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(46) The ΔH_f of the unprotonated diradical was estimated to be 28 kcal/mol from the bond dissociation energy (BDE = 93.3 kcal/mol) of the C–H bond of dimethyl ether[47] and the BDE of ~91 kcal/mol for the methylene C–H bond of methyl ethyl ether which was estimated to be lower than the BDE of the C–H bond of dimethyl ether by the same amount that the BDE of the methylene C–H bond of ethanol[48] is less than the BDE of the C–H bond of methanol.[49] The proton affinity of the diradical was estimated to be the same as the PA of methyl ethyl ether.[16]
(47) F. R. Cruickshank and S. W. Benson, *Int. J. Chem. Kinet.*, **1**, 381 (1969).
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(51) R. D. Bowen, D. H. Williams, and G. Hvistendahl, *J. Am. Chem. Soc.*, **99**, 7509 (1977).
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(53) This intermediate ion was considered unlikely[44] because there were no ions characteristic of protonated oxirane. However, there should be discrimination against an intermediate which has a more ordered transition state than dissociation.
(54) The ΔH_f of the unprotonated diradical was estimated to be 38 kcal/mol from the BDE of 93.3 kcal/mol for the C–H bond of dimethyl ether.[47] The PA of this diradical was estimated to be the same as the PA of dimethyl ether.[16]
(55) An adjustment for the PA values as discussed for ions 2 and 4 would require an equal adjustment for the experimental TSE, because it is based on the ΔH_f of 157 kcal/mol for $CH_2{=}O^+CH_3$[45] which is relative to the ΔH_f's of ions which have similar ΔH_f's found from PA values.
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Mechanism of Indole–Singlet Oxygen Reactions. Interception of Zwitterionic Intermediates and "Ene" Reaction[1]

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Abstract: The trapping reaction of zwitterionic peroxides formed in singlet oxygen reaction of *N*-methylindoles is described. The zwitterionic peroxide derived from 1,3-dimethylindole (**1**) was intercepted by methanol, ethanol, isopropyl alcohol, and β-methoxyethanol. The trend of the efficiency of the trapping reactions by these alcohols was parallel to that for the interception of zwitterions from tetracyanoethylene and enol ethers by alcohols. It has been shown that the introduction of an electron-withdrawing substituent into the indole ring favors the trapping reaction over the oxidative cleavage of the 2,3 double bond. Thus, the photooxygenation of 1,2,3-trimethyl-5-nitroindole (**7c**), 9-methyl-6-nitro-1,2,3,4-tetrahydrocarbazole (**10a**), and 9-acetyl-1,2,3,4-tetrahydrocarbazole (**10b**) in methanol gave the corresponding trapping products **9, 11a,** and **11b,** respectively, whereas 1,2,3-trimethylindole (**7a**), 5-methoxy-1,2,3-trimethylindole (**7b**), and 9-methyl-1,2,3,4-tetrahydrocarbazole (**10c**) yielded only the ring cleavage products. Photooxygenation of **7a** in alcohols gave the ring cleavage product **8a** as the major product, whereas in aprotic solvents **7a** produced the ene-type product **13a.** In contrast, photooxygenation of 1,2-dimethyltryptophol (**7e**) gave only the trapping product **16** in both protic and aprotic solvents. The result suggests that a common intermediate for both "ene" and 1,2 cycloaddition is captured intramolecularly by the nucleophilic group of the side chain. The experimental results have been explained by the mechanism involving gauche and cis zwitterions as the intermediates.

Introduction

Electron-rich alkenes such as enamines and enol ethers are known to react readily with singlet oxygen to yield unstable dioxetanes which can subsequently cleave to two carbonyl fragments.[2] The mechanisms of the 1,2 cycloaddition are the subjects of much current controversy, the main question being whether the reactions are concerted or involve intermediates. A symmetry-allowed concerted $[{}_\pi 2_s + {}_\pi 2_a]$ process has been first proposed for the 1,2 cycloaddition of singlet oxygen to olefins.[2b,3-5] According to the orbital and state correlation diagrams, the $[{}_\pi 2_s + {}_\pi 2_s]$ approach should be forbidden.[2b] However, this process might occur in the case of alkenes with particularly low ionization potentials.[2b,3,4] Stepwise 1,2 cycloaddition might occur via short-lived intermediates such as perepoxides,[2b,8] zwitterions,[4,7] or 1,4 biradicals.[9] An electron transfer mechanism involving a radical cation and superoxide radical anion pair has also been proposed for the 1,2 cycloaddition of singlet oxygen to enamines.[10] Recent theoretical studies have reported that zwitterionic intermediates should be important in the reaction of singlet oxygen with electron-rich olefins,[4,7] whereas Harding and Goddard have proposed by GVB-CI calculations the mechanism involving a 1,4 biradical stabilized by an anomeric effect for the hydroperoxidation of methoxy-substituted olefins.[9b]

Considerable experimental work has been done in order to elucidate the mechanism of the 1,2 cycloaddition. Bartlett and Schaap[5] were the first to propose a concerted mechanism or one involving short-lived, stereochemically stable intermediates, based on the experimental observations, namely, the lack of a solvent effect on the rate of photooxygenation of *cis*-diethoxyethylene and the absence of stereochemical leakage during the photooxygenation in a polar solvent. On the other hand, we proposed over 10 years ago a zwitterionic precursor in the photooxygenation of highly electron-rich enamines such as fully N-alkylated uric acids.[11] Thereafter, there have been reported several examples in which products might be most reasonably explained in terms of zwitterions.[12] Recently, Conia et al.[13] and Jefford[14] have proposed a zwitterionic intermediate in explaining the high regioselectivity in the singlet oxygenation of cyclopropylethylenes. Zwitterionic intermediates are also postulated to play an important role in the reaction of triplet molecular oxygen with ketenes[15] or strained acetylenes.[16] However, these results do not provide conclusive evidence for the zwitterionic precursors. A chemical confirmation by in-

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terception would be highly desirable. We have recently demonstrated that low-temperature photooxygenation of *N*-methylindoles gives a polar peroxide which is efficiently intercepted intramolecularly by alcohols or secondary amines.[17] More recently, similar types of trapping reactions have been observed with singlet oxygenations of norbornenyl ethers,[18] norbornadienol ethers,[19] ketenes,[20] and indene[21] at low temperatures. Thus, the formation of such polar peroxides seems to be quite general in the singlet oxygen reactions of many electron-rich olefins. The present paper describes experimental evidence which strongly supports the intermediacy of zwitterionic peroxides in singlet oxygen reactions of *N*-methylindoles. In addition, we show that the enamine system having allylic hydrogens (-C=C(NR$_2$)CH$_2$-) can undergo an "ene" reaction by appropriately modifying the reaction conditions, and that the common intermediate for the 1,2 cycloaddition and "ene" reaction has a long enough lifetime to be captured intramolecularly by nucleophilic alcohols.

