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MICRO-ORGANIZATIONAL CONTROL of PHOTOCHEMICAL OXIDATIONS: ROSE BENGAL AND DERIVATIVES (XV)

by

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ABSTRACT: We define a microheterogeneous photo-oxidation to be a photosensitized oxidation reaction whose efficiency is enhanced beyond that of diffusion control by the covalent bonding of a sensitizer to a ligand. The ligand is responsible for enhancing the local concentration of a specific substrate susceptible to reaction with an excited state derived from the proximate sensitizer. We illustrate the principle with several applications in singlet oxygen processes.

INTRODUCTION:

Singlet oxygen is a short-lived intermediate whose lifetime in solution is highly dependent on solvent. In biological systems, where water is the predominant medium, singlet oxygen (τ = 2 μsec) will travel less than 50 Å before deactivation. Under circumstances such as the cell which is compartmentalized, heterogeneous collisional deactivation becomes crucial and the lifetime of singlet oxygen in the fluid solution is only one parameter which influences reaction rate.[1] Collisional deactivation of singlet oxygen may either be deleterious to the cell or it may prevent a desired photo-oxidation process from occurring in a biological system.[2,3]

In dye-sensitized photo-oxidation, Type I processes also may complicate matters.[4,5] In the Type I process, the photosensitizer reacts directly with the substrate either by atom transfer or electron transfer and this is followed by reaction with ground state triplet oxygen in a free radical chain process. Though the products of the Type I process are often similar to those of sensitized oxidation, the mechanism is quite different from the dye sensitized process. Inhibition of the Type I process requires radical inhibitors not quenchers as does the dye-sensitized reaction.

It is our intention to demonstrate that one can increase the concentration of singlet oxygen in the presence of a singlet oxygen acceptor by synthesizing photosensitizers which have a specific recognition for the expected singlet oxygen acceptor. We call this the principle of micro-organization in dye sensitized photo-oxidation.[6] In this paper we use this concept to demonstrate that one can increase the reactivity of specific acceptors of singlet oxygen over the reactivity predicted from thermal diffusion parameters by organizing the system in such a way that the acceptor is in nearby proximity to the source of the singlet oxygen. The implications of this in directing singlet oxygen to specific targets are obvious.[7,8]

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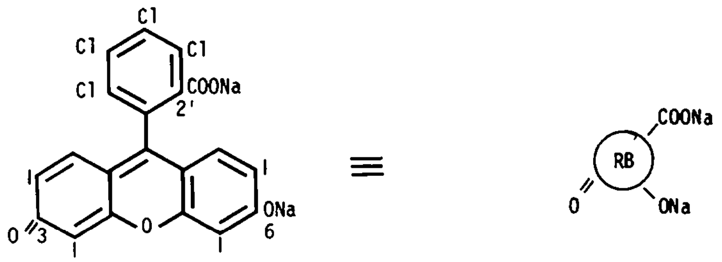
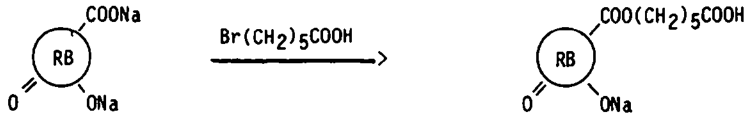
Our experimental design was to synthesize photosensitizers to which ligands were attached which were known to complex specific acceptors of singlet oxygen. The work is made possible by the experiments of Lamberts and Neckers[9,10] who showed that rose bengal could be selectively functionalized at the C-2' position (1-2). In practice the ability to direct an acceptor of singlet oxygen to the source of the intermediate reduces to a problem of functionalizing rose bengal at C-2' with a ligand which is also capable of complexing an acceptor for singlet oxygen.



