Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 4.96; N, 9.93. Found: C, 50.25; H, 4.85; N, 9.59.

Photochemical Reactions of 1 with Aromatic Compounds. General Procedure. A suspension of 1 (386 mg, 1 mmol) in acetonitrile (10 mL) and the corresponding aromatic compound (10 mL for benzene, furan, and thiophene and 5 mL for the others) was irradiated under continual stirring until the complete disappearance of 1 (2–4 h). After concentration the solution was either chromatographed on column (silica gel, 2:1 dichloromethan–hexane as eluant) or was extracted with 10% NaOH, and the phenols were obtained after acidification of the alkaline solution.

2,4-Dinitro-6-phenylphenol (7a) (192 mg; 74% yield): mp 202–204 °C (from chloroform–hexane(lit.[11] mp 203–204 °C); MS, *m/e* (relative intensity) 260 (M^+, 100).

2,4-Dinitro-6-(2-furyl)phenol (7b) (175 mg; 70% yield): mp 175–175 °C (from chloroform–hexane); UV λ_{max} 278 nm (ϵ 19000), 240 (11300), 212 (11300); IR (Nujol mul) 3100, 1620, 1590, 1560, 1350, 750 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 9.01 (2 H, s), 7.88 (1 H, m), 7.53 (1 H, d, J = 4 Hz), 6.85 (1 H, m), 6.47 (1 H, br); MS, *m/e* (relative intensity) 250 (M^+, 100), 204 (10), 157 (15), 148 (20), 104 (60), 95 (35), 76 (60).

Anal. Calcd for $C_{10}H_6N_2O_6$: C, 48.00; H, 2.40; N, 11.20. Found: C, 48.16; H, 2.24; N, 10.64.

2,4-Dinitro-6-(2-thienyl)phenol (7c) (170 mg; 64% yield): mp 157–159 °C (from chloroform–hexane); UV λ_{max} 397 nm (ϵ 5950), 280 (16100), 242 (13000), 212 (13300); IR (Nujol mull) 3145, 1610, 1560, 1540, 1340, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.55 (1 H, br), 9.01 (1 H, d, J = 2 Hz), 8.78 (1 H, d, J = 2 Hz), 7.78 (1 H, m), 7.53 (1 H, m), 7.30 (1 H, m); MS, *m/e* (relative intensity) 266 (M^+, 100), 250 (13), 220 (21), 173 (15), 145 (26), 111 (35).

Anal. Calcd for $C_{10}H_6N_2O_5S$: C, 45.11; H, 2.25; N, 10.52. Found: C, 45.13; H, 2.21; N, 10.58.

2,4-Dinitro-6-(5-methyl-2-furyl)phenol (7d) (143 mg; 54% yield): mp 165–166 °C (from hexane); UV λ_{max} 283 nm (ϵ 17800), 238 (9000), 210 (9600); IR (Nujol mull) 3145, 3105, 1610, 1560, 1360, 1030, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.93 (2 H, s), 7.71 (1 H, br), 7.20 (1 H, d, J = 4 Hz), 6.25 (1 H, d, J = 4 Hz), 2.45 (3 H, s); MS, *m/e* (relative intensity) 264 (M^+, 100), 218 (8), 109 (15).

Anal. Calcd for $C_{11}H_8N_2O_6$: C, 50.00; H, 3.03; N, 10.60. Found: C, 49.89; H, 2.88; N, 10.20.

From the photoreactions of 1 with anisole and *p*-dimethoxybenzene, 2,4-dinitro-6-phenylphenol (**7a**) was isolated in 76% and 69% yields, respectively.

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Photochemical Reactions of 1 with Alkynes. General Procedure. A suspension of 1 (193 mg, 0, 5 mmol) in acetonitrile (15 mL) and the alkyne (500 mg of diphenylacetylene, diethyl acetylenedicarboxylate, and 2 mL of phenylacetylene) was irradiated for 8 h under continual stirring. After concentration the solution was chromatographed on column (silica gel, 1.5:1 dichloromethane–hexane as eluant). After iodobenzene and excess alkyne, the benzo[*b*]furans **8a–c** were isolated.

5,7-Dinitro-2,3-diphenylbenzo[*b*]furan (8a) (54 mg; 30% yield: mp 221–222 °C (from chloroform–hexane); UV λ_{max} 278 nm (ϵ 3000); IR (Nujol mull) 3100, 1600, 1540, 1340, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.02 (1 H, d, J = 2 Hz), 8.57 (1 H, d, J = 2 Hz), 7.52 (10 H, m); MS, *m/e* (relative intensity) 360 (M^+, 100), 314 (8), 268 (20), 239 (35), 86 (40).

Anal. Calcd for $C_{20}H_{12}N_2O_5$: C, 66.66; H, 3.35; N, 7.77. Found: C, 66.61; H, 3.51; N, 7.56.

5,7-Dinitro-2,3-dicarbethoxybenzo[*b*]furan (8b) (56 mg; 16% yield): mp 115–116 °C (from chloroform–hexane); UV λ_{max} 254 nm (ϵ 30400), 208 (21800); IR (Nujol mull) 3080, 1760, 1740, 1600, 1540, 1350, 1230, 1190, 1150, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 926 (1 H, d, J = 2 Hz), 9.20 (1 H, d, J = 2 Hz), 4.58 (4 H, q, J = 7 Hz), 1.57 (6 H, t, J = 7 Hz); MS, *m/e* (relative intensity) 352 (M^+, 42), 324 (18), 308, 307 (20), 296 (17), 279 (100), 252 (27).

Anal. Calcd for $C_{14}H_{12}N_2O_9$: C, 47.73; H, 3.41; N, 7.95. Found: C, 47.53; H, 3.33; N, 7.71.

5,7-Dinitro-2-phenylbenzo[*b*]furan (8c) (51 mg; 18% yield); mp 136–137 °C (from chloroform–hexane); UV λ_{max} 255 nm (ϵ 2700), 203 (4500); IR (Nujol mull) 3120, 1610, 1540, 1340, 1270, 830 cm^{-1}; ^1H NMR δ 9.01 (1 H, d, J = 2 Hz), 8.76 (1 H, d, J = 2 Hz), 8–7.83 (2 H, m), 7.58–7.43 (3 H, m), 7.25 (1 H, s); MS, *m/e* (relative intensity) 284 (M^+, 100), 238 (38), 192 (44), 180 (22), 163 (42), 139 (29), 102 (54).

Anal. Calcd for $C_{14}H_8N_2O_5$: C, 59.15; H, 2.82; N, 9.86. Found: C, 59.47; H, 2.72; N, 9.43.

Registry No. 1, 89563-18-8; **4a**, 110-83-8; **4b**, 498-66-8; **4c**, 563-79-1; **4d**, 530-48-3; **4e**, 100-42-5; **4f**, 108-05-4; **4g**, 109-53-5; **5a**, 103068-25-3; **5c**, 103068-33-3; **5d**, 103068-26-4; **5e**, 103068-27-5; **5f**, 103068-34-4; **5g**, 103068-35-5; **6a**, 103068-28-6; **6b**, 103068-32-2; **6d**, 103068-29-7; (*E*)-**6e**, 103068-31-1; (*Z*)-**6e**, 103068-30-0; **7a**, 731-92-0; **7b**, 103068-36-6; **7c**, 103068-37-7; **7d**, 103068-38-8; **8a**, 59955-07-6; **8b**, 103068-39-9; **8c**, 17392-13-1; PhH, 71-43-2; $PhOCH_3$, 100-66-3; 4-$H_3COC_6H_4OCH_3$, 150-78-7; furan, 110-00-9; thiophene, 110-02-1; 2-methylfuran, 534-22-5; PhC≡CPh, 501-65-5; $H_3CCH_2O_2CC{\equiv}CCO_2CH_2CH_3$, 762-21-0; PhC≡CH, 536-74-3.