Results and Discussion

Interception of the Intermediates. Rose bengal sensitized photooxygenation of 1,3-dimethylindole (**1**) in methanol at room temperature gave a normal C_2–C_3 ring cleavage product, **2** (90%), which is generally considered to be formed through dioxetane **3**.[22] The photooxygenation was inhibited by the addition of singlet oxygen quenchers such as 1,4-diazabicyclo[2.2.0]octane.[17a,23] Singlet oxygen generated by the microwave discharge method was found to react with **1** adsorbed on silica gel to give the same product **2**.[24] The results indicate that the photooxygenation is a singlet oxygen mediated reaction. When, however, the photooxygenation of **1** was carried out in methanol at −70 °C and the reaction mixture was stripped of the solvent under vacuum at 0 °C, unstable 3-hydroperoxyindoline **4a** was obtained in 97% yield. The structure of **4a** was assigned on the basis of spectral data and by converting it to 2,3-dihydro-1,4-benzoxazine derivatives **5** with alcohols containing HCl.[17a,b] The hydroperoxide **4a** slowly decomposed in methanol with a half-life of ca. 15 min at 30 °C to give a complex mixture of products including **2** (30%), **5a** (23%), and polymeric materials, in sharp contrast to the finding that the photooxygenation of **1** in methanol at room temperature gave a high yield of **2** (Scheme I).[22]

We next examined the photooxygenation of **1** in various alcohols at low temperature (−60 °C). Photooxygenation of **1** in ethanol at −60 °C, followed by the workup at 0 °C, gave a similar trapping product, **4b** (72%), but in competition with the formation of **2** (21%). Photooxygenation of **1** at −60 °C in isopropyl alcohol under the identical condition gave a mixture of **4c** (51%) and **2** (44%). The portion of the trapping product drops from 97% in methanol to 51% in isopropyl alcohol with its increased steric requirements and its reduced molar hydroxyl concentration. β-Methoxyethanol is less nucleophilic than ethanol and the photooxygenation of **1** in the solvent under the conditions gave rise to a smaller percentage (60%) of the trapping product **4d** in addition to **2** (30%). The trend of the efficiency for the trapping reactions is parallel to that for the interception of zwitterions from tetracyanoethylene and enol ethers reported by Huisgen.[25]

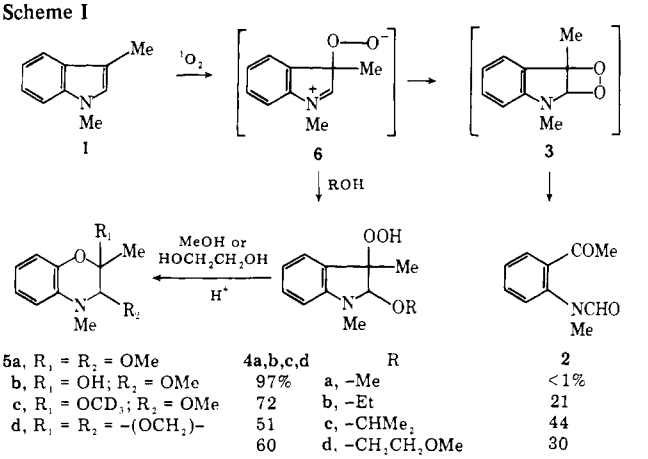
These results clearly indicate that the initial intermediate is a polar peroxide which is capable of undergoing an efficient addition reaction with nucleophilic methanol at low temperature. As we described earlier, similar types of intramolecular trapping reactions have been observed with *N*-methyltryptophol and N_b-methoxycarbonyl-N_a-methyltryptamine.[17] It seems highly unlikely that dioxetane **3** is the precursor of the trapping products **4**, since many dioxetanes,[18-20,26-28] including an indole dioxetane,[29] cannot react with alcohols but decompose exclusively to carbonyl fragments. The results are most

Table I. Relative Rates of Photooxygenation of N-Substituted Indoles[a]

compd	**10b**	**10a**	**7c**	**1**	**10c**	**7a**	**7b**
rel rate[b]	1	4.8	5.0	12.5	59	70	98
trapping by methanol	*c*	*c*	*c*	*d*	*e*	*e*	*e*

[a] In methanol at 20 °C. [b] Relative rate of disappearance of substrates determined at ca. 10% conversion. [c] Trapped at 0 °C. [d] Not trapped at 0 °C but efficiently trapped at −70 °C. [e] Not trapped even at −70 °C.

Scheme I

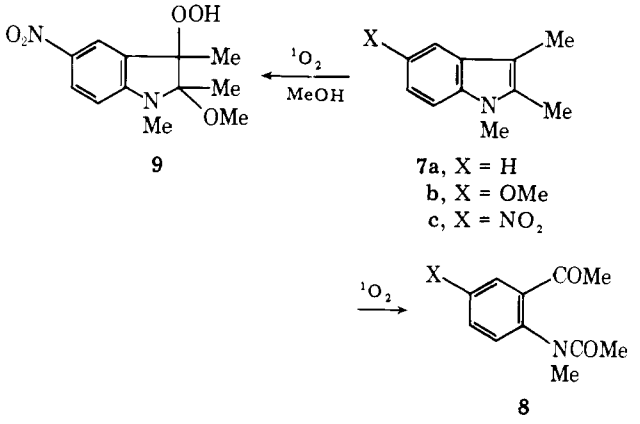


5a, $R_1 = R_2 =$ OMe	**4a,b,c,d**	R	**2**
b, R_1 = OH; R_2 = OMe	97%	a, -Me	<1%
c, R_1 = OCD_3; R_2 = OMe	72	b, -Et	21
d, $R_1 = R_2 = -(OCH_2)-$	51	c, $-CHMe_2$	44
	60	d, $-CH_2CH_2OMe$	30

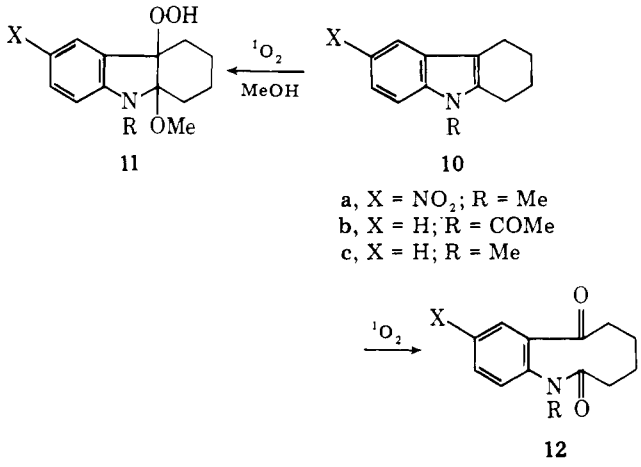
reasonably explained by a two-step mechanism involving a 1,4 zwitterion such as **6**, not by a concerted mechanism. The remarkable temperature dependency of the trapping reactions may probably be concerned with the lifetime of the zwitterion **6**.[7,17b] The lifetime of the zwitterion would be longer at lower temperature, permitting the trapping reactions to take place more efficiently. In addition, the unfavorable negative activation entropy of any bimolecular trapping reaction can be overcome more easily at low temperature.

