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SYNTHESIS AND KINETIC STUDIES OF A NOVEL SINGLET OXYGEN DONOR WITH ACCEPTOR-BINDING CAPABILITY

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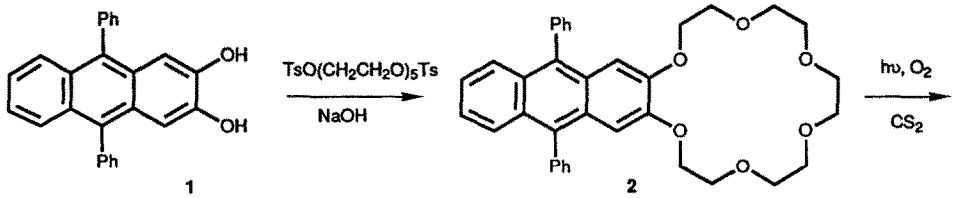
Abstract: A singlet oxygen donor has been prepared in which an 18-crown-6 ether residue is attached to the 2,3-position of a 9,10-diphenylanthracene peroxide. Kinetic and preliminary donor-acceptor recognition studies are reported.

In connection with our interest in preparing a singlet oxygen transfer reagent capable of mimicking enzymatic recognition, we have designed a singlet oxygen donor with unique acceptor-binding capability. A crown ether-functionalized anthracene, 9,10-diphenylanthraceno-2,3-(18-crown-6) **2**, has been synthesized by cyclizing 2,3-dihydroxy-9,10-diphenylanthracene **1** with pentaethylene glycol ditosylate.[1,2] Self-sensitized photooxygenation of **2** in carbon disulfide yielded the corresponding endoperoxide **3** quantitatively.[3]

The structure of the transannular peroxide **3** was established by the ^{1}H NMR, IR and mass spectroscopic data along with elemental analysis.[4] In particular, the UV spectrum showed absence of the strong absorption of the anthracene system at 395 and 375 nm and none of the tailing above 300 nm which is characteristic of the substituted naphthalenic framework embodied in the alternative peroxidic structure **4**.



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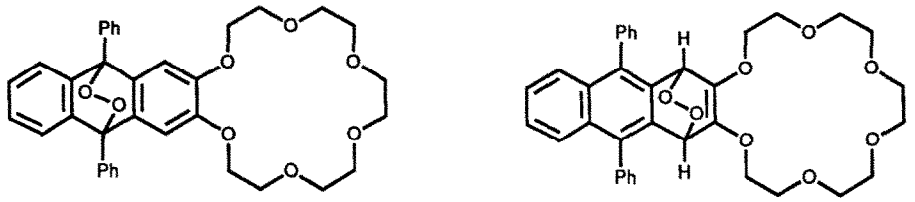
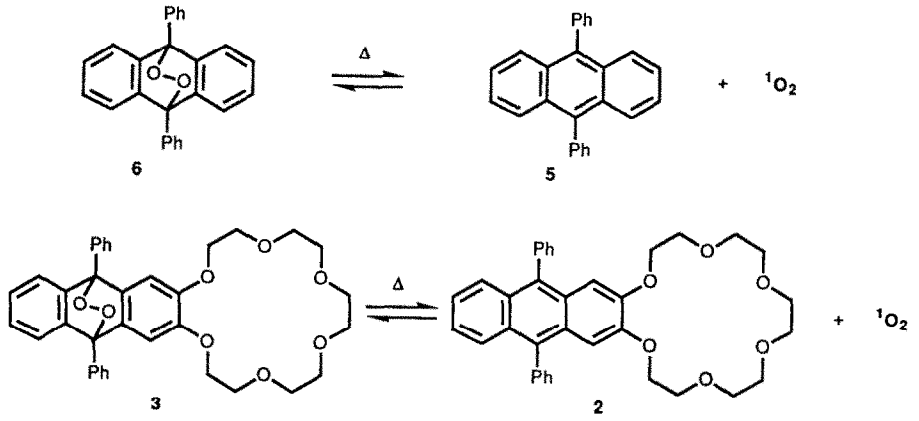
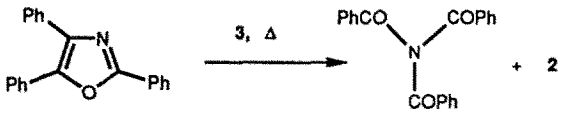