9,10-Disubstituted-2-anthracenyl *tert*-Butyl Nitroxides. ESR Spectroscopic Indicators for Singlet Oxygen[1]

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Received April 25, 1986

Our purpose is to develop a nitroxide-based ESR probe for singlet oxygen. Among the new anthracenyl nitroxides 1–4 prepared, nitroxide 1 is the most useful. 1 reacts with singlet oxygen to give endoperoxide 18 quantitatively in organic solvents as well as when 1 is incorporated in the bilayers of DMPC vesicles. The reaction is sufficiently rapid and the resulting changes in the ESR spectra are sufficiently characteristic so that the conversion of 1 into 18 may serve as an ESR-based probe for singlet oxygen.

Singlet oxygen[3-5] is an oxidant of broad significance.[6] It is the likely oxidant associated with the photodynamic effect exhibited by biological systems and it may be generated in vivo enzymatically as well.[7] Methods[8] used to

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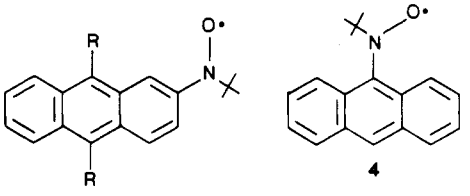
(2) On leave from the Deparatment of Medicinal Chemistry, Hoshi College of Pharmacy, Tokyo, Japan.

(3) *Singlet O_2*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1984; Vol. 1–4.

0022-3263/86/1951-3456$01.50/0

infer the intermediacy of singlet oxygen include product analysis when substrates such as substituted furans, benzofurans, or cholesterol are present, inhibition by singlet oxygen quenchers, chemiluminescence measurements, the effect of a change to D_2O as solvent, monitoring the generation of a stable nitroxide radical by singlet oxygen oxidation of 2,2,6,6-tetramethylpiperidine,[9] and monitoring the action of singlet oxygen on the water soluble substrates rubrene 2,3,8,9-tetracarboxylate[10,11] and 9,10-anthracenedipropionic acid.[12]

Electron spin resonance (ESR) spectroscopy has been used extensively for the detection of certain reactive intermediates, especially through spin-trapping methodology.[13] Advantages include high sensitivity without the usual requirement of optical transparency of the sample. Heretofore, no ESR-based method for the detection of singlet oxygen was available.[14] We sought to prepare nitroxides[15] that would exhibit a characteristic change in the ESR spectrum upon reaction with singlet oxygen. Specifically, anthracenyl *tert*-butyl nitroxides 1–4 were

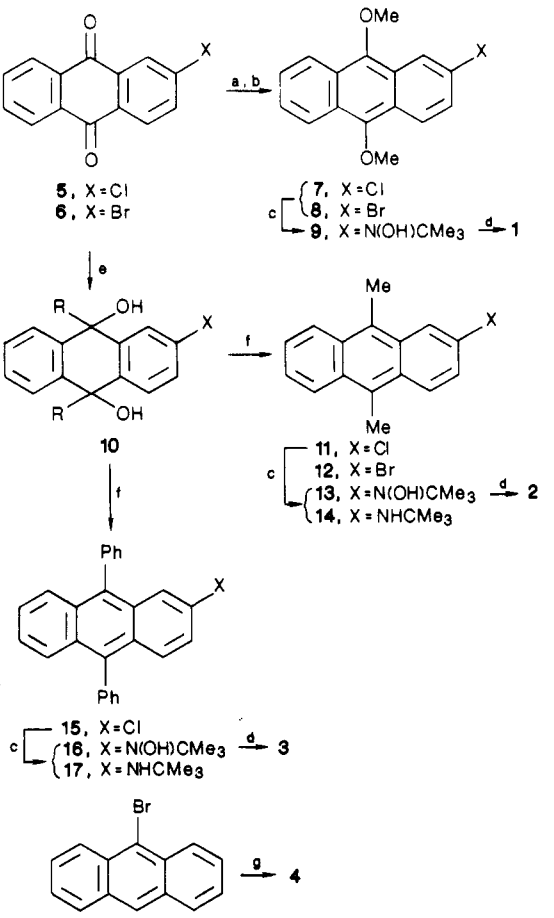


1, R = OMe
2, R = Me
3, R = Ph

chosen as targets, reasoning that formation of the corresponding endoperoxides[16] by singlet oxygen might be accompanied by distinctive changes in the ESR spectrum owing to changes in the extent of conjugation.

Synthesis of Anthracenyl *tert*-Butyl Nitroxides 1–4. Scheme I summarizes the synthetic routes to nitroxides 1–4. 2-Chloroanthraquinone (**5**) was reduced to the dihydroxy intermediate which was then methylated to give anthracene **7**.[17] The Grignard reagent was prepared from **7** by using activated Mg[18] and then allowed to react with 2-methyl-2-nitrosopropane,[19] affording *N*-hydroxy anthracene **9**. Comparable yields of **9** were obtained starting with bromoanthraquinone **6** via **8**. Oxidation of **9** to nitroxide **1** could be accomplished either with Cu^{2+}–air[20] or preferably with potassium ferricyanide in a two-phase system.[21] Nitroxide **1** could be stored at 0 °C in the solid state for several months without noticeable decomposition. We prefer, however, to store and mail its precursor, *N*-hydroxylamine **9**, and then generate **1** immediately prior to use.

Scheme I[a]



[a] (a) $Na_2S_2O_4$, aqueous EtOH; (b) $(MeO)_2SO_2$, aqueous NaOH; (c) activated Mg, THF, then Me_3CNO, then H_3O^+; (d) $Cu(OAc)_2$, O_2, MeOH, H_2O or $K_3Fe(CN)_6$, aqueous NaOH, CH_2Cl_2; (e) MeLi or PhLi; (f) $SnCl_2$, aqueous HCl; (g) Mg, THF, then Me_3CNO, then H_3O^+, then chromatography.

Chlorodimethylanthracene **11**[22] and chlorodiphenylanthracene **15**[23] were prepared from **5** via **10** and then converted to nitroxides **2** and **3**, respectively, via **13** and **16** in a manner similar to the preparation of **1**. Small amounts of the respective amine byproducts **14** and **17** were observed in these latter reactions. Bromide **12** was prepared in the methyl series (**6** → **10** → **12**) as an alternative to chloride **11**. Nitroxide **4** was obtained from the reaction of the Grignard reagent derived from 9-bromoanthracene with 2-methyl-2-nitrosopropane followed by chromatography. Nitroxide **2**, while isolable, decomposed either in benzene solution or in the solid state upon standing at 0 °C for a few hours. Nitroxide **3** proved to be the most robust among 1–4 toward purification and storage, while **4** and **1** (see above) behaved similarly.