Substituent Effects on the Trapping Reactions. Photooxygenation of 1,2,3-trimethylindole (**7a**) and 5-methoxy-1,2,3-trimethylindole (**7b**) in methanol at −70 °C proceeded much faster than that of **1** to give the corresponding C_2–C_3 ring cleavage products **8a** and **8b**, respectively, as the only product. Methanol did not intercept the intermediates even at −70 °C, in contrast to the case of **1**. However, photooxygenation of 1,2,3-trimethyl-5-nitroindole (**7c**) in methanol at 0 °C led to much slower but clean formation of the trapping product **9** (95%) (Scheme II). Similarly, 9-methyl-6-nitro-1,2,3,4-tetrahydrocarbazole (**10a**) and 9-acetyl-1,2,3,4-tetrahydrocarbazole (**10b**) gave the corresponding trapping products **11a** (90%) and **11b** (85%), respectively, upon photooxygenations in methanol at 0 °C, whereas photooxygenation of 9-methyl-1,2,3,4-tetrahydrocarbazole (**10c**) in methanol proceeded rapidly to give only the ring cleavage product **12c** (95%) (Scheme III). Thus, the introduction of an electron-withdrawing substituent into the indole ring decreases the reactivity toward singlet oxygen but favors the trapping reaction over the oxidative cleavage of the C_2–C_3 double bond. As shown in Table I, methanol did not trap the zwitterions derived from highly reactive indoles (**7a,b, 10c**) even at −70 °C, whereas less reactive indoles (**7c, 10a,b**) gave the trapping products in high yields at 0 °C. This is not so surprising, since a similar finding has also been observed in the interception of the zwitterion from cyano olefins and enol ethers; in related work it was found that the addition of tetracyanoethylene (TCNE) to tetramethoxyethylene was so fast that the zwitterionic intermediate could not be trapped by alcohols, whereas alcohols intercept the zwitterion from TCNE and a less reactive enol ether.[25] Very fast dioxetane formation of the zwitterion derived

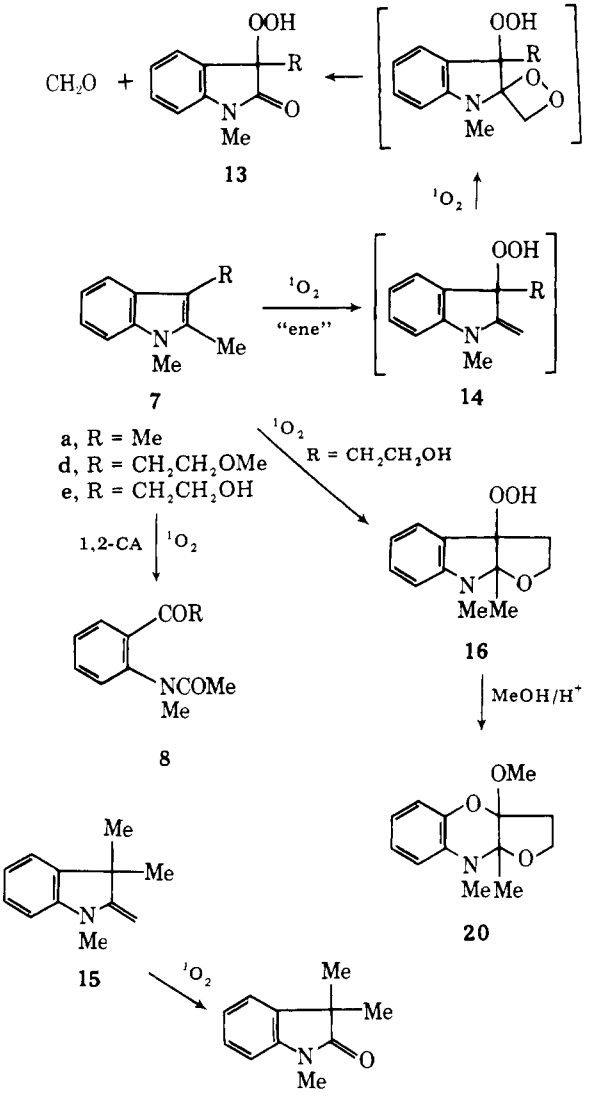
Scheme II



Scheme III



Scheme IV

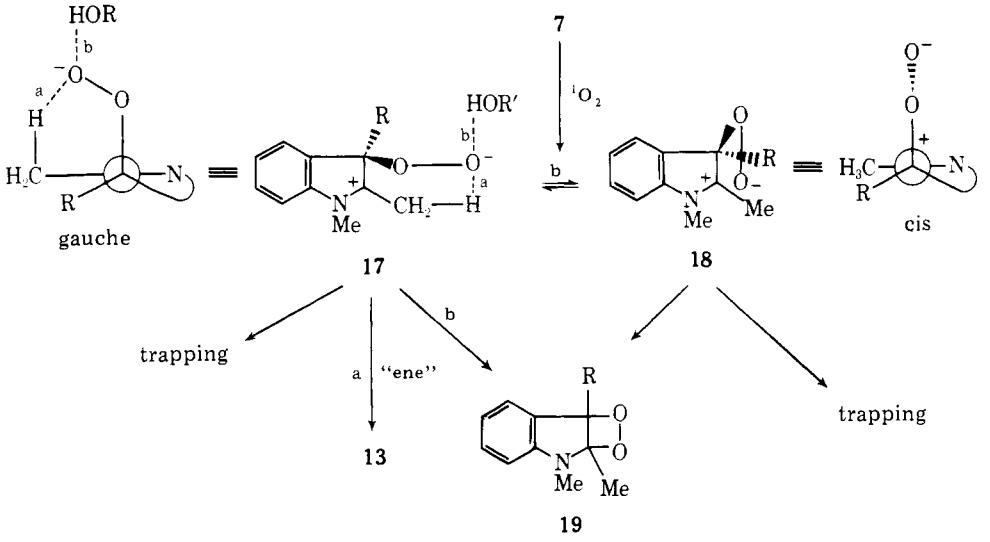


from a highly reactive indole such as **7a,b** or **10c** would not be suppressed by the addition of methanol, whereas zwitterions from less reactive indoles (**7c, 10a,b**) would have long enough lifetimes to be captured by methanol. Interestingly, the substituent effects and the trapping efficiencies we have obtained seem to share some common features with those of the thermal [2 + 2] cycloaddition of cyano olefins and enol ethers.[25]