Rose Bengal
di sodium
salt

Rose Bengal
di sodium
salt

(1)

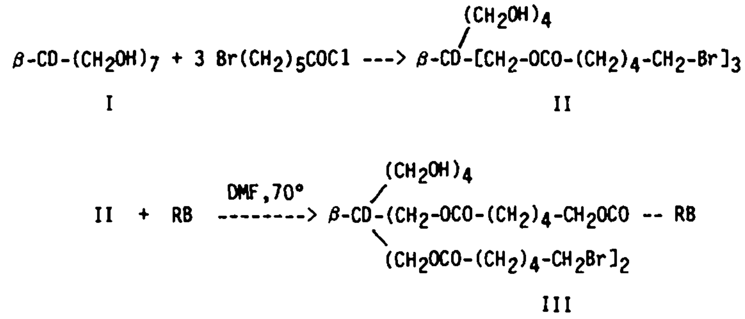


(2)

β-Cyclodextrin is a naturally occurring, water soluble heptamer (cycloheptaamylose) of α-glucose.[11] The molecule is of a relatively inflexible donut-like structure with a central cavity which is predominantly hydrophobic and approximately 7Å in diameter. The external surface is poly-hydroxylated and characterized by seven primary hydroxyl functions (-CH$_2$OH), on the top of the cavity as well as fourteen secondary hydroxyls (-CHOH)[12-14], located on the bottom surface of the cyclo(amylose). Many catalysts have been constructed by attachment of appropriate functional groups to cyclodextrins[15]. In the most prevalent of these approaches, the hydroxyls are modified by activated ester functions such as an anhydrides and acid chlorides. The alteration in the properties of the cyclodextrin which result provide a floor for the cavity, or a plug, and and the proximity of the cap to the reagent complexed by the hydrophobic surface of the cyclo(amylose) causes important changes in properties[16]. In the only cases in which a photochemical process has been examined, this enforced proximity has been tested by capping a cyclodextrin with either an azobenzene[17], or with a benzophenone[18]. In the former case the photoisomerization (*trans* to *cis*) was shown to alter the size of the hydrophobic cavity, thus effecting its capability to complex smaller molecules. In the latter case, it is shown that the phosphoresence of benzophenone is quenched by low concentrations of naphthalene in aqueous DMF. This results due to the enforced proximity of the naphthalene to the benzophenone-like triplet. No similar results are observed with model compounds.

In our experiments we chose to modify the 1° hydroxyl surface of β-cyclodextrin with a rose bengal function. Our interest in the initial experiments was not to cap the cyclodextrin, nor to totally functionalize all of the seven 1° hydroxyls. The goal was to simply enforce the proximity of some small numbers of molecules of the sensitizer to the bound acceptor without greatly altering, and thus losing, the properties of either. Rose bengal is ideally suited for this test, because even after modifying the C-2' function, the C-6 function remains in ionic form. Thus the sensitizer can be modified at C-6 to either render it water/polar solvent compatible, or soluble in non-polar solvents depending on the desired condition. The modification chemistry in outlined in Scheme I.

SCHEME I



$$\underset{\text{I}}{\beta\text{-CD-}(CH_2OH)_7} + 3\ Br(CH_2)_5COCl \text{ ---> } \underset{\text{II}}{\beta\text{-}\overset{(CH_2OH)_4}{CD}\text{-}[CH_2\text{-OCO-}(CH_2)_4\text{-}CH_2\text{-}Br]_3}$$

$$\text{II} + \text{RB} \xrightarrow{\text{DMF},70^\circ} \underset{\text{III}}{\beta\text{-}\underset{(CH_2OCO\text{-}(CH_2)_4\text{-}CH_2Br]_2}{\overset{(CH_2OH)_4}{CD}}\text{-}(CH_2\text{-OCO-}(CH_2)_4\text{-}CH_2OCO\text{ -- RB}}$$

RB = Rose Bengal
β-CD = β-Cyclodextrin

In the esterification reaction, three molar equivalents of 6-bromohexanoyl chloride were added under reaction conditions in which the 1° hydroxy groups of the cyclodextrin react preferentially. This effectively forms a hydrophobic crown on the top of the cavity of the cyclodextrin to which the rose bengal is eventually to be attached. Scheme IIa. The dye is attached by nucleophilic displacement of bromide and fixes a larger, more polar molecule to the top of the cyclo(amylose). The cap may other reside more predominantly in solution, (polar solvent; Scheme IIb) or close to the hydrophobic cavity, (non-polar solvent; Scheme IIc).