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(13) For a review, see: Perkins, M. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 1.
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(20) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1976**, *41*, 3237.
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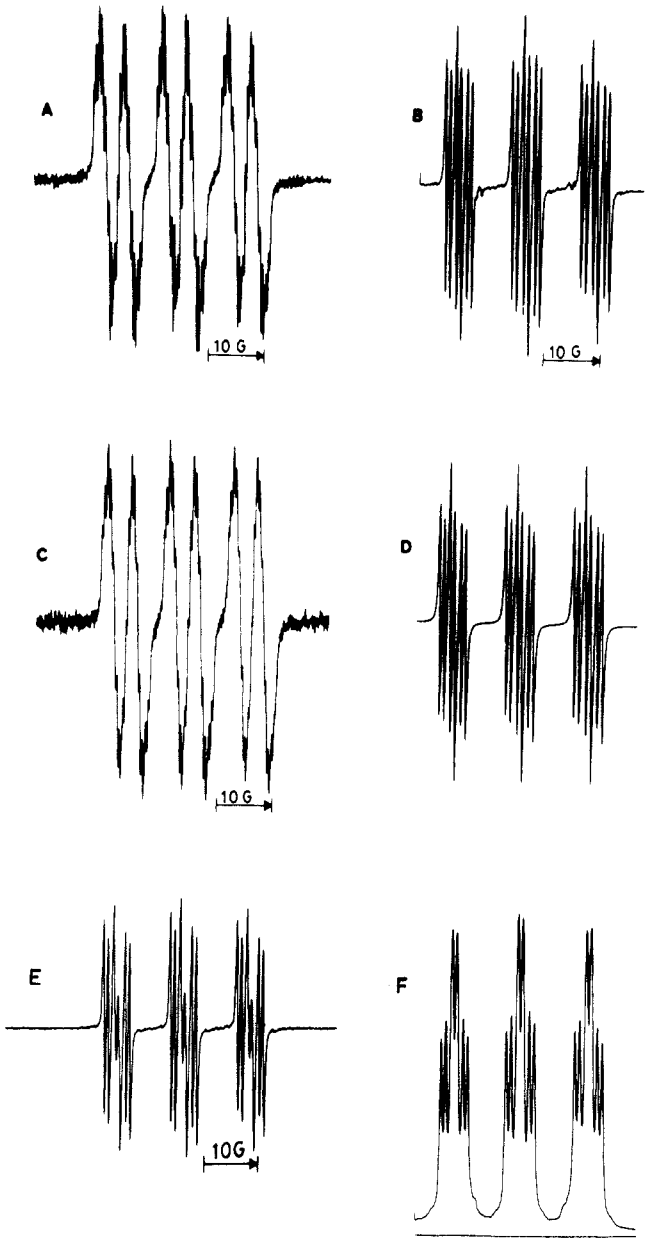
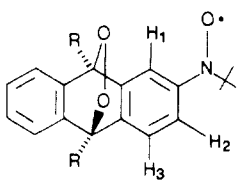


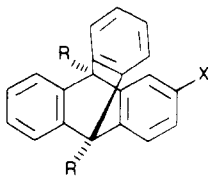
Figure 1. X-band ESR spectra of 2×10^{-4} M solutions of (A) anthracenyl nitroxide **1**, (B) endoperoxide nitroxide **18**, (C) anthracenyl nitroxide **3**, and (E) tryptacenyl nitroxide **27** in deoxygenated (3 freeze–thaw cycles or N_2 bubbling) benzene. Instrument parameters: modulation amplitude, 0.25 G; time constant, 0.3 s; scan rate, 6.25 G/min; microwave power, 5 mW. Computer simulation[26] of spectrum B gave the essentially indistinguishable spectrum D. The hyperfine splitting constants (G) used in the simulation: a_N, 12.125; a_{1H}, 2.185; a_{3H}, 1.917; a_{4H}, 0.891; line width, 0.319. The digitized single integral of spectrum B is shown in F.

ESR Spectra of Nitroxides 1–4. The ESR spectrum of nitroxide **1** is shown in Figure 1A.[24] The ESR spectrum of nitroxide **3** (Figure 1C) is similar to that of **1**. Nitroxide **2** showed a less well-resolved ESR spectrum consisting of the basic ^{14}N triplet (a_N = 11.63 G) in which each member was split into two broad peaks of unequal intensity. Nitroxide **4** showed essentially a three-line ESR spectrum, indicating that the NO· group likely was twisted out of conjugation with the aromatic ring as is the case with certain other sterically hindered aryl *tert*-butyl nitroxides.[25]

Reaction of Nitroxides 1–4 with Singlet Oxygen and Associated ESR Spectra. Sunlamp irradiation of a CH_2Cl_2 solution of nitroxide **1** containing methylene blue with gentle stirring under air was accompanied by a smooth, characteristic change in the ESR spectrum to that of endoperoxide **18** (Figure 1B) over 5 min. Workup of



18, R = OMe
19, R = Me
20, R = Ph



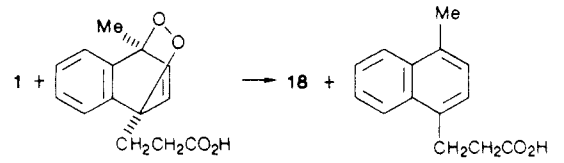
21, R = OMe; X = Br
22, R = Me; X = Br
23, R = Me; X = Cl
24, R = OMe; X = N(OH)CMe$_3$
25, R = OMe; X = N(O·)CMe$_3$
26, R = Me; X = N(OH)CMe$_3$
27, R = Me; X = N(O·)CMe$_3$

the reaction mixture gave the analytically pure endoperoxide nitroxide **18** in good yield. While solid **18** decomposed on standing for a day at 25 °C, dilute solutions were stable over several days.

Figure 1D shows a computer-simulated[26] close match of the spectrum of endoperoxide **18**. The spectrum is dominated by the ^{14}N splitting into three groups of lines. Within each group one observes nearly equivalent coupling to H-1 and H-3 and a smaller coupling to H-4. The expected approximate 1,1,2,2,1,1 absorption pattern is most easily seen from the digitized single integral (Figure 1F).

Nitroxide **18** was further characterized by an in situ reduction in $CDCl_3$ with phenylhydrazine[27] to give the diamagnetic *N*-hydroxy derivative. This substance showed a singlet at 3.98 ppm (two methoxy groups) in the NMR spectrum but was unstable and underwent decomposition during the NMR measurement. An analogous reduction of nitroxide **1** gave an NMR spectrum identical with that of **9** in which the methoxy groups appeared as a singlet at 4.08 ppm. This change in chemical shift of the methoxy groups (4.08 → 3.98 ppm) in the *N*-hydroxy series upon going from the anthracene to the endoperoxide was consistent with values observed for halides **7** and **8** and their corresponding endoperoxides under similar conditions.

The intermediacy of singlet oxygen in the conversion of **1** to **18** was supported by additional evidence. Formation of **18** proceeded well in CH_2Cl_2 when either *meso*-tetraphenylporphine or immobilized rose bengal was used as the sensitizer or when benzene was the solvent. The ESR spectrum of starting nitroxide **1** remained essentially unchanged over 5 min under the photolysis conditions either when the sensitizer was omitted, when oxygen was excluded from the reaction, or when the singlet oxygen quencher β-carotene[28] was present (benzene solvent). The conversion of **1** into **18** could also be observed (ESR) by reaction with singlet oxygen generated in situ chemically by continuous decomposition at 25 °C of 1-methyl-4-(2-carboxyethyl)naphthalene endoperoxide.[29]



(24) This spectrum has been simulated by computer.[1]
(25) See, for example: Duncan, J. L.; Forrester, A. R.; McConnachie, G.; Mallinson, P. D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 718.
(26) Details of the computer simulation are given in footnotes 19 and 20 of ref 1.
(27) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1975**, *40*, 3145.
(28) Foote, C. S. Chapter 5 in ref 4.

