flavin is used in catalysis. The flavin catalyst has been shown to have good efficiency, as reflected by the high TON obtained when only 0.4 mol % catalyst was used. Moreover, this is the first catalytic system where a fully reduced alloxazine acts as a precursor of the active flavin catalyst, which is easily generated in the presence of molecular oxygen (air). In the oxidation of a number of tertiary amines a considerable rate enhancement was observed compared to the noncatalyzed reactions. The product amine *N*-oxides have been isolated in good yields using 0.4−1 mol % flavin catalyst under these mild conditions.

Further studies are in progress on the application of the flavin-based N-oxidation system on different catalytic systems where an in situ generation of an amine *N*-oxide would be desirable.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz or 300 and 75.4 MHz, respectively. Chemical shifts (δ) are reported in ppm, using residual solvent or Me_4Si as internal standard. Most reagents were purchased from Lancaster except for *N*-methylmorpholine (**7**) (Fluka), dodecyl bromide (Fluka), *N*,*N*-dimethyl(cyclohexylmethyl)amine (**13**) (Aldrich) and dimethylamine (40% aqueous solution, Merck). MeOH-d_4 was from Dr. Glaser, AG Basel. Merckoquant peroxide test strips were bought from Merck. Alloxan monohydrate (**4**) was prepared by oxidation of barbituric acid.[78] *N*,*N*-Dimethyldodecylamine (**9**), *N*,*N*-dimethyl-2-octylamine (**11**), *N*,*N*-dimethylbenzylamine (**15**), and *N*,*N*-dimethylcycloheptylamine (**17**) were prepared by reacting the corresponding bromides with *N*,*N*-dimethylamine (see Supporting Information for details). DMF was dried over CaH_2 and distilled at reduced pressure before use. Acetaldehyde was distilled over catalytic amounts of *p*-toluenesulfonic acid. Other commercial chemicals were used as received without further purification. The amine *N*-oxides were purified by chromatography on basic aluminum oxide (Aldrich, 150 mesh), while other compounds were purified on silica gel (Merck silica gel 60, 230−400 mesh). Progress of the amine oxidation reactions was followed by TLC on Merck aluminum oxide 60 F_{254} plates (neutral) or Merck silica gel 60 F_{254} plates. For hydrogenation reactions a Parr pressure reaction apparatus was used.

Alloxazine (5). *o*-Phenylenediamine (6.75 g, 62 mmol) was dissolved in HOAc (100 mL). To this solution was added a mixture of **4** (10.0 g, 62 mmol) and H_3BO_3 (4.25 g, 69 mmol) in hot HOAc (400 mL). The reaction mixture was stirred for 75 min at room temperature. The precipitate formed during the reaction was filtered off and washed with HOAc and then with ether. Drying gave **5** as a green solid (9.34 g, 70%). The ^{1}H and ^{13}C NMR spectra of the product were identical to those of commercial **5**.

1,3-Dimethylalloxazine (6). Alloxazine (**5**) (3.99 g, 18.6 mmol) and K_2CO_3 (13.35 g, 96.6 mmol) were added to dry DMF (150 mL) (all of the **5** did not dissolve). The atmosphere was changed to N_2, and MeI (2.7 mL, 43.4 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed at reduced pressure, and the remaining solid was dissolved in CH_2Cl_2 and H_2O. The phases were separated, and the aqueous phase was extracted with 7 × CH_2Cl_2. The combined organic phases were washed with saturated aqueous NaCl and dried over $MgSO_4$. Evaporation of the solvent gave **6** as a yellow powder. Purification of the crude product by column chromatography (95:5 CH_2Cl_2/EtOAc) gave **6** as a yellow powder (3.99 g, 88%). NMR data were in accordance with those previously reported in the literature.[79,80]