Solvent Effect and "Ene" Reaction. While alkenes having allylic hydrogens are known to undergo "ene" reaction with singlet oxygen, no "ene" reaction has been observed with enamines, even though they have active allylic hydrogens. For example, photooxygenation of *N,N*-dimethylisobutenylamine[27] and *N*-(1-cycloalkenyl)morpholines[28] did not give the "ene" product and yielded only the 1,2-cycloaddition products. In this regard, reaction of 1,2,3-trimethylindole (**7a**) is of particular interest, since it has allylic hydrogens at both sides of the electron-rich double bond. Regardless of the reaction temperature, photoxygenation of **7a** in methanol gave the ring cleavage product **8a** as the major product; none of the trapping product has been detected. The photooxygenation in aprotic solvents at 0 °C, however, absorbed 2 equiv mol of oxygen to give 3-hydroperoxy-2-indolinone (**13a**) as the main product. Liberation of formaldehyde was observed during the reaction. The formation of **13a** indicates an "ene" reaction giving **14** in the first stage, followed by rapid 1,2 cycloaddition of a second singlet molecular oxygen (Scheme IV). In fact, the Fischer base **15**, a model compound of **14**, is known to react rapidly with singlet oxygen to give 1,3,3-trimethyl-2-indolinone.[30] Thus, it has been demonstrated for the first time that an enamine system having allylic hydrogens is capable of undergoing "ene" reaction by appropriately modifying the reaction conditions. The ratio of **8a** to **13a** is considered to represent a measure of the competitive rates of 1,2 cycloaddition to "ene" reaction. As shown in Table II, the product ratio (**8a**:**13a**) is highly solvent dependent. Protic solvents favor the 1,2-cycloaddition mode of reaction over the ene type. Actually, addition of small amounts of trifluoroethanol to the reaction system in acetone considerably increased the ratio of the 1,2-cycloaddition product. The solvent polarity or the lifetime of singlet oxygen in solutions does not seem to play a significant role (Table II). A similar solvent effect on the competitive reaction between 1,2 cycloaddition and "ene" reaction has been observed with 2,5-dimethyl-2,4-hexadiene[31] and 1-ethylthio-2-ethylhexene-1,[32] where protic solvents increased the ratio of the 1,2 cycloaddition to the ene-type reaction.

Photooxygenation of 1,2-dimethyltryptophol methyl ether (**7d**) gave essentially the same results; in acetone **7d** gave the ene-derived product **13d** (87%), whereas **8d** (80%) was the only isolable product on the photooygenation in methanol. However, photooxygenation of 1,2-dimethyltryptophol (**7e**) in acetone or in methanol gave the trapping product **16** efficiently; neither **8e** nor **13e** has been detected. These results seem to be very important from the mechanistic point of view. They indicate that a common intermediate for both "ene" reaction and 1,2 cycloaddition is captured intramolecularly by the nucleophilic group of the side chain of **7e** before it collapses to "ene" product **13e** or to dioxetane mode product **8e.** Thus a zwitterionic peroxide appears to be responsible for both "ene" and 1,2-cycloaddition reactions. The results are consistent with a recent hypothesis that 1,2-cycloaddition and "ene" reaction would

Scheme V



involve a common intermediate in singlet oxygen reactions of monoolefins.[9,13]

Mechanism of the Reaction. All the experimental results described above strongly support the zwitterionic peroxide precursors in the singlet oxygen reactions of *N*-methylindoles. Recent theoretical calculations using the INDO-RHF CI method have also indicated that the $[2_s + 2_s]$ type reaction of singlet oxygen with 1,2,3-trimethylindole (**7a**) gives a cisoid 1,4 zwitterion, whereas the approach of singlet oxygen to **7a** leading to the perepoxide formation results in the formation of a 1,4 zwitterion with its gauche-like conformation rather than a perepoxide.[33]

In order to account for the experimental results, particularly for the dramatic solvent effect, we propose the following mechanism in which a 1,4 zwitterion with a gauche-like conformation **17** is equilibrated with a cisoid conformer **18** (Scheme V).[34] The cisoid zwitterion **18** stabilized by Coulomb attraction between two charge centers readily undergoes ring closure to dioxetane **19.** On the other hand, the gauche zwitterion **17** in which the terminal oxygen is close enough to the methyl group to be able to remove a proton may be responsible for the "ene" product **13** (path a).[33] In the presence of a protic group of the solvent or the side chain, the negative charge on the terminal oxygen of **17** may decrease by protonation (path b), thus preventing the "ene" reaction.[32] As a result, **17** may be transformed into the dioxetane **19** directly or by way of **18.** Thus, protic solvents favor the 1,2-cycloaddition mode of reaction over the "ene" type. Both zwitterions (**17, 18**) can undergo trapping reactions with nucleophiles. The proposed mechanism does not require perepoxide intermediates[2b,8] for the "ene" reaction.

Summary

The zwitterionic peroxide intermediates proposed theoretically in enamine–singlet oxygen reactions[4,7,33] have been intercepted by nucleophiles. The experimental results obtained strongly suggest that 1,2 cycloaddition and "ene" reaction proceed via a common zwitterionic intermediate in the singlet oxygen reactions of *N*-methylindoles. Solvent and substituent effects observed in the photooxygenations of *N*-methylindoles are most reasonably explained in terms of a primary zwitterionic intermediate.

Experimental Section

General Procedure. Melting points were determined using a hot-stage apparatus and are uncorrected. The following spectrometers were used: NMR, Varian T-60 or HA-100; IR, Jasco IRA-1; UV, Shimazu UV-200; mass, Hitachi RMS-4. Microanalyses were performed by the Microanalytical Center of Kyoto University. Preparative or analytical TLC was performed on a plate coated with Merck Kieselgel 60 PF.

Irradiation was made with a 500-W tungsten-bromine lamp (Ushio JPC-C) through a Pyrex cooling jacket and an appropriate filter solution. Aqueous $CuCl_2$–$CaCl_2$ and $K_2Cr_2O_7$ filter solutions were used for rose bengal and methylene blue sensitized photooxygenations, respectively.[35] During irradiation dry oxygen was bubbled through the solution. For measuring oxygen consumption the photooxygenation was carried out in a close circulating system and the oxygen consumption was measured manometrically. Low-temperature photooxygenation was carried out in a reaction vessel placed in an acetone bath which was maintained at a desired temperature (−80 to 0 °C) by a CryoCool cooling system.