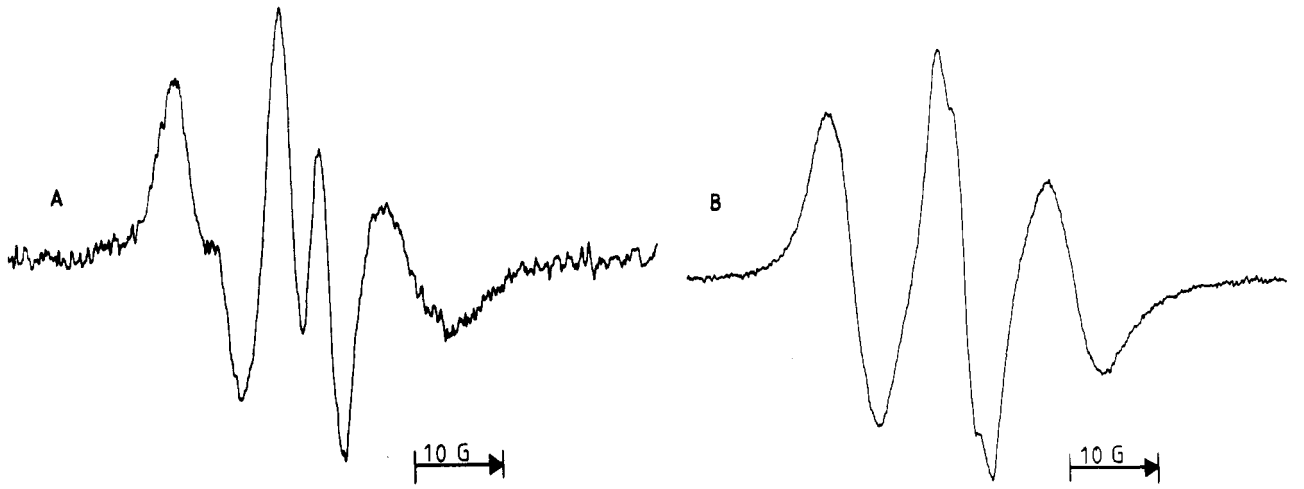


Figure 2. ESR spectrum of (A) anthracene nitroxide 1 and (B) endoperoxide nitroxide 18 incorporated in the bilayers of DMPC vesicles that are suspended in phosphate buffer pH 7.4 at 32 °C (T_m = 24 °C).

Nitroxide **2** reacted with singlet oxygen somewhat more slowly than did **1**. However, the resulting endoperoxide **19** and its precursor **2** were both too unstable to be of much use as a singlet oxygen indicator. In the case of nitroxide **3**, 2.5 h of irridation time were required for complete consumption, rendering the use of **3** less practical than that of **1**. In the early stages of the reaction TLC analysis indicated that endoperoxide **20** was the only product formed. However, as the reaction proceeded other (diamagnetic) spots appeared, indicating that **20** was undergoing further transformations during the extended reaction time. Essentially pure **20** could be obtained but it was not sufficiently stable for full characterization. The ESR spectra of endoperoxides **19** and **20** were similar to that of **18**.

Photooxygenation of nitroxide **4** proceeded slowly and without significant change in the ESR spectrum other than a smooth decrease in intensity. After 3 h about 10% of the original signal intensity remained. Anthraquinone was isolated as the major product by preparative TLC of the reaction mixture.

Two other 9,10-bridged-anthracenyl nitroxides, **25** and **27**, were synthesized so that their ESR spectra may be compared to those of endoperoxide nitroxides **18–20**. Tryptacenyl nitroxide **25** was prepared by the addition of benzyne[30] to **8** to give **21**. Halogen–metal exchange[31] with butyllithium followed by reaction with 2-methyl-2-nitrosopropane gave **24**. Oxidation of **24** with alkaline potassium ferricyanide then gave nitroxide **25**. Nitroxide **27** was prepared similarly from **22** via **26**. Bromide **22** and chloride analogue **23** were prepared from **12** and **11**, respectively.

Figure 1E shows the ESR spectrum of **27**, and that of **25**[24] is similar. The similarity in the spectra of all of the 9,10-bridged-anthracenyl nitroxides herein prepared constitutes additional confirmation of the endoperoxide nitroxide structures.

Vesicle Studies with Nitroxides 1 and 3. Oxygen is known to partition effectively into lipid bilayers from aqueous solution[32] and is likely involved in lipid peroxidation. Singlet oxygen might well behave similarly. With an eye toward the possible use of nitroxide **1** for the detection of singlet oxygen within cellular or vesicular systems, **1** was incorporated within the bilayer structures of multilamellar[33] dimyristoylphosphatidylcholine (DMPC) vesicles. The partially immobilized character of the ESR spectrum (Figure 2A) confirmed that nitroxide **1** was located within the bilayer of the vesicle. Addition of 2 volumes of MeOH caused destruction of the vesicles and led to an isotropic ESR spectrum essentially identical with that shown in Figure 1A.

Presynthesized endoperoxide nitroxide **18** was also incorporated within the bilayer of DMPC vesicles and gave the ESR spectrum shown in Figure 2B. Dilution with MeOH as above gave an isotropic ESR spectrum identical with that shown in Figure 1B. Nitroxide **3** and its endoperoxide **20** behaved similarly.

The vesicle suspension was then exposed to singlet oxygen generated in situ photochemically in the aqueous phase by using methylene blue as the sensitizer. In the case of nitroxide **1**, over a period of a few minutes the ESR spectrum changed smoothly from that shown in Figure 2A to a spectrum essentially identical with that shown in Figure 2B. The clean conversion of **1** to **18** in the vesicles was confirmed by dilution of the photolyzed vesicle suspension with MeOH. An isotropic ESR spectrum of **18** essentially identical with that shown in Figure 1B was observed.[34] Consistent with the rate differences observed in organic solvent, vesicle-incorporated diphenylanthracenyl nitroxide **3** reacted some 20-fold times more slowly with singlet oxygen than did **1**. The final ESR spectrum after dilution with methanol was quite weak, owing to decomposition during the long irradiation time (see above), but did confirm that endoperoxide **20** had been produced.

We conclude that nitroxide **1** dissolved in organic solvents or incorporated in the bilayer of DMPC vesicles reacts with singlet oxygen to form endoperoxide **18**. The reaction is sufficiently rapid and the resulting changes in the ESR spectra are sufficiently characteristic so that **1** may serve as an ESR-based probe for singlet oxygen. The synthesis of water-soluble analogues of **1** and the use of **1** to study the possible diffusion of singlet oxygen into human cultured bronchial epithelial cells[35] is in progress and will be reported in due course.

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(32) Subczynski, W. K.; Hyde, J. S. *Biophys. J.* **1983**, *41*, 283.
(33) Unilamellar vesicles behaved similarly.
(34) Spectral titration (Jost, P.; Griffith, O. H. In *Spin Labeling. Theory and Application*; Berliner, L. J., Ed.; Academic Press: New York, 1976; pp 268–271) of the isotropic digitized spectra of **1** and **18** indicated that as little as a 15% conversion of **1** into **18** could be detected.
(35) Nye, A. C.; Rosen, G. M.; Gabrielson, E. W.; Keana, J. F. W.; Prabhu, V. S.; manuscript submitted.