3 4



Heating of **3** in benzene afforded a quantitative recovery of **2** as determined by the UV spectra. In the presence of triphenyloxazole, a potent singlet oxygen acceptor, triphenyltriamide was obtained as the oxidation product.[5] Thus, the crown ether endoperoxide **3** fully resembles the well-studied case of 9, 10-diphenylanthracene endoperoxide **6**, which reversibly binds singlet oxygen.[3]



The rates of reactions for **6** and **3** in benzene at various temperatures were studied by monitoring the formation of **5** and **2** *via* UV spectrometry. A large excess of 2,5-dimethyl furan was maintained in solution during the kinetic studies to scavenge the singlet oxygen and to minimize the reverse process. Excellent first order kinetic rates were obtained throughout the study.

While the mode of reaction is the same, we found that the rate of singlet oxygen release from **3** to **2** is 25 times faster than release from **6** to **5** in the temperature range examined. Since oxazoles undergo rapid oxidation with singlet oxygen, we prepared a trisubstituted oxazole **7** connected to an ammonium salt by a seven carbon atom chain. Based on examination of CPK space-filling models, the ammonium ion complexed in the crown would hold the oxazole ring in a favorable spacial orientation relative to the endoperoxide. We hoped to demonstrate acceptor recognition at the site of the crown ether as pictured in Figure 1, with special consequences relative to the transfer of singlet oxygen to the oxazole at the end of the tether.

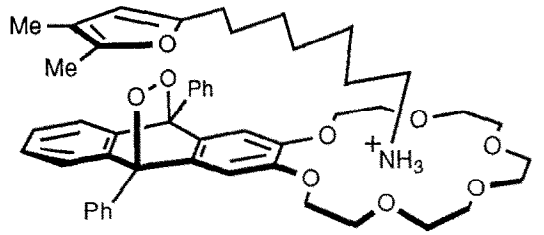
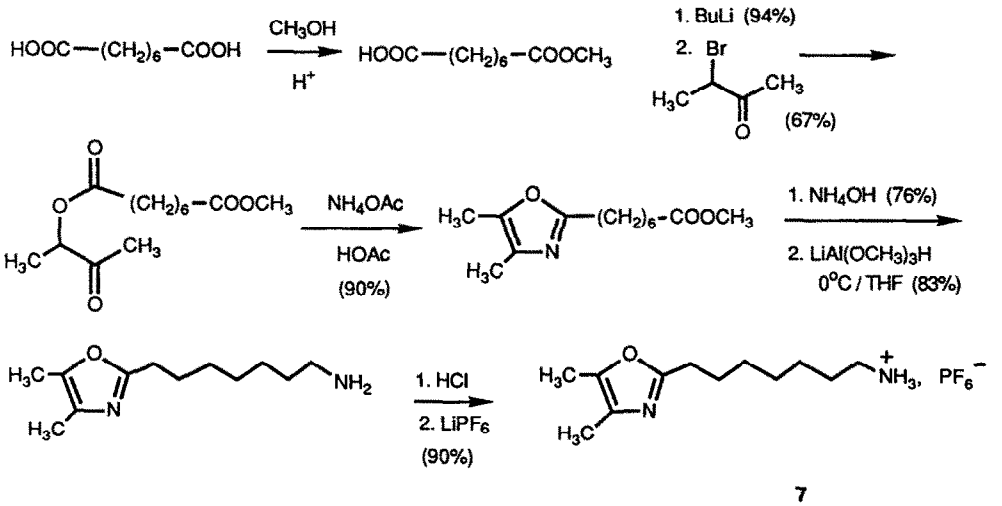


Figure 1

Compound **7** was prepared as shown in the Scheme by monoesterification of suberic acid, followed by condensation with 3-bromobutane-2-one in the presence of butyl-lithium. Ring closure with ammonium acetate/ acetic acid gave the oxazole ester. The methyl ester was converted to the amide with ammonium hydroxide and then reduced to the amine with lithium trimethoxyaluminum hydride at 0°C. The amine thus formed was then converted to the ammonium hexafluorophosphate salt.