Photooxygenation of 1,3-Dimethylindole (1) in Methanol at −70 °C. A solution of **1** (150 mg, 1 mmol) in dry methanol (180 mL) containing rose bengal (3 mg) was photooxygenated at −70 °C in a low-temperature reaction vessel as described above. The progress of

Table II. Solvent Effect on the Product Distributions in the Photooxygenation of 1,2,3-Trimethylindole (**7a**)[a]

solvent system	dielectric constant[b] ϵ	E_T[b]	$^1O_2$ lifetime,[c] μs	product yield,[d] % **8a** (1,2-CA)	**13a** (ene)
CH_3OH	32.7	55.5	7	90	5
C_2H_5OH	24.6	51.9	12	50	31
$(CH_3)_2CHOH$	19.9	48.6		30	61
CH_3CN	37.5	46.0	30	*e*	85
$(CH_3)_2CO$	20.7	42.2	26	*e*	80
$(CH_3)_2CO$ + CF_3CH_2OH (2.8 mM)				7	73
$(CH_3)_2CO$ + CF_3CH_2OH (5.6 mM)				10	70
benzene[f,g]	2.3	34.5	24	15	51[h]
CCl_4[g]	2.2	32.5	700	13	75
pyridine	12.4	40.2	33	25	60

[a] Substrate concentration (5.6 mM). Unless otherwise stated, the reactions were carried out at 0 °C with rose bengal (10^{-3} M) as sensitizer. [b] The values are cited from S. L. Murov, "Handbook of Photochemistry", Marcel Dekker, New York, 1973, p 85. [c] The values are cited from D. Bellus in ref 10, p. 64. [d] Determined by NMR analysis of the reaction mixture. [e] Not detected. [f] At 20 °C. [g] Tetraphenylporphyrin (10^{-3} M) as sensitizer. [h] Considerable amounts of polymeric materials were formed.

the reaction was monitored by TLC and the photooxygenation was continued until the starting material (**1**) completely disappeared (6 h). Careful removal of the solvent below 0 °C under vaccum gave a viscous oil which liberated iodine from an aqueous alcohol solution of potassium iodide. NMR (100 MHz) analysis and iodometric titration of the peroxidic residue showed that it consisted of an almost pure (97%) hydroperoxide. The structure of the peroxidic product **4a** was assigned on the basis of the following spectral data and by the chemical confirmation described below. 2,3-Dihydro-2-methoxy-1,3-dimethyl-1*H*-indol-3-yl hydroperoxide (**4a**): UV λ_{max} (EtOH) 245, 294 nm; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 2.90 (s, 3 H), 3.58 (s, 3 H), 4.45 (s, 1 H), 6.30–7.40 (m, 4 H, aromatic H), 9.70 (s, 1 H, OOH); mass spectrum *m/e* (rel intensity) 177 ($M^+ - 32$, 7), 161 (21), 134 (100), 118 (19), 91 (19). The formation of the formamide **2** could not be detected by the NMR of the crude reaction mixture. However, TLC of the reaction mixture revealed the presence of a trace of **2** (ca. 1%). Attempts to isolate **4a** as a pure, crystalline compound by column chromatography or by recrystallization have been unsuccessful.

The half-life of **4a** at 30 °C in CD_3OD measured by NMR was 15 min. The NMR spectrum after standing for 3 h at 30 °C showed the presence of a complex mixture of products including **2** (30%), **5c** (23%), and polymeric materials.

When the photooxygenation was carried out at −60 °C, essentially the same result was obtained.

Conversion of 4a into 2,3-Dihydro-1,4-benzoxazines (5a–d). To a solution of **4a** (150 mg, 0.72 mmol) in methanol (100 mL) was added a few drops of 2 N HCl and the solution was kept standing for 30 min at 20 °C. After removal of the solvent, the residue was purified by preparative TLC (silica gel, $CHCl_3$–acetone, 1:1). Elution of the band (R_f 0.5) gave 2,3-dihydro-2,3-dimethoxy-1,3-dimethyl-1,4-benzoxazine (**5a**) as a viscous, yellow oil (80 mg, 50%): UV λ_{max} (EtOH) 241 nm (log ϵ 3.57), 285 (3.20); IR (neat) 1610, 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 3.18 (s, 3 H), 3.23 (s, 3 H), 3.35 (s, 3 H), 4.28 (s, 1 H), 6.50–7.10 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 223 (M^+, 1), 193 (22), 146 (43), 134 (100), 120 (65). From the band (R_f 0.3) 2,3-dihydro-3-hydroxy-2-methoxy-1,3-dimethyl-1,4-benzoxazine (**5b**) was obtained as an oil (50 mg, 33%): UV λ_{max} (EtOH) 243 nm (log ϵ 3.95), 292 (3.18); IR (neat) 3400, 1610, 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 3.05 (s, 3 H), 3.28 (s, 3 H), 3.40 (s, 1 H, OH), 4.63 (s, 1 H), 6.50–7.10 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 209 (M^+, 3), 208 (11), 192 (100), 161 (15), 148 (34), 134 (42). In order to obtain analytical samples, **5a,b** were distilled (Kugelrohr) at 90–110 °C (1 mmHg) but with some decomposition.

To a solution of **4a** (234 mg, 1.1 mmol) in ethylene glycol (25 mL) was added 0.1 mL of 2 N HCl and the solution was kept at 20 °C for 0.5 h. To the solution were added ether (100 mL) and water (100 mL), and the ether layer was separated, washed with water (100 mL), and dried (Na_2SO_4). Evaporation of ether gave a yellow, viscous oil which was purified by preparative TLC (silica gel, $CHCl_3$). Elution of a single band with ethyl acetate gave **5d** (183 mg, 77%): UV λ_{max} (EtOH) 243 nm (log ϵ 3.88), 290 (3.88); IR (neat) 3400, 1620, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s, 3 H), 3.10 (s, 3 H), 3.38–4.33 (m, 4 H), 4.40 (s, 1 H), 6.50–7.00 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 221 (M^+, 100), 178 (17), 161 (40), 149 (41), 134 (40), 123 (48). An analytical sample was obtained by distillation (Kugelrohr) at 115–117 °C (3 mmHg).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.95; H, 6.89; N, 6.39.

Photooxygenation of 1,3-Dimethylindole (1) in Various Alcohols at −60 °C. Photooxygenation of **1** (150 mg, 1 mmol) was carried out in 180 mL of ethanol, 2-propanol, and β-methoxyethanol, respectively, at −60 °C under the same conditions as described above for methanol. After removal of the solvent below 0 °C under vacuum, the residue was analyzed by NMR (100 MHz). In every case a mixture of the hydroperoxide (**4b–d**) and *N*-(2-acetylphenyl)-*N*-methylformamide (**2**) was obtained. The product ratios (**4**:**2**) were determined by intergration of the corresponding methyl signals in the NMR spectra of the reaction mixtures and the results are listed in Scheme I. The structures of hydroperoxides (**4b–d**) were assigned by the following spectral data.