Experimental Section[36]

2-Chloro-9,10-dimethoxyanthracene (7). To a stirred refluxing suspension of 2-chloroanthraquinone (4.68 g, 19.3 mmol) in 95% EtOH (60 mL) was added dropwise a solution of sodium dithionite (10.0 g, 57.4 mmol) in water (80 mL). After a 45-min reflux period the precipitated yellow dihydroxy derivative was isolated by rapid filtration and washed with water. The precipitate was dissolved in a solution of sodium hydroxide (2.4 g, 60 mmol) in water (100 mL). To the resulting red solution was added dropwise over 15 min dimethyl sulfate (7.2 g, 57.1 mmol, freshly distilled). After 2 h at 25 °C the yellow-orange precipitate was collected and dried to yield crude **6** (4.70 g). This was chromatographed in benzene over silica gel to give pure **6** (3.81 g, 72%), mp 153–154 °C. Crystallization from EtOH–CH_2Cl_2 gave the analytical sample as fluorescent greenish yellow flakes, mp 154.5–155.5 °C:[17] NMR δ 4.12 (s, 6), 7.32–7.62 (m, 3), 8.18–8.38 (m, 4). Anal. Calcd for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.38, H, 4.81.

2-Bromo-9,10-dimethoxyanthracene (8). Following a procedure similar to that above, 2-bromoanthraquinone was converted into **8** (62%), mp 168–169 °C: NMR δ 4.12 (s, 6), 7.44–7.62 (m, 3), 8.12–8.36 (m, 3), 8.42–8.48 (m, 1). Anal. Calcd for $C_{16}H_{13}BrO_2$: C, 60.57; H, 4.10. Found: C, 60.38; H, 4.20.

***N*-[2-(9,10-Dimethoxyanthracenyl)]-*N*-*tert*-butylhydroxylamine (9).** To a stirred suspension of activated Mg (prepared[18] from 180 mg of Mg shavings) in THF (18 mL) at −78 °C was added dropwise a solution of **7** (1.47 g, 5.40 mmol) in THF (18 mL). After 30 min the mixture was allowed to warm to 25 °C over 2 h. To the mixture was added dropwise a solution of 2-methyl-2-nitrosopropane[19] (704 mg, 8.09 mmol) in THF (4 mL), and the resulting mixture was stirred for 12 h. Saturated aqueous NH_4Cl (8 mL) was added and the mixture was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated to dryness. This residue (1.68 g) was chromatographed over silica gel (45 g). The first eluent (benzene, 500 mL) was discarded. Elution with benzene–ether (50:1) gave 369 mg (21%) of crude **9** which was purified by two precipitations from hot benzene–hexanes to give 275 mg (16%) of pure **9** as a yellow solid, mp 154–156 °C dec: IR 3570 cm^{-1}; NMR δ 1.25 (s, 9), 4.06 (s, 3), 4.08 (s, 3), 7.35–7.60 (m, 3), 8.00–8.40 (m, 4). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.67; H, 7.16; N, 4.12.

The yield of **9**, mp 152–154 °C, by the above procedure starting with **8** was 21%.

2-(9,10-Dimethoxyanthracenyl) *tert*-Butyl Nitroxide (1). Method A. To a solution (0 °C) of **9** (20 mg) in MeOH (20 mL) containing a few drops of CH_2Cl_2 were added 3% aqueous NH_4OH (0.5 mL) and $Cu(OAc)_2 \cdot H_2O$ (2 mg). Oxygen was bubbled through the solution for 5 min and then it was concentrated to dryness. The residue was extracted with several portions of hexanes. The combined extracts (40 mL) were filtered and concentrated to dryness. The residue was dissolved in a few drops of benzene and MeOH was added slowly with cooling in order to precipitate the product. The product was redissolved in benzene and reprecipitated by the slow addition of pentane to give 12 mg (60%) of pure **1** as a yellow solid, mp 115–117 °C dec: MS, *m/e* (relative intensity) 325 (5, $M^+ + 1$), 324 (10, M^+), 309 (86), 294 (90), 268 (62), 264 (17), 253 (29), 238 (100), 223 (26); ESR, see text; NMR (after phenylhydrazine reduction[27]) δ 1.26 (s, 9), 4.08 (s, 6) and aromatic proton absorption. Anal. Calcd for $C_{20}H_{22}NO_3$: C, 74.05; H, 6.84; N, 4.32. Found: C, 74.23; H, 6.79; N, 4.43.

Method B. To a stirred solution of $K_3Fe(CN)_6$ (100 mg) in 2 M NaOH (4 mL) was added a solution of **9** (19.0 mg) in CH_2Cl_2 (3 mL). After 15 min CH_2Cl_2 was added, the layers were separated, and the organic layer was washed well with water and then dried ($MgSO_4$). The solvent was removed to afford 18.2 mg (96%) of nitroxide **1** which was purified by benzene–hexane precipitation as above, giving 12.2 mg (64%) of pure **1**, mp 115–117 °C dec.

2-Bromo-9,10-dimethylanthracene (12). To a stirred suspension of 2-bromoanthraquinone (8.61 g, 30.0 mmol) in THF (150 mL) at −78 °C was added dropwise 1.12 M methyllithium in ether (58.6 mL, 66 mmol) over 1 h. The mixture was allowed to warm to 25 °C over 1 h and then saturated NH_4Cl (100 mL) was added. Ether extraction afforded the crude diol (9.56 g, 100%), mp 165–167 °C (recrystallization from benzene gave white needles, mp 171–172 °C dec), which was dissolved in THF (20 mL) and added over a 15-min period to a clear stirred solution consisting of $SnCl_2$ (50 g), concentrated HCl (50 mL), and ether (250 mL).[37] After a 20-min stir, water (100 mL) was added and the mixture was extracted with ether. The extract was dried ($MgSO_4$) and concentrated to dryness to afford 5.65 g of crude **12**. Chromatography over basic alumina (100 g) and elution with hexanes gave 4.73 g (56%) of **12**, mp 106–107 °C, suitable for the next reaction. Sublimation at 110 °C/2.3 mm gave the analytical specimen as yellow needles, mp 106.5–107.5 °C. Anal. Calcd for $C_{16}H_{13}Br$: C, 67.36; H, 4.60; Br, 28.04. Found: C, 67.22; H, 4.54; Br, 28.23.

***N*-[2-(9,10-Dimethylanthracenyl)]-*N*-*tert*-butylhydroxylamine (13) and 2-(9,10-Dimethylanthracenyl)-*tert*-butylamine (14).** The procedure used to prepare **9** was employed. From 2-chloro-9,10-dimethylanthracene (973 mg)[22] there was obtained 1.12 g of crude material which was chromatographed over silica gel (25 g). After elution with hexane–benzene (7:3, 500 mL, discarded), elution with hexane–benzene (6:4, 200 mL) afforded 150 mg of crude amine **14**. This was purified by preparative TLC, giving pure **14** as a yellow-brown powder: mp 118–119 °C dec; IR 3420 cm^{-1} (w, NH); NMR δ 1.52 (s, 9), 2.98 (s, 3), 3.02 (s, 3), 6.90–7.55 (m, 4), 8.05–8.32 (m, 3); MS, *m/e* 277.183 (calcd for $C_{20}H_{23}N$, 277.183). Continued elution with the same solvent gave 243 mg (21%) of **13** which was purified by precipitation from a benzene solution by the addition of hexane to give 193 mg (16%) of **13** as a yellow powder, mp 180–181 °C dec: IR 3570 cm^{-1}; NMR δ 1.26 (s, 9), 2.72 (s, 3), 2.92 (s, 3), 7.32–7.64 (m, 3), 7.66–8.32 (m, 4); MS, *m/e* (relative intensity) 294 (1.43, $M^+ + 1$), 293.179 (2.86) (M^+, calcd for $C_{20}H_{23}NO$, 293.1780), 292 (4.29), 291 (14.29), 290 (1.43), 289 (1.43), 279 (4.29), 278 (22.86), 277 (100). Anal. Calcd for $C_{20}H_{23}NO \cdot 0.4H_2O$: C, 79.90; H, 7.99; N, 4.66. Found: C, 80.05; H, 7.96; N, 4.45.