β-Carotene

The photochemical properties of the system were tested both with a physical quencher of singlet oxygen (β-carotene) and with a chemical quencher of singlet oxygen (anthracene). The photo-oxidation of a singlet oxygen trap, 1,2-diphenyl-p-dioxene was compared using III with oxidation carried out with a mixture of rose bengal and β-cyclodextrin. The data for β-carotene is shown in Figure 1, Table 1.

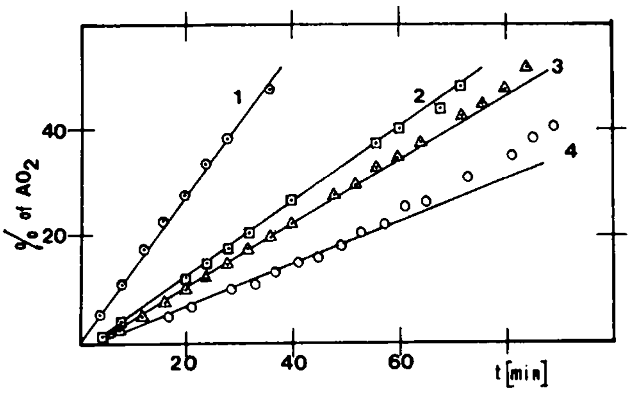


FIGURE I

Photooxidation of 1,2-Diphenyl-p-dioxene (9 x 10^{-6}).

1) Rose Bengal (2.9 x 10^{-4}M)

2) Rose Bengal (2.9 x 10^{-4}M) + CD(2.3 x 10^{-4}M) + β-carotene (9 x 10^{-6}M)

3) III (2.9 x 10^{-4}M) + β-carotene (9 x 10^{-6}M)

4) III (2.9 x 10^{-4}M) + β-carotene (9 x 10^{-6}M) - 1,2-Diphenyl-p-dioxene added just before measurement.

Solvent: EtOH: RB = Rose Bengal; CD = β-cyclodextrin; DABCO = diazobicyclooctane.

TABLE 1

Observed Efficiency of Photo-oxidation Product Formation for III and RB In the Presence of β-Carotene (0.9 x 10^{-5} M)

System	RB	III	RB + β-Carotene	RB + β-CD + β-Carotene	III + β-Carotene
Efficiency 1,2-diphenyl-p-dioxene oxidation	0.76	0.81	0.39	0.36	0.29 0.20*

* 1,2-Diphenyl-p-dioxene was added to the solution immediately before measurement.

β-Carotene has a very high rate of singlet oxygen quenching in solution (3.0 x $10^{10}M^{-1}sec^{-1}$) in benzene[19,20]. However, with sensitizer III, the efficiency of singlet oxygen quenching by β-carotene is greater than in the case of a mixture of rose bengal and β-cyclodextrin under identical conditions in the same solvent. Since the singlet oxygen in the case of III is formed in much closer proximity to the quencher than it would be in fluid solution, an enhanced microlocal concentration of β-carotene increases the probability of collision between singlet oxygen and β-carotene, Scheme IIb. Under similar conditions of concentration, singlet oxygen is quenched approximately from 1.2 to 1.8 times more rapidly by β-carotene complexed to III, than it is when the quencher is complexed to an unbound cyclodextrin residing in solution.

The quantity of β-carotene held in the cyclodextrin hydrophobic cavity is controlled by the equilibrium constant between cyclodextrin and the β-carotene which is included. Under conditions of higher concentration, the quenching ability of the system due to the proximity of the quencher should be greater. A typical Stern-Volmer relationship confirms that this is the case for the micro-organized system III. When compared with a homogeneous solution containing β-carotene and RB, Figure II, the micro organized system shows a $k_q\tau$ 2.70 larger than the rose bengal free in solution.