2-Ethoxy-2,3-dihydro-1,3-dimethyl-1*H*-indol-3-yl hydroperoxide (**4b**): UV λ_{max} (EtOH) 247, 295 nm; NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz), 1.55 (s, 3 H), 2.88 (s, 3 H), 3.80 (q, 2 H, J = 7 Hz), 4.50 (s, 1 H), 6.30–7.40 (m, 4 H, aromatic H), 9.65 (s, 1 H, OOH); mass spectrum *m/e* (rel intensity) 223 (M^+, 1), 222 (1), 206 (6), 189 (3), 161 (36), 144 (75), 134 (100), 118 (31).

2,3-Dihydro-2-isopropoxy-1,3-dimethyl-1*H*-indol-3-yl hydroperoxide (**4c**): NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 6 Hz), 1.38 (d, 3 H, J = 6 Hz), 1.52 (s, 3 H), 2.83 (s, 3 H), 4.00 (m, 1 H), 4.60 (s, 1 H), 6.40–7.30 (m, 4 H, aromatic H), 10.26 (br s, 1 H, OOH).

2,3-Dihydro-2-(2-methoxyethyl)-1,3-dimethyl-1*H*-indol-3-yl hydroperoxide (**4d**): NMR ($CDCl_3$) δ 1.60 (s, 3 H), 2.87 (s, 3 H), 3.30–3.80 (m, 4 H), 3.70 (s, 3 H), 4.60 (s, 1 H), 6.30–7.30 (m, 4 H, aromatic H), 10.40 (br s, 1 H, OOH).

Attempts to isolate pure **4b–d** by low-temperature column chromatography resulted in a decomposition of the hydroperoxides, whereas almost pure **4b** (95%) was obtained when the photooxygenation of **1** was carried out in ethanol below −70 °C.

Photooxygenation of 1,2,3-Trimethylindole (7a). A. In Methanol. A solution of **7a** (160 mg, 1 mmol) in dry methanol (180 ml) containing rose bengal (3 mg) was photooxygenated at −70 °C for 3 h. The solvent was removed at 0 °C under vacuum and the residue was purified by preparative TLC (silica gel, $CHCl_3$). Elution of the band (R_f 0.1) with ethyl acetate gave *N*-(2-acetylphenyl)-*N*-methylacetamide (**8a**, 170 mg, 88%): bp 135–140 °C (1 mmHg); UV λ_{max} (EtOH) 227 nm (log ϵ 3.92), 285 (3.05); IR (neat) 1695, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.77 (s, 3 H), 2.53 (s, 3 H), 3.19 (s, 3 H), 7.19–7.87 (m, 4 H, aromatic H); mass spectrum *m/e* 191 (M^+).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.01; H, 6.86; N, 7.46.

Elution of the band (R_f 0.3) followed by recrystallization from ether gave **13a** (5 mg, 3%) (see below).

The photooxygenation at 0 °C gave a similar result (see Table II).

B. In Acetone. A solution of **7a** (160 mg, 1 mmol) in dry acetone (180 mL) containing rose bengal (5 mg) was photooxygenated at 0 °C in a closed circulating system for 2.5 h. During the reaction 50 mL (2.23 mmol) of oxygen was consumed. The solvent was carefully removed at 0 °C under vacuum and the residue was chromatographed on a short silica gel column. Elution with $CHCl_3$–ethyl acetate (1:1) gave a white solid which was recrystallized from ether to give 3-hydroperoxy-1,3-dimethyl-2-indolinone (**13a**, 137 mg, 77%): mp 183–184 °C; UV λ_{max} (EtOH) 257 nm (log ϵ 3.78), 288 (3.08); IR (Nujol) 3350, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s, 3 H), 3.17 (s, 3 H), 6.65–7.40 (m, 4 H), 9.67 (br s, 1 H, OOH); mass spectrum *m/e* (rel intensity) 177 (M^+, 47), 162 (32), 149 (76), 134 (100), 106 (32).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.96; H, 5.71; N, 7.06.

NMR analysis of the crude reaction mixture revealed the presence of **13a** in 80% yield.

The same photooxygenation was carried out in a separate run in order to detect formaldehyde. In this run a water trap containing aqueous Na_2SO_3 and phenolphthalein was connected to the outlet of the reaction vessel. During irradiation oxygen was circulated in a closed system. As the photooxygenation progressed, the trap solution became red, indicating the generation of formaldehyde. Titration of the trap solution with 0.1 N HCl indicated that 1.2 equiv mol of formaldehyde based on **13a** was formed during the reaction.

The photooxygenation at −70 °C followed by a similar workup gave **13a** in 85% yield.

Photooxygenation of 5-Methoxy-1,2,3-trimethylindole (7b) in Methanol. A solution of **7b**[36] (100 mg, 0.53 mmol) in dry methanol (180 mL) in the presence of rose bengal (3 mg) was photooxygenated at −70 °C for 2 h. TLC of the reaction mixture showed the presence of a single photoproduct. After removal of the solvent, the residue was chromatographed on a silica gel column. Elution with $CHCl_3$ gave *N*-(2-acetyl-4-methoxyphenyl)-*N*-methylacetamide (**8b**, 95 mg, 81%) as a viscous, yellow oil: bp 115–117 °C (3 mmHg); UV λ_{max} (EtOH) 235 nm (log ϵ 3.85), 295 (3.02); IR (neat) 1690, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (s, 3 H), 2.53 (s, 3 H), 3.20 (s, 3 H), 3.93 (s, 3 H), 7.13–7.41 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 221 (M^+, 13), 178 (97), 164 (100), 136 (22).

Anal. Calcd for $C_{12}H_{18}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.96; H, 7.05; N, 6.25.

The photooxygenation at 0 °C gave **8b** (80%) as the only isolable product.

Photooxygenation of 1,2,3-Trimethyl-5-nitroindole (7c) in Methanol. A solution of **7c**[37] (102 mg, 0,5 mmol) in dry methanol (180 mL) containing rose bengal (3 mg) was photooxygenated at 0 °C for 4 h. The progress of the reaction was monitored by TLC. After **7c** com-

pletely disappeared, the solvent was removed at 0 °C under vacuum to give a dark brown solid. Recrystallization of the solid from ether gave **9** (94 mg, 70%). A second recrystallization of the mother liquor yielded another crop of **9** (20 mg). NMR analysis of the crude reaction mixture revealed the presence of **9** in 95% yield.

