PHOTO-INDUCED ELECTRON-TRANSFER OXIDATION OF NICOTINE[#]

Shuzo Yamada, Toshiaki Sakai, and Mamoru Ohashi[*]

Department of Materials Science, The University of Electro-Communications

Chofu, Tokyo 182, Japan

Abstract——Irradiation of nicotine in acetonitrile in the pres-
ence of TiO_2 or 9,10-dicyanoanthracene under oxygen with a 100 W
high pressure mercury lamp gave nicotyrine, cotinine, and dehydro-
nornicotine. A reaction mechanism leading to these products
through nicotine radical cation and superoxide anion is proposed.

Absorption and metabolism of nicotine (1) after smoking tobacco were well estab-
lished by the identification of cotinine (2) in the smoker's urine.[1] This
metabolic pathway has been demonstrated with the microsomal fraction of rabbit
liver in the presence of NADPH and O_2.[2] Nicotine is also metabolized to yield
nornicotine and its diastereoisomeric N-oxides by liver microsomal preparations
from various species.[3] Castagnoli, Jr. et al. demonstrated the generation of the
N-methyleniminium species during the course of metabolic oxidative N-demethylation
of nicotine.[4] It has been established that the metabolic oxidation of xenobiotics
is mediated by cytochrome P-450 with which the oxidation processes include
electron-transfer steps and the superoxide anion ($O_2^{\overline{\cdot}}$) formation. As a model
reaction for the enzymatic oxidation we chose photo-induced electron-transfer
reactions on the surface of illuminated semiconductor such as TiO_2 or in a solu-
tion of an electron acceptor such as 9,10-dicyanoanthracene (DCA) in the oxygen
atmosphere in which participation of superoxide anion was reported. We report
here that oxidation of nicotine by irradiation in the presence of an electron
acceptor such as TiO_2 or DCA and O_2 gave various products including the expected
cotinine (2), the same product as the metabolite, nicotyrine (3) and dehydro-

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[#] Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.
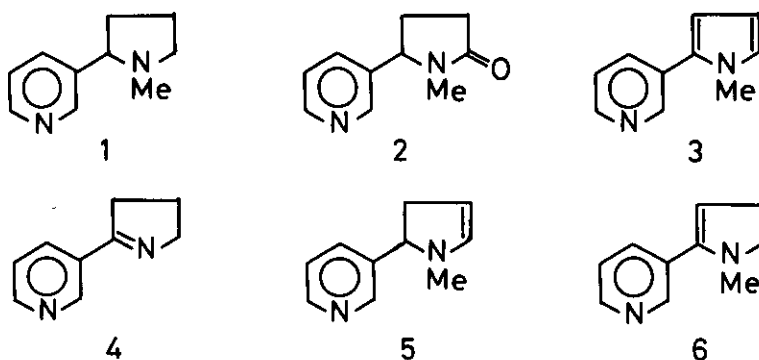
nornicotine (4).

Semiconductors such as TiO_2 or ZnS have attracted great interest in the field of organic photochemistry since Fujishima and Honda reported the sustained oxidation of water at illuminated TiO_2 in 1972.[5] Applications of semiconductors as redox sensitizers to photo-induced oxidation reactions of olefins have been initiated by Tokumaru and co-workers[6] and ever since numerous reactions have been reported.[7] Fox and Chen reported photocatalytic formylation of primary and secondary amines on irradiated semiconductor powders in the presence of oxygen.[8] Participation of superoxide anion produced by electron-transfer from the excited TiO_2 to molecular oxygen has been assumed in those reactions as one of the oxidation processes.[7] Typical reaction conditions utilizing TiO_2 are as follows; nicotine(68 mg) was irradiated in acetonitrile(10 ml) in the presence of TiO_2(anatase, 75 mg) under oxygen by means of a high pressure mercury lamp(500 W) with a Corning 0-52 filter (light 366 nm) for 22 h. The products were analyzed by GC/MS using OV-17 column and the yields of products were estimated on the basis of integrated peak areas having cotinine as the internal standard. The structure of cotinine (2) was identified by direct comparison of the spectral data with those of the authentic sample prepared according to literature.[9] Nicotyrine (3)[10] and dehydronornicotine (4)[11] were identified by mass spectral comparison with the standard spectra. Table 1 summarizes the yields of products. Although the efficiency is poor as is the usual case of semiconductor-catalyzed photooxidation, we have discovered for the first time that a pyrrolidine ring is converted into a pyrrolidinone and a pyrrole group by photo-induced TiO_2-catalyzed oxidation, while oxidation of amides to imides under similar conditions has been reported.[12]