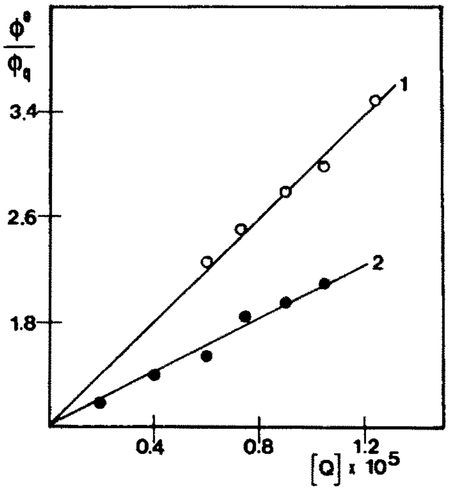


FIGURE II

Stern-Volmer Plot; Photooxidation of 1,2-Diphenyl-p-dioxene (4.0×10^{-4}M); Quencher; β-carotene; Solvent - EtOH

1) III

2) RB + CD

1,2-Diphenyl-p-dioxene is also included in the hydrophobic cavity of III. In experiment (4), Figure I, 1,2-diphenyl-p-dioxene was added just before the measurement of the oxidation rate. The rate of quenching by β-carotene is much larger than it was in the case when both the physical quencher and 1,2-diphenyl-p-dioxene were allowed to compete for the carbohydrate's hydrophobic cavity. When there is no competition, as in (4), Figure I, the maximum concentration of β-carotene is captured by the hydrophobic cavity in the pre-equilibration step. The quenching ability by β-carotene also decreases as the reaction continues. This is not observed in the cases such as with rose bengal and β-carotene free in solution or with rose bengal, β-carotene + CD in solution. Either the product of photo-oxidation, ethylene glycol dibenzoate, also competes for the β-cyclodextrin cavity or the β-carotene is chemically oxidized during the reaction. The latter oxidation of the physical quencher would decrease the concentration of the quencher in solution and in the cavity. This, in turn, would decrease the effectiveness of the physical quencher.

Anthracene:

The formation of an inclusion complex of anthracene with β-cyclodextrin can be demonstrated using fluoresence spectroscopy.[21] Thus the fluorescence spectrum of anthracene was studied in various solvents as well as in water in the presence of either III or of β-cyclodextrin. The fluorescence maxima of anthracene were essentially the same in CH_2Cl_2 as they were in the presence of III and in the presence of β-cyclodextrin in water. Thus the microenvironment in which anthracene finds itself in water, but in the presence of both III and β-cyclodextrin is the same as it is in the non-polar solvent, methylene chloride. This can only be the case if the anthracene is complexed by the hydrophobic cavity of the β-cyclodextrin, Table 2.

Anthracene is essentially insoluble in water, save in the presence of the cyclodextrin. Thus the anthracene/ β-cyclodextrin system presents a most favorable case to enforce microlocal proximity of anthracene to a Rose Bengal source of singlet oxygen.

TABLE 2

Positions of Anthracene Fluorescence Maxima (λ_{ex} = 330 nm) in Presence of Cyclodextrin Derivatives

Anthracene Fluorescence Maxima (nm)	RB + CD$^{1)}$	III$^{1)}$	III$^{2)}$	III$^{3)}$
1	380	380	376-377	380
2	402	402	398	402
3	425	425	421	425

1) Water 2) MeOH 3) CH_2Cl_2

In water the difference between the rate of oxidation of anthracene by III and by rose bengal in the presence of CD is almost zero, Figure III. However, under conditions where the lifetime of singlet oxygen is reduced, as is the case in the presence of the water soluble quencher DABCO (1,4-diazobicyclo[2.2.2]octane), the difference in oxidation rate between III and the case of β-cyclodextrin/RB pair becomes significant. This is shown in Figure III. The oxidation of anthracene was also studied at different concentrations of anthracene.

In the oxidation of anthracene in water in the presence of III a typical Stern Volmer relationship was observed, but DABCO is approximately 10X less effective as a quencher of singlet oxygen in the case of III/anthracene, Figure IV.