2-(9,10-Dimethylanthracenyl) *tert*-Butyl Nitroxide (2). A 15-mg sample of **13** was dissolved in CH_2Cl_2 (3 mL) and added to a stirred solution of $K_3Fe(CN)_6$ (50 mg) in 2 M NaOH (4 mL). After 15 min the organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness, affording 11 mg (75%) of crude **2**: NMR (after phenylhydrazine[27] addition) δ 1.28 (s, 9), 2.78 (s, 3), 2.94 (s, 3) and aromatic proton absorption; MS, *m/e* (relative intensity) 292 (4), 291.164 (14), ($M^+ - 1$, calcd for $C_{20}H_{21}NO$, 291.162), 278 (30), 277 (77), 262 (30), 221 (100). The usual attempts to purify **2** led to its decomposition.

***N*-[2-(9,10-Diphenylanthracenyl)]-*N*-*tert*-butylhydroxylamine (16) and 2-(9,10-Diphenylanthracenyl)-*tert*-butylamine (17).** The procedure used to prepare **9** was employed. From 2-chloro-9,10-diphenylanthracene (1.47 g)[23] there was obtained 1.75 g of crude material which was chromatographed over silica gel. A yellow-green band was eluted with hexane–benzene (4:1). This yielded 140 mg of amine **17** as a yellow solid, mp 79–81 °C: IR 3420 cm^{-1} (w, NH); NMR δ 1.26 (s, 9), 3.72 (br s, 1), 6.64–6.82 (m, 2), 7.14–7.35 (m, 4), 7.38–7.72 (m, 11); MS, *m/e* 401.215 (calcd for $C_{30}H_{27}N$, 401.214). Continued elution with hexane–benzene (3:7) afforded 461 mg (27%) of **16** as a yellow solid, mp 197–199 °C. Crystallization from hexane–benzene gave the analytical specimen, mp 206.5–208 °C; IR 3565 cm^{-1}; NMR δ 1.10 (s, 9), 7.02–7.80 (m, 17). Anal. Calcd for $C_{30}H_{27}NO$: C, 86.29; H, 6.52; N, 3.36. Found: C, 86.23; H, 6.80; N, 3.25.

2-(9,10-Diphenylanthracenyl) *tert*-Butyl Nitroxide (3). A 30-mg sample of **16** was oxidized with $K_3Fe(CN)_6$ (see synthesis of **1** above) to afford 29 mg (96%) of nitroxide **3** as a greenish-

(36) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded in $CDCl_3$ on a 3-200 Sargent-Welch spectrometer. NMR spectra were recorded either on a Varian XL-100 or a Nicolet QE-300 spectrometer in $CDCl_3$. Chemical shifts are expressed in δ units with Me_4Si as an internal standard. ESR spectra were recorded on a Varian E-3 or a E-9 9.5-GHz spectrometer interfaced with a 32K Varian 620/L100 computer for spectral analysis. Elemental analyses were determined either at the University of Oregon by Dr. R. Wielesek or at Mic Anal., Tuson, AZ. All reactions were routinely run under a N_2 atmosphere. Solvents were routinely distilled.

(37) Newman, M. S.; Prabhu, V. S.; Veeraraghavan, S. *J. Org. Chem.* **1983**, *48*, 2926.

yellow solid after preparative TLC over silica gel (benzene): mp 108–110 °C dec; ESR, see text; NMR (after phenylhydrazine[27] addition) δ 1.10 (s, 9) and aromatic proton absorption. Anal. Calcd for $C_{30}H_{26}NO$: C, 86.50; H, 6.30; N, 3.36. Found: C, 86.22; H, 6.35; N, 3.26.

9-Anthracenyl *tert*-Butyl Nitroxide (4). To a stirred suspension of Mg turnings (14 mg, 0.58 mmol) in THF (0.5 mL) was added 9-bromoanthracene (138 mg, 0.54 mmol, Aldrich, recrystallized from EtOH) in THF (1 mL). The mixture was stirred at 50 °C for 3 h, cooled to 25 °C, and treated with a solution of 2-methyl-2-nitrosopropane (48 mg, 0.55 mmol) in THF (1 mL). After 15 min saturated NH_4Cl (1 mL) was added, and the mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to dryness. The residue was subjected to preparative TLC over silica gel using CH_2Cl_2 as the eluent. The yellow band was removed, affording crude **4** (13 mg) as a yellow paste. This was dissolved in benzene and precipitated by the addition of MeOH with cooling, affording 8 mg (6%) of pure **4** as a yellow solid, mp 73–73.5 °C dec: ESR (benzene) 3 lines, a_N = 13.4 G; MS, *m/e* (relative intensity) 265.147 (2, $M^+ + 1$, calcd for $C_{18}H_{19}NO$, 265.147), 264.138 (3, M^+, calcd for $C_{18}H_{17}NO$, 264.139), 263 (1), 249 (17), 208 (33), 193 (100), 165 (13).

2-(9,10-Dihydro-9,10-dimethoxy-9,10-epidioxyanthracenyl) *tert*-Butyl Nitroxide (18). Method A. A solution of nitroxide **1** (9 mg) and methylene blue (3 mg) in CH_2Cl_2 (90 mL) was irradiated with a 150-W sunlamp for 5 min at 20–25 °C with gentle stirring under air and then concentrated to dryness. The residue was extracted several times with cyclohexane. The combined extract (50 mL) was concentrated to dryness and the brown residue was dissolved in a small amount of benzene. Addition of hexane followed by cooling to −8 °C gave a pale brown solid that was collected by centrifugation (7.2 mg, 71%): ESR, see text; IR no C=O absorption; MS, *m/e* (relative intensity) 357 (3), 356 (1), 325 (19), 309 (68), 294 (68), 279 (21), 268 (25), 264 (49), 254 (26), 238 (83), 223 (38), 128 (100); NMR (after phenylhydrazine[27] addition) δ 1.15 (s, 9), 3.98 (s, 6) and aromatic proton absorption. The sample was decomposing slowly during the NMR measurement. Anal. Calcd for $C_{20}H_{22}NO_5$: C, 67.40; H, 6.22; N, 3.93. Found: C, 67.70; H, 5.98; N, 4.22.

Method B. To a stirred solution of 0.17 mg (0.52×10^{-3} mmol) of **1** in 0.70 mL of THF was added 12 mg (24×10^{-3} mmol of endoperoxide) of a 1:1 mixture of 1-methyl-4-(2-carboxyethyl)-naphthalene and its endoperoxide[29] and 0.3 mL of 0.1 M phosphate buffer pH 7.4. The vessel was sealed with a serum cap, flushed with N_2, and placed in a bath at 35 °C. Aliquots were removed periodically, diluted with 2 vol of THF, treated with N_2 to remove dissolved O_2, and then monitored by ESR. After 4.5 h essentially complete conversion of nitroxide **1** to endoperoxide **18** was indicated by the ESR spectra.