2,3-Dihydro-2-methoxy-1,3-dimethyl-5-nitro-1*H*-indol-3-yl hydroperoxide (**9**): mp 64–66 °C; UV λ_{max} (EtOH) 248 nm (log ϵ 3.61), 254 (3.62), 260 (3.54), 379 (4.05); IR (Nujol) 3420, 1620, 1500, 1340 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.67 (s, 3 H), 2.96 (s, 3 H), 3.20 (s, 3 H), 6.37 (d, 1 H, J = 8 Hz), 8.00 (d, 1 H, J = 2 Hz), 8.20 (dd, 1 H, J = 2, 8 Hz), 9.22 (br s, 1 H, OOH); mass spectrum *m/e* (rel intensity) 218 (M^+ − 50, 13), 202 (17), 193 (100), 179 (61), 149 (65).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.86; H, 6.09; N, 10.18.

The photooxygenation at −70 °C followed by a similar workup gave **9** (90%).

Photooxygenation of 9-Methyl-6-nitro-1,2,3,4-tetrahydrocarbazole (10a) in Methanol. A solution of **10a**[37] (115 mg, 0.5 mmol) in dry methanol (180 mL) containing rose bengal (3 mg) was photooxygenated at 0 °C for 3 h. The solvent was removed at 0 °C under vacuum. NMR analysis and iodometric titration of the residue showed that it contained almost pure hydroperoxide **11a** (90%): NMR ($CDCl_3$) δ 1.10–2.23 (m, 8 H), 2.90 (s, 3 H), 3.20 (s, 3 H), 6.37 (d, 1 H, J = 8 Hz), 7.92 (d, 1 H, J = 2 Hz), 8.10 (dd, 1 H, J = 8, 2 Hz), 9.23 (br s, 1 H, OOH). Attempts to isolate a pure crystalline compound by recrystallization or by chromatography resulted in a decomposition of the hydroperoxide.

Photooxygenation of 9-Acetyl-1,2,3,4-tetrahydrocarbazole (10b) in Methanol. A solution of **10b**[38] (100 mg, 0.47 mmol) in dry methanol (180 mL) containing rose bengal (5 mg) was photooxygenated at 0 °C. The photooxygenation was continued until **10b** disappeared on TLC (6 h). Careful removal of the solvent below 0 °C under vacuum followed by recrystallization from methanol gave **11b** (98 mg, 75%) as colorless crystals: mp 97–99 °C dec; UV λ_{max} (EtOH) 232 nm (log ϵ 4.42), 260 (4.03), 325 (3.50); IR (Nujol) 3380, 1730, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.76–1.98 (m, 4 H), 2.23 (s, 3 H), 2.14–2.34 (m, 2 H), 2.90–3.18 (m, 2 H), 3.68 (s, 3 H), 6.93–8.03 (m, 3 H), 8.83 (dd, 1 H, J = 2, 7 Hz), 11.77 (br s, 1 H, OOH); mass spectrum *m/e* (rel intensity) 277 (M^+, 13), 235 (4), 186 (6), 162 (100), 135 (23), 120 (82). Attempts to obtain an analytically pure sample by repeated recrystallizations resulted in a partial decomposition of the hydroperoxide **11b**. The yield of **11b** determined by NMR was 85%.

Photooxygenation of 9-Methyl-1,2,3,4-tetrahydrocarbazole (10c) in Methanol. A solution of **10c**[39] (105 mg, 0.57 mmol) in dry methanol (180 mL) containing rose bengal (10 mg) was photooxygenated at 0 °C for 1 h. TLC of the reaction mixture showed a single photoproduct. Evaporation of the solvent followed by chromatography (silica gel, $CHCl_3$) gave **12a** (117 mg, 95%), which was identical with the authentic sample prepared by the known method.[40]

The photooxygenation at −70 °C gave essentially the same result.

Preparation of 1,2-Dimethyltryptophol (7e) and Its Methyl Ether (7d). To a solution of 2-methyltryptophol[41] (5.0 g, 29 mmol) in dry Me_2SO (30 mL) containing 50% NaH (1.37 g, 29 mmol) was added CH_3I (5.66 g, 40 mmol) under nitrogen at 0 °C. The solution was stirred vigorously at room temperature for 0.5 h. After addition of water (50 mL), the mixture was extracted with ether. The ether layer was washed several times with water and dried over anhydrous Na_2SO_4. After evaporation of ether, the residue was chromatographed on an alumina column. Elution with $CHCl_3$ gave **7e** (1.05 g, 17%); bp 140–141 °C (4 mmHg); IR (neat) 3200, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.40–1.60 (br s, 1 H, OH), 2.37 (s, 3 H), 2.93 (t, 2 H, J = 6 Hz), 3.63 (s, 3 H), 3.77 (t, 2 H, J = 6 Hz), 6.80–7.43 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 189 (M^+, 29), 158 (100), 144 (10).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.90; H, 8.06; N, 7.29.

Further elution with $CHCl_3$ gave **7d** (3.48 g, 63%): bp 145–146 °C (4 mmHg); NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.80–3.18 (m, 2 H), 3.38–3.70 (m, 2 H), 3.40 (s, 3 H), 3.60 (s, 3 H), 6.93–7.63 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 203 (M^+, 34), 172 (3), 158 (100), 143 (7).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.66; H, 8.56, N, 7.06.

Photooxygenation of 1,2-Dimethyltryptophol Methyl Ether (7d). A. In Acetone. A solution of **7d** (150 mg, 0.74 mmol) in dry acetone (180 mL) containing rose bengal (5 mg) was photooxygenated at 0 °C for 1.5 h. Removal of acetone at 0 °C gave a solid residue which was purified by preparative TLC (silica gel, $CHCl_3$–ethyl acetate, 1:1). Elution of the band (R_f 0.6) gave a white solid which was recrystallized from ether to yield 3-hydroperoxy-3-(2-methoxyethyl)-1-methyl-2-indolinone (**13d**, 132 mg, 75%): mp 86–88 °C; UV λ_{max} (EtOH) 258 nm (log ϵ 3.82), 286 (3.15); IR (Nujol) 3300, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.80–2.60 (m, 2 H), 3.13 (s, 3 H), 3.18 (s, 3 H), 3.10–3.30 (m, 2 H), 6.63–7.43 (m, 4 H, aromatic H), 9.80 (br s, 1 H, OOH); mass spectrum *m/e* (rel intensity) 221 (M^+ − 16, 36), 193 (60), 163 (100).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.58; H, 6.50; N, 5.83.