1,3-Dimethyl-5-ethyl-5,10-dihydroalloxazine (3).[62] Compound **6** (200 mg, 0.83 mmol) and Pd/C (10%, 81 mg, "preactivated" under reduced pressure for 30 min) were suspended in degassed EtOH (17 mL) and H_2O (16 mL) under Ar bubbling. Concentrated HCl (1.4 mL) and freshly distilled acetaldehyde (1.4 mL, 25 mmol) were added to the mixture. The mixture was hydrogenated at room temperature and 1.1 atm pressure for 26 h. *The workup was done under inert atmosphere using conventional Schlenk techniques.* The mixture was filtrated through Celite giving a yellow solution. The pH was adjusted to 7−8 by addition of concentrated NH_3 (5

(78) Holmgren, A. V.; Wenner, W. *Org. Synth. Coll. Vol.* **1963**, *IV*, 23.

(79) Grande, H. J.; van Schagen, C. G.; Jarbandhan, T.; Müller, F. *Helv. Chim. Acta* **1977**, *60*, 348.

(80) Grande, H. J.; Gast, R.; van Schagen, C. G.; van Berkel, W. J. H.; Müller, F. *Helv. Chim. Acta* **1977**, *60*, 367.

mL). At this pH the product seemed to be extremely air sensitive. As soon as the color of the mixture started to change from yellow to orange-brown, small amounts of aqueous $Na_2S_2O_4$ were added which gave the yellow color back again. Most of the solvents were evaporated. The solution was cooled in ice−water bath, and the solid was collected by filtration. The solid was suspended in degassed H_2O (1.4 mL) containing small amounts of dissolved $Na_2S_2O_4$ and stirred for 20 min. Filtration gave a yellow powder, which was washed several times with degassed H_2O. The solid was dried overnight at reduced pressure to give **3** as a yellow powder (166 mg, 74%). When **3** was stored at −30 °C under argon, its catalytic activity remained for several months. Since **3** is very sensitive toward molecular oxygen, the NMR sample was prepared in $CDCl_3$ having a layer of aqueous (D_2O) $Na_2S_2O_4$ on top. The sample was prepared under argon. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.86 (m, 2H), 6.78 (dt, 1H, J = 2.0, 7.4 Hz), 6.60 (dd, 1H, J = 1.2, 7.7 Hz), 4.8 (br s, 1H), 3.47 (s, 3H), 3.44 (q, 2H, J = 7.1 Hz), 3.34 (s, 3H), 1.13 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 158.0, 150.3, 146.3, 136.2, 134.9, 125.0, 123.5, 122.5, 114.7, 99.6, 50.6, 28.7, 28.3, 11.4.[81]

General Procedure for the Kinetic Study. The conversion rates for reactions performed with flavin catalysis and for those run in the absence of the catalyst were determined by integration of the corresponding ^{1}H signals in amine and the product amine *N*-oxide. For most compounds the CHN*Me* signals were integrated; however, in a few cases the C*H*NMe or C*H*$_2$NMe signals were integrated due to better separation from other peaks. The rate enhancement was calculated by division of the rate at low conversion (10%) for the catalyzed and noncatalyzed reactions, respectively.

A. With Flavin Catalyst. *N*-Methylmorpholine *N*-Oxide (8). Flavin **3** (1.7 mg, 0.006 mmol) was added to a solution of *N*-methylmorpholine (27 μL, 0.25 mmol) in MeOH-d_4 (0.6 mL) in an NMR tube. To this mixture H_2O_2 (75 μL of a 27% aqueous solution, 0.655 mmol) was added, and the time measurement was started. After a few minutes almost all **3** had dissolved to give a clear and yellow solution. During the course of the reaction small amounts of a white precipitate were formed. The reaction was monitored by ^{1}H NMR (5 min intervals for the first 35 min, thereafter with 10 min intervals until the reaction time was 65 min (80% conversion)). The sample was manually shaken between the NMR measurements. The ^{1}H and ^{13}C NMR spectra of the product were identical to those of commercial **8**.