2-(9,10-Dihydro-9,10-dimethyl-9,10-epidioxyanthracenyl) *tert*-Butyl Nitroxide (19). A 20-mg sample of hydroxyamine **13** was oxidized to nitroxide **2** as described above. The crude **2** was dissolved in CH_2Cl_2 (75 mL) containing methylene blue (6 mg) and the stirred solution was irradiated at 15–20 °C under air as above for 1 h. The solution was concentrated and then rapidly passed over silica gel (2 g) to remove the dye. Evaporation of the eluent gave 20 mg (90%) of crude endoperoxide **19**: ESR, see text; IR no C=O absorption. A 15-mg sample was dissolved in ether (3 mL), treated with $LiAlH_4$ (4 mg), and stirred at 25 °C for 10 min. The usual workup followed by filtration through silica gel afforded 12 mg (81%) of the corresponding *N*-hydroxy endoperoxide: NMR δ 1.15 (s, 9), 2.13 (s, 6), 7.06–7.50 (m, 7); IR 3560 cm^{-1}.

2-(9,10-Dihydro-9,10-diphenyl-9,10-epidioxyanthracenyl) *tert*-Butyl Nitroxide (20). A solution of nitroxide **3** (28 mg) and methylene blue (5 mg) in CH_2Cl_2 (75 mL) was irradiated as above at 10–15 °C for 2.5 h. The workup used for **18** was followed, affording 31.5 mg of crude **20**. Preparative TLC over silica gel and elution of the yellow band with CH_2Cl_2 gave 15.6 mg (52%) of **20** as a yellow solid, mp 123–125 °C dec: ESR, see text; IR no C=O absorption; NMR (after phenylhydrazine[27] addition) δ 1.19 (s) and aromatic proton absorption; MS, *m/e* (relative intensity) 448 (3), 432.194 (35, $M^+ - 16$, calcd for $C_{30}H_{26}NO_2$, 432.195), 401 (100). Anal. Calcd for $C_{30}H_{26}NO_3 \cdot 0.15CH_2Cl_2$: C, 78.54; H, 5.75; N, 3.04. Found: C, 78.59; H, 5.98; N, 2.82. Elemental analyses of three independently prepared samples of **20** all showed varying amounts of entrapped solvent.

2-Chloro-9,10-dihydro-9,10-diphenyl-9,10-epidioxyanthracene (Not Shown). A 60-mg sample of 2-chloro-9,10-diphenylanthracene[23] was converted into the title epidioxide (61 mg, 93%), mp 152–154 °C dec, as described above: MS, *m/e* 396.093 (calcd for $C_{26}H_{17}ClO_2$, 396.092). Anal. Calcd for $C_{26}H_{17}ClO_2$: C, 78.77; H, 4.33; Cl, 8.83. Found: C, 78.47; H, 4.45; Cl, 8.76.

This substance was stable indefinitely at 25 °C and did not react with phenylhydrazine in $CDCl_3$ under the NMR conditions used with the nitroxide endoperoxides.

2-Bromo-9,10-dihydro-9,10-dimethoxy-9,10[1′,2′]-benzenoanthracene (21). To a refluxing solution of bromide **8** (2.052 g, 6.47 mmol) and isoamyl nitrite (1.823 g, 15.6 mmol) in THF (35 mL) was added a solution of anthranilic acid (1.95 g, 14.2 mmol) in THF (15 mL) over a period of 4 h. Then after a 1.5-h reflux period the THF was distilled off, xylene (50 mL) and maleic anhydride (1.90 g, 19.4 mmol) were added, and the mixture was refluxed for 1 h. The solvents were removed and the residue was extracted with ether. The extract was washed with 5% aqueous NaOH, dried ($MgSO_4$), and concentrated to dryness to afford 2.46 g of gummy product. This was dissolved in a small amount of benzene and chromatographed over silica gel (60 g). Elution with hexane (1.5 L) gave 1.43 g (59%) of crude **21** as a slightly oily solid. Hexane (10 mL) was added and the mixture was filtered to yield 1.22 g (50%) of **21** as a whitish solid, mp 176–177 °C. Crystallization from methylcyclohexane afforded the analytical specimen as pale yellow needles, mp 177–178 °C: NMR δ 4.34 (s, 6), 6.94–7.78 (m, 11). Anal. Calcd for $C_{22}H_{17}BrO_2$: C, 67.17; H, 4.36; Br, 20.33. Found: C, 67.43; H, 4.50; Br, 20.46.

***N*-[2-(9,10-Dihydro-9,10-dimethoxy-9,10[1′,2′]-benzenoanthracenyl)]-*N*-*tert*-butylhydroxylamine (24).** To a stirred solution of **21** (566 mg, 1.50 mmol) in ether (20 mL) at 0–5 °C was added 2.25 M butyllithium in hexane (0.66 mL, 1.5 mmol) dropwise over 5 min. After a 2-h stir, the solution was allowed to warm to 25 °C over 1 h. It was again cooled to 0 °C and then treated with a solution of 2-methyl-2-nitrosopropane (157 mg, 1.8 mmol) in ether (2 mL). After a 15-h stir at 25 °C, saturated NH_4Cl (10 mL) was added and the mixture was worked up by ether extraction to yield 608 mg of crude product which was chromatographed over silica gel (25 g). Elutions with hexane and 3:7 benzene–hexane were discarded. Elution with 1:1 benzene–hexane gave 63 mg of crude nitroxide **25**. Continued elution with benzene afforded 419 mg (70%) of **24**, mp 210–212 °C dec. Crystallization from benzene–hexane gave the analytical specimen as pale pink crystals, mp 216–218 °C dec: IR 3580 cm^{-1}; NMR δ 1.08 (s, 9), 4.30 (s, 6), 6.82–7.16 (m, 5), and 7.30–7.68 (m, 6). Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.77; H, 6.78; N, 3.49. Found: C, 78.04; H, 6.87; N, 3.29.

2-Bromo-9,10-dihydro-9,10-dimethyl-9,10[1′,2′]-benzenoanthracene (22). This substance was prepared in 83% yield from bromide **12** following the procedure for the synthesis of **21**. Tryptacene **22** as white plates: mp 218.5–219.5 °C; NMR δ 2.38 (s, 6), 6.92–7.50 (m, 11). Anal. Calcd for $C_{22}H_{17}Br$: C, 73.12; H, 4.75; Br, 22.13. Found: C, 73.42; H, 4.80; Br, 22.02.

2-Chloro-9,10-dihydro-9,10-dimethyl-9,10[1′,2′]-benzenoanthracene (23). This substance was prepared in 86% yield from chloride **11** following the procedure for the synthesis of **21**. Tryptacene as colorless rhombic crystals: mp 222–223 °C; NMR δ 2.40 (s, 6), 6.92–7.46 (m, 11). Anal. Calcd for $C_{22}H_{17}Cl$: C, 83.52; H, 5.42; Cl, 11.06. Found: C, 83.23; H, 5.33; Cl, 10.98.