Scheme



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The operation of donor-acceptor complexation was evident by the fact that the oxazole-ammonium salt **7** was only 7.6 wt % soluble in chloroform ether, but became completely soluble in the presence of the anthracene-crown ether. The rate of oxazole oxidation was monitored in control experiments using the 9,10-diphenylanthracene peroxide **6** and 18-crown-6 as separate entities. Thus far, however, we have not been able to demonstrate a donor-acceptor recognition effect *via* enhancement of the oxidation rate. It is clear that in a non-rigid conformation, the most favorable geometry for oxygen transfer is realized only a fraction of the time average as the flexible chain of the oxazole acceptor swings freely within the hemisphere of the seven carbon radius above the plane of the anthracene-crown ether. The dissociation constant of the crown-ammonium salt complex in organic solution and the short life and high gas diffusion rate of singlet oxygen once liberated from the solvent cage, are all factors to be taken into account in seeking evidence for rate enhancement. We plan to continue these studies in further work.

Acknowledgement: We thank the General Medical Sciences Institute of the NIH, Grant GM-13854, for support of this work.

References and Footnotes

1. The synthesis of 2,3-dihydroxy-9,10-diphenylanthracene was accomplished by the method of Etienne, A.; Bourdon, J. *Bull. Soc. Fr.* **1955**, 380.

2. For a review of crown ether syntheses, see Cram, D.J.; Cram, J.M. *Science* **1974**, *183*, 803.

3. a) Wasserman, H.H.; Scheffer, J.R. *J. Amer. Chem. Soc.* **1967**, *89*, 3073. b) Wasserman, H.H.; Scheffer, J.R.; Cooper, J.L., *J. Amer. Chem. Soc.* **1972**, *94*, 4991, and references therein.

4. The crown ether peroxide **3** was prepared as follows: A solution of the anthracene-18-crown-6 (**2**) (0.01 molar) was cooled in an ice-bath and saturated with O_2. This solution was then irradiated with a 650 watt Sylvania Tunsten Lamp (at 100 v) for 2 hr. After removal of the CS_2 *in vacuo*, pale-yellow crystals were obtained, which could be recrystallized by dissolution in a minimum amount of CS_2 followed by trituration with pentane, yielding white crystals, m.p. 146°C (dec.) (85%).
For 2: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.44-7.61 (m, 12 H), 7.26 (m, 2 H), 6.86 (s, 2 H), 3.98 (m, 4 H), 3.81 (m, 4 H), 3.67-3.76 (m, 12 H). IR ($CHCl_3$, cm^{-1}) 3050, 2970, 1500, 1460, 1225, 1130. UV ($CHCl_3$) nm 395 (ε, 10,100), 356 (ε, 6340). MS M^+, 564. Anal. Calcd for $C_{36}H_{36}O_6$: C, 76.59; H, 6.38. Found: C, 76.31; H, 6.35.
For 3: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.52-7.69 (m, 10 H), 7.10-7.20 (m, 4 H), 6.76 (s, 2 H), 3.96 (m, 4 H), 3.81 (m, 4 H), 3.62-3.72 (m, 12 H),. IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1520, 1420, 1110. UV ($CHCl_3$) ≤ 300 nm Anal. Calcd for $C_{36}H_{36}O_8$: C, 72.48; H, 6.04. Found: C, 72.25; H, 6.12.

5. a) Wasserman, H.H.; Gambale, R.J. *J. Am. Chem. Soc.* **1985**, *107*, 1423 ; b) Wasserman, H.H. ; Gambale, R.J.; Pulwer, M.J. *Tetrahedron* **1981**, Symposium in Print, *37*, 4059; c) Wasserman, H.H.; Gambale, R.J.; Pulwer, M.J. *Tetrahedron Lett.* **1981**, *22*, 1737; d) Wasserman, H.H.; Lu, T.-J. *Tetrahedron Lett.* **1982**, *23*, 3831.