Oxidation of Other Tertiary Amines. The reactions were followed by ^{1}H NMR for 35−65 min (5 min intervals for the first 35 min, thereafter with 10 min intervals until >85% conversion). The NMR spectra of the products were compared to literature data (*N*,*N*-dimethyldodecylamine *N*-oxide (**10**),[82] *N*,*N*-dimethylbenzylamine *N*-oxide (**16**),[83] *N*-methylpiperidine *N*-oxide (**20**),[84,85] and triethylamine *N*-oxide (**22**)[86]) or to authentic samples prepared by H_2O_2 oxidation of the amines according to literature procedures (*N*,*N*-dimethyl-2-octylamine *N*-oxide (**12**),[87] *N*,*N*-dimethyl(cyclohexylmethyl)amine *N*-oxide (**14**),[39] and *N*,*N*-dimethylcycloheptylamine *N*-oxide (**18**)[88]).

B. Without Flavin Catalyst. *N*-Methylmorpholine *N*-Oxide (8). To a solution of *N*-methylmorpholine (27 μL, 0.25 mmol) in MeOH-d_4 (0.6 mL) in an NMR tube was added H_2O_2 (75 μL of a 27% aqueous solution, 0.655 mmol). The time measurement was started, and the reaction was followed by ^{1}H NMR for 10 h (28% conversion). The ^{1}H and ^{13}C NMR spectra of the product were identical to those of commercial **8**.

Oxidation of Other Tertiary Amines. The reactions were followed for 7−12 h. The products were characterized as described above.

General Procedure for Preparation of Amine *N*-Oxides. *N*,*N*-Dimethyldodecylamine *N*-Oxide (10). Amine **9** (214 mg, 1.0 mmol) was stirred in MeOH (2.5 mL). To this mixture the flavin catalyst **3** (3.1 mg, 0.011 mmol, 1.1 mol %) and H_2O_2 (125 μL of a 27% aqueous solution, 1.1 mmol) were added. After 2 h of stirring at room temperature, excess H_2O_2 was destroyed by addition of solid MnO_2 (93 mg). Filtration through Celite, followed by evaporation of the solvents under reduced pressure, gave the crude product, which was purified on basic Al_2O_3 (gradient 100% CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH). Immediate evaporation of the solvents afforded 195 mg (85%) of **10** as a white solid. The NMR spectra of the product were in accordance with literature data.[82]

Acknowledgment. Financial support from the Swedish Research Council for Engineering Sciences and the Swedish Natural Science Research Council is gratefully acknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of flavin **3**, experimental procedure for the preparation of amines **9**, **11**, **15**, and **17**, spectral data for amine *N*-oxides **12**, **14**, and **18**, and experimental details for amine oxidations as described in the kinetic study (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any masthead page for ordering information.

JO980926D

(81) The ^{13}C NMR shifts of the N^5-ethyl group were found to be almost identical to what has been reported for the similar compound 5-ethyl-3,7,8,10-tetramethyl-1,5-dihydroisoalloxazine: van Schagen, C. G.; Müller, F. *Helv. Chim. Acta* **1980**, *63*, 2187.

(82) Brycki, B.; Szafran, M. *Magn. Reson. Chem.* **1992**, *30*, 535.

(83) Lorand, J. P.; Anderson, J. L. J.; Shafer, B. P.; Verral, D. L. *J. Org. Chem.* **1993**, *58*, 1560.

(84) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 2911.

(85) Al-Rawi, J. M. A.; Flamerz, S.; Khuthier, A. H. *Spectrochim. Acta A.* **1985**, *41*, 1391.

(86) Bravo, R.; Laurent, J.-P. *J. Chem. Res., Miniprint* **1983**, 710.

(87) Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun.* **1973**, *38*, 2102.

(88) Cope, A. C.; Pike, R. A.; Spencer, C. F. *J. Am. Chem. Soc.* **1953**, *75*, 3212.