2-[9,10-Dihydro-9,10-dimethoxy-9,10[1′,2′]-benzenoanthracenyl] *tert*-Butyl Nitroxide (25). A 50-mg sample of **24** was oxidized with $K_3Fe(CN)_6$ as described above. There was obtained 46 mg of crude orange **25** which was purified by preparative TLC and elution with CH_2Cl_2. The orange band afforded 36 mg (73%) of pure **25** as an orange powder, mp 103–105 °C dec: ESR, see text; NMR (after phenylhydrazine[27] addition) δ 1.10 (s, 9), 4.30 (s, 3), 4.32 (s, 3) and aromatic proton absorption. Anal. Calcd for $C_{26}H_{26}NO_3$: C, 77.96; H, 6.55; N, 3.50. Found: C, 77.53; H, 6.38; N, 3.67.

***N*-[2-(9,10-Dihydro-9,10-dimethyl-9,10[1′,2′]-benzenoanthracenyl)]-*N*-*tert*-butylhydroxylamine (26).** This substance was prepared from bromide **22** (542 mg) following the procedure for the synthesis of **24**. From chromatography there was obtained crude nitroxide **27** (33 mg, elution with hexane–

benzene, 4:1) and hydroxylamine **26** (429 mg, 77%), mp 218–220 °C dec. The analytical specimen, mp 224–226 °C dec, was obtained as pale pink crystals by crystallization from benzene–hexane: IR 3580 cm^{-1}; NMR δ 1.10 (s, 9), 2.38 (s, 6), 6.76–7.46 (m, 11). Anal. Calcd for $C_{26}H_{27}NO$: C, 84.50; H, 7.37; N, 3.97. Found: C, 84.20; H, 7.40; N, 3.73. A Grignard reaction involving chloride **23** failed, even when activated Mg was used.

2-[9,10-Dihydro-9,10-dimethyl-9,10[1′,2′]-benzenoanthracenyl] *tert*-Butyl Nitroxide (27). A 45-mg sample of **26** was oxidized with $K_3Fe(CN)_6$ as above to afford 44 mg of **27**. Preparative TLC and elution with CH_2Cl_2 gave 36 mg (80%) of pure **27** as an orange-red powder, mp 123–125 °C dec: ESR, see text; NMR (after phenylhydrazine[27] addition) δ 1.10 (s, 9), 2.38 (s, 6) and aromatic proton absorption. Anal. Calcd for $C_{26}H_{26}NO$: C, 84.74; H, 7.12; N, 3.80. Found: 84.54; H, 7.12; N, 3.52.

Vesicle Experiments. Multilamellar vesicles were prepared according to the general procedure of Bangham and Johnson.[38] The following procedure is representative. To a solution of dimyristoylphosphatidylcholine (45 mg) in 3 mL of $CHCl_3$ was added 3.78 mL (0.378 mg) of a CH_2Cl_2 stock solution of nitroxide **1** (0.10 mg/mL). The solvent was removed under a stream of nitrogen, leaving a thin film that was dried under vacuum (0.05 mm). Then phosphate buffer (2.25 mL, 0.1 M, pH 7.4) was added and the mixture was vortexed for 7 min at 32 °C. A 0.2-mL aliquot was transferred to an ESR tube, nitrogen as bubbled through the solution for 5 min, and then the spectrum was recorded (Figure 2A). In separate experiments, vesicles containing either nitroxide **3** or nitroxide endoperoxides **18** or **20** were similarly prepared and the ESR spectra recorded. In one series of experiments an isotropic ESR spectrum of each nitroxide was obtained after the addition of two volumes of MeOH to the respective ESR tubes. In another series of experiments the ESR tubes containing either nitroxide **1** or **3** in the bilayer of the vesicles and methylene blue (final concentration, 1 mg/4.5 mL) in the aqueous phase were irradiated at 32 °C open to the atmosphere with a 150-W sunlamp. At appropriate intervals the tubes were removed from the light source, two volumes of MeOH were added, nitrogen was bubbled through the solution, and the isotropic ESR spectrum was recorded in order to follow the progression of the reaction with singlet oxygen.

(38) Johnson, S. M.; Bangham, A. D. *Biochim. Biophys. Acta* **1969**, *193*, 92.

Acknowledgment. This research was supported by PHS Grant GM 27137 from the National Institute of General Medical Sciences. Some of the NMR spectra were measured on a 300-MHz spectrometer purchased with funds from PHS Grant RR02336 and NSF Grant CHE 8411177.

Registry No. **1**, 97634-94-1; **2**, 103438-60-4; **3**, 103438-61-5; **4**, 103438-62-6; **5**, 131-09-9; **6**, 572-83-8; **7**, 56971-01-8; **8**, 103438-63-7; **9**, 97634-97-4; **10** (R = CH_3, X = Br), 103456-61-7; **10** (R = H, X = Cl), 103438-77-3; **11**, 43217-24-9; **12**, 103438-64-8; **13**, 103438-65-9; **14**, 103438-66-0; **15**, 43217-28-3; **16**, 103438-67-1; **17**, 103438-68-2; **18**, 97634-95-2; **19**, 103438-69-3; **19** (*N*-hydroxy), 103438-78-4; **20**, 103438-70-6; **21**, 103438-71-7; **22**, 15254-40-7; **23**, 103438-72-8; **24**, 103438-73-9; **25**, 97634-96-3; **26**, 103438-74-0; **27**, 103438-75-1; 2-methyl-2-nitrosopropane, 917-95-3; 9-bromoanthracene, 1564-64-3; anthranilic acid, 118-92-3; maleic anhydride, 108-31-6; 1-methyl-4-(2-carboxyethyl)naphthalene, 76673-34-2; 3-(1,4-epidoxy-4-methyl-1,4-dihydro-1-naphthyl)propionic acid, 76673-35-3; 2-chloro-9,10-dihydro-9,10-diphenyl-9,10-epidioxyanthracene, 103438-76-2.

Polymer-Assisted Asymmetric Reactions. 4. Polymer-Bound Ephedrine, Its Use and Limitations in Supported $LiAlH_4$ Reductions†

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Received April 9, 1986

A cross-linked polystyrene resin containing (1*R*,2*S*)-(−)-ephedrine moieties bound through nitrogen to some of its *p*-methylene-substituted aromatic rings is a useful regenerable chiral auxiliary in the enantioselective reduction of acetophenone by the chiral polymer-bound complexes of lithium aluminum hydride and an added achiral phenol. Evidence is presented to explain the capacity-dependent behavior of the polymer in the formation of chiral complexes and its effect on the enantioselectivity of the reduction of acetophenone. At high capacities, both unbound achiral and multiply bound chiral complexes are formed while numerous chiral ligands appear to be inaccessible to the hydride; under such conditions the enantioselectivity of the reaction is poor. In contrast, at low capacities corresponding to 8–10% substitution of the styrene repeating units, the polymer-bound chiral moieties can act independently from one another and are fully accessible to the hydride. The reduction then proceeds with a high enantioselectivity, comparable to that of similar small chiral molecules. This mechanism is consistent with and explains the phenomena observed with other polymer-supported hydride reagents.

Introduction

The use of polymers containing chiral groups in asymmetric processes has received increasing attention over the past few years following the notable success which has been achieved in the area of the chromatographic separation of enantiomers.[1,2] Extensive efforts have also been devoted to the development of polymer-supported chiral moieties containing quaternary ammonium or phosphonium salts for use as catalysts in simple asymmetric phase transfer catalyzed reactions.[3] The latter application has only met with limited success in most cases due to the lack of intimate contact between the chiral moiety and the reaction loci. More successful approaches have involved reactions[4]

† Dedicated to Professor Dr. Georg Manecke on his 70th birthday.

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