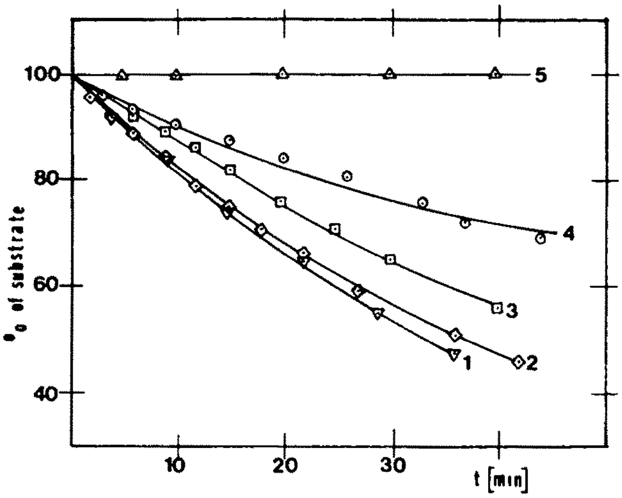


FIGURE III

Photo-Oxidation of Anthracene (3.82 x 10^{-6} M in water)

1) III (2.80 x 10^{-4}M)

2) RB (4.36 x 10^{-5}M) + CD (6.0 x 10^{-4}M)

3) III (2.80 x 10^{-4}M) + DABCO (2.5 x 10^{-2}M)

4) RB (4.36 x 10^{-5}M) + CD (6.0 x 10^{-4}) + DABCO (2.5 x 10^{-2}M)

5) III (2.80 x 10^{-4}M) - Solution saturated with argon.

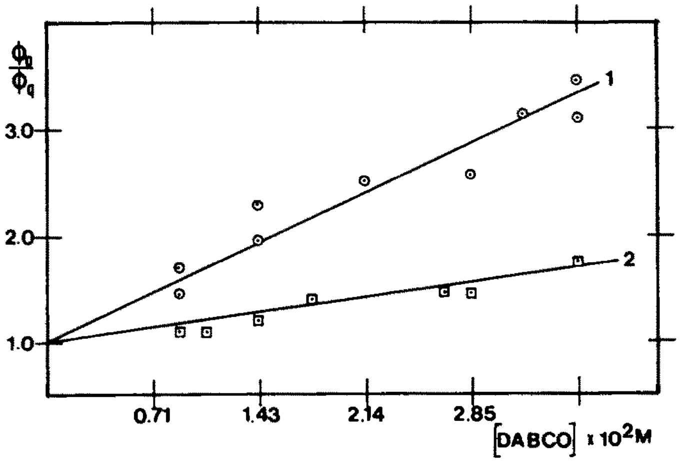


FIGURE IV

Stern-Volmer Plot Photooxidation of Anthracene (3.82 x 10^{-6}M in water); Quencher DABCO.

1) RB (4.36 x 10^{-5}M) + CD (6.0 x 10^{-4}M)

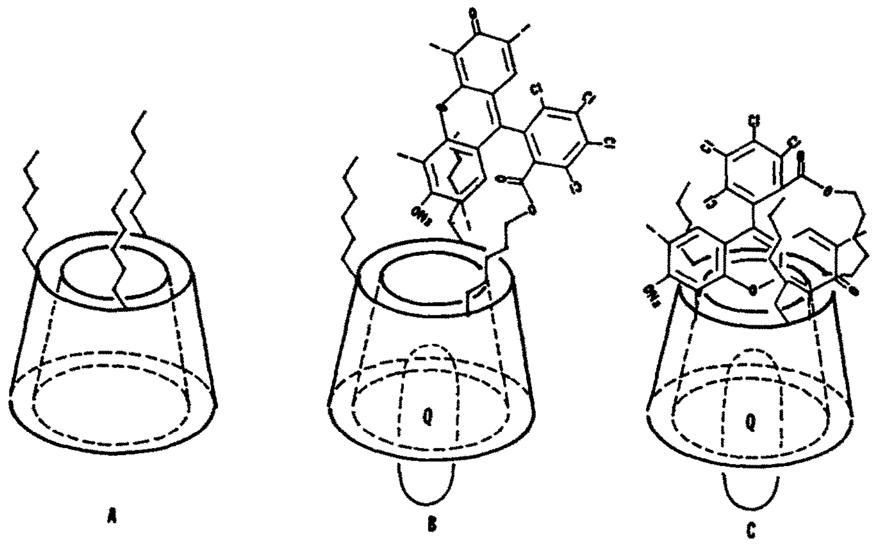
2) III (2.80 x 10^{-4}M)