B. In Methanol. Rose bengal sensitized photooxygenation of **7d** (120 mg, 0.6 mmol) was carried out in methanol (180 mL) at 0 °C. Evaporation of the solvent followed by preparative TLC (silica gel, $CHCl_3$–methanol, 1:1) gave **8d** (80%) as a viscous, yellow oil: bp 122 °C (1 mmHg); UV λ_{max} (EtOH) 223 nm (log ϵ 3.90), 2.53 (3.46), 280 (3.11); IR (neat) 1695, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 3.07 (t, 2H, J = 6 Hz), 3.43 (t, 2 H, J = 6 Hz), 6.93–7.67 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 235 (M^+, 0.2), 192 (1), 148 (100).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.19; H, 7.48; N, 6.02.

Photooxygenation of 1,2-Dimethyltryptophol (7e). A. In Methanol. A solution of **7e** (112 mg, 0.6 mmol) in dry methanol (180 mL) containing rose bengal (3 mg) was photooxygenated at 0 °C. The photooxygenation was continued until all the starting material (**7e**) was consumed (1 h). Removal of the solvent below 0 °C under vacuum gave a viscous oil which showed a positive starch–KI test. The peroxidic residue was chromatographed on a short alumina column. Elution with ethyl acetate gave 2,3,8,8a-tetrahydro-8,8a-dimethyl-3a*H*-furo[2,3-*b*]indol-3a-yl hydroperoxide (**16**, 100 mg, 77%) as an oil: IR (neat) 3300, 1610, 1320 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 2.77 (s, 3 H), 2.17–2.38 (m, 2 H), 3.35 (s, 1 H, OOH), 3.40–3.85 (m, 2 H), 6.18–6.63 (m, 2 H, aromatic H), 6.90–7.13 (m, 2 H, aromatic H); mass spectrum *m/e* (rel intensity) 221 (M^+, 84), 205 (95), 176 (100), 160 (47), 134 (84).

Treatment of **16** (40 mg) with methanol (20 mL) containing 0.1 mL of 1 N HCl at room temperature followed by preparative TLC (silica gel, $CHCl_3$–ethyl acetate, 1:1) gave **20** (33 mg, 78%) as an yellow oil: bp 115 °C (3 mmHg); UV λ_{max} (EtOH) 249 nm (log ϵ 3.97), 275 (3.50); IR (neat) 1620, 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 2.12–2.47 (m, 2 H), 2.93 (s, 3 H), 3.45 (s, 3 H), 3.82–4.20 (m, 2 H), 6.47–7.20 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 235 (M^+, 100), 220 (45), 192 (21), 148 (33).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.63; H, 7.43; N, 5.95.

B. In Acetone. A solution of **7e** (110 mg, 0.58 mmol) in dry acetone (180 mL) containing rose bengal (3 mg) was photooxygenated at 0 °C for 3 h. A similar workup as described in A gave **16** (90%).

Low-temperature photooxygenation (−70 °C) of **7e** in acetone or methanol gave **16** as the only isolable product (80–90%).

Relative Rates of Photooxygenation. Solutions of N-substituted indoles (0.02 M) in oxygen-saturated methanol containing rose bengal (2×10^{-6} M) were prepared in sealed tubes. The solutions were irradiated simultaneously in a merry-go-round apparatus at 20 °C. Relative rates of the disappearance of the substrates were determined by UV spectroscopy at ca. 10% conversion. The results are listed in Table I.

Solvent Effect on the Photooxygenation of 1,2,3-Trimethylindole (7a). A solution of **7a** (90 mg, 0.56 mmol) in an appropriate solvent (100 mL) containing rose bengal (10^{-3} M) was photooxygenated at 0 °C until **7a** was no longer detected on TLC. When the photooxygenation was carried out in benzene or CCl_4, *meso*-tetraphenylporphyrin was used as sensitizer. After removal of the solvent at 0 °C under vaccum, the residue was analyzed by NMR. The results are shown in Table II.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan (No. 343019). We are indebted to K. Inoue, O. Yokoi, and Dr. M. Imuta for partial contribution to this work and to Professor K. Yamaguchi, Osaka University, for helpful discussion.

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Mechanistic Study of Anodic Intramolecular Coupling Reactions

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Received May 31, 1979

Abstract: Anodic cyclization reactions of several methoxybibenzyls were studied. The reactions were: 2-methyl-3′,4′,5-trimethoxy-4-ethoxybibenzyl (**1**) to 9,10-dihydro-10a-methyl-2-ethoxy-6,7-dimethoxy-3(10a*H*)phenanthrone; laudanosine (**2**) to *O*-methylflavinatine (**5**) and 4,4′-dimethoxy[2,2]metacyclophane (**3**) to 2,7-dimethoxy-4,5,9,10-tetrahydropyrene (**6**). The solvent was acetonitrile and the anode was platinum. When using cyclic voltammetry, each of these compounds shows a $2e^-$ oxidation peak at + 0.5–1.1 V vs. Ag|0.1 M $AgNO_3$ which is irreversible at all sweep rates due to the rapid chemical reactions following electron transfer. At slightly more positive potentials, there is a reversible couple due to the products. Preparative electrolysis gave $n = 2$ and high isolated yields of the products. The reaction kinetics were studied by using the shift in the first peak potential (E_p) in linear sweep voltammetry as a function of sweep rate, concentration of substrate, and the acidity of the medium. The rate law was also elucidated by using the convolution potential sweep voltammetry method. The two techniques led to similar conclusions. For compound **1** the mechanism involves reversible electron transfer (e) and disproportionation (d) steps followed by a rate-limiting step which is most probably cyclization (c) of the dication. Compound **2** was studied in acidic media so that the amine group was initially protonated. The mechanism under these conditions involves reversible electron transfer from $\mathbf{2H^+}$, cyclization, and deprotonation of the amine followed by a rate-limiting solution phase electron transfer from a cyclized cation radical to a dication radical $\mathbf{2H^{+}\cdot}$. The importance of the amine/ammonium function in controlling the reaction pathway is discussed. Compound **3** reacts via an ec-type process in which the initial electron transfer and follow-up chemical reaction have a similar rate.

The oxidative, intramolecular coupling reactions of alkoxy aromatic compounds have received considerable attention in the past few years.[1-28] Although the reaction pathways and product structures differ in detail, many of the reactants which cyclize can be considered bibenzyls and, as shown in the following examples,[1,2,7] coupling involves two electrons/molecule and usually takes place para to an alkoxy group. Reactions of this type have been performed chemically with VOF_3,[17-21,25] thallium trifluoroacetate,[22,23] and manganic tris(acetylacetonate)[11] and electrochemically. The latter approach has proven to be particularly successful in providing useful routes to complex natural products such as morphinandienones.[2-6,14-16,24-26] In spite of this synthetic utility, there is considerable mechanistic ambiguity. A major question of interest is whether cation radicals or dications cyclize. The former corresponds to an ece (electrochemical-chemical-elec-

0002-7863/79/1501-7338$01.00/0