We next tried Foote's oxidation i.e. 9,10-dicyanoanthracene (DCA)-sensitized electron-transfer photo-oxygenation, of which mechanism has been proposed as follows: the initial step is electron-transfer from the substrate to the singlet excited DCA to generate DCA anion radical ($DCA^{\bar{\cdot}}$) and the substrate radical cation. Subsequent steps involve transfer of an electron from $DCA^{\bar{\cdot}}$ to oxygen to generate $O_2^{\bar{\cdot}}$ which reacts with the substrate radical cation to yield the peroxidic products.[13] Thus, an acetonitrile solution(10 ml) of nicotine(68 mg) and DCA(14 mg) was irradiated under oxygen by means of a high pressure mercury lamp (500 W) using a Corning 0-52 filter for 11 h. The compounds 2, 3, and 4 were identified in the same manner as the case of TiO_2-oxidation.[14] The yields of the products are also summarized in Table 1.

Table 1. Yields[a] of the products in the presence of electron acceptors under O_2 or N_2

Acceptor	Atmosphere	2	3	4
TiO_2	O_2	0.12	0.36	1.01
	N_2	–	–	0.36
DCA	O_2	1.05	0.11	0.27
	N_2	–	–	trace

a) Yield(%) based on starting nicotine. Conversions of the starting nicotine were less than 10%.

The products of both reactions catalyzed with either TiO_2 or DCA are similar to each other, hence the mechanism of both oxidation reactions must resemble to each other. In both reactions probable participation of electron-transfer and super-oxide anion formation in the oxidation process may account for the generation of compounds 2-4. The difference of the yields between the two reactions may be ascribable to the difference of the circumstances around radical ions. On the other hand, Khuong-Huu et al. demonstrated that methylene blue-sensitized oxida-tion of nicotine gave 2, 3, and N-oxide.[9] Their result is similar to ours, and electron-transfer from nicotine to singlet excited oxygen ($^1O_2$) leading to the superoxide anion formation may be conceivable. However, Saito et al. have recently demonstrated that electron-transfer between $^1O_2$ and an amine giving rise to $O_2^{\bar{\cdot}}$ is possible only for amines with oxidation potential less than -0.5 V vs. SCE in aqueous media.[15] Also, such electron-transfer reactions have not been observed in

acetonitrile or in the case of benzylamine-O_2 system, therefore the mechanism for the formation of $O_2^{\overline{\cdot}}$ via $^1O_2$ is excluded.

Although the oxygenation mechanism of nicotine has not been yet specified, we conclude here safely that photo-induced electron-transfer reactions catalyzed by an electron acceptor (TiO_2 or DCA) under oxygen generate cotinine, similarly to the enzymatic oxygenation in the nicotine metabolism.

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14) In addition to above products we found small amounts of two dehydronicotines (5 and 6), probable intermediates to give nicotyrine, in the TiO_2- and DCA-catalyzed reactions, respectively. Their structures were deduced based on the mass spectral fragmentations. MS(20 eV) m/z(relative intensity); 5: 160 (M^+,44) 159(29) 145(11) 132(22) 105(25) 82(100). 6: 160(M^+,58) 159(31) 145 (21) 131(37) 118(41) 106(67) 105(100) 84(50) 82(58) 80(66).

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