The electronic absorption maximum for III occurs at 562.0 nm suggesting that the dye resides in a non-polar environment in III, Table 3. This is likely enforced because microenvironment of the dye is altered by the cyclo(amylose). Addition of β-cyclodextrin does not change either the slope or the position of the rose bengal absorption spectra, though esterification at C-2' shifts the maximum toward the red from that of the parent dye by about 4 nm.[10,23] (552 nm for RB-COOMe and 551.5 for RB-COO$(CH_2)_5$COO$^-$). Thus no inclusion complex forms between Rose Bengal and cyclodextrin. For essentially an ester with a longer side chain attached at C-2', (RB-COO$(CH_2)_{10}$COO$^-$) an additional red shift is observed [about 5 nm; 557nm]. This suggests that the long chain in RB-COO$(CH_2)_{10}$COO$^-$ resides in such a way that the rose bengal chromophore lies over or is surrounded by a non-polar area in the side chain; Scheme III. For RB-COO$(CH_2)_5$COO$^-$, we surmize the $(CH_2)_5$ chain is too short and not able to present the dye with essentially a non-polar environment. β-Cyclodextrin esterified with 6-bromohexanoyl chloride is not entirely converted to the rose bengal derivative when II reacts with RB to form III. The additional methylenes, $(CH_2)_5$COO$^-$ used to tether rose bengal to β-cyclodextrin must be responsible for the dye residing in the non-polar environment of the sugar. The dye is even closer to the hydrophobic crown in water than it is in ethanol (λ=558 nm; ε_{max} = 87,500). The various options for the tethered dye are shown in Scheme IIb and IIc. β-CD-RB in water (above) forms a very tight complex in which the dye is located in the hydrophobic cavity of the cyclodextrin. It is almost in the same region in space as is the singlet oxygen chemical trap if that trap is anthracene. Thus as the singlet oxygen is formed, it is rapidly trapped by the proximate anthracene in aqueous solution.

TABLE 3

Absorption Spectra of Rose Bengal Derivatives in Water

Compound	$A_{\lambda_{max}}$nm	$\varepsilon_{\lambda_{max}}$	$F_{\lambda_{max}}$nm
Rose Bengal	548.0	1.136×10^5	566.0
Rose Bengal, C-2' Methyl Ester	552.0	2.85×10^4	572.0
Rose Bengal + β-CD	548.0	1.136×10^5	--
Rose Bengal, C-2' Hexanoate Ester	551.5	8.21×10^4	--
Rose Bengal, C-2' Undecanoate Ester	557.0	7.92×10^4	--
III	562.0	3.02×10^4	576-77



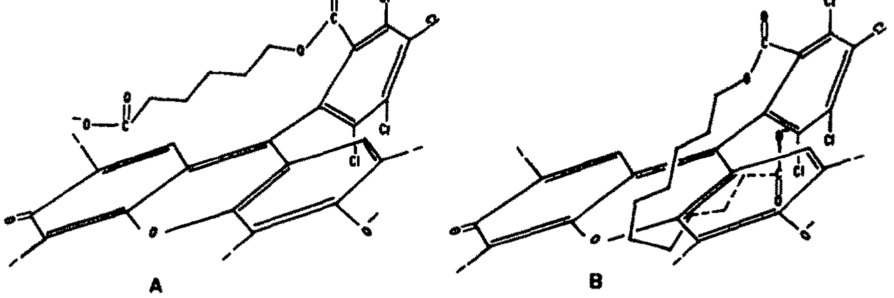
SCHEME II

Functionalized Cyclodextrins

A) II

B) III - RB side chain residing in the bulk solvent

C) III - RB side chain residing over the cyclodextrin cavity; Q = quencher



SCHEME III

Rose Bengal Derivatives

A) C-2' Hexanoate Ester

B) C-2' Undecanoate Ester

It is important to point out that all our observations have been made in dilute solutions (anthracene concentration 3.82 x 10^{-6} M). For dilute solutions, with no organization, as is the case of RB + β-cyclodextrin, singlet oxygen may be or may not be formed in the collisional sphere of the included quencher. If singlet oxygen is not formed in the quenching sphere, the singlet oxygen, to be quenched, must diffuse to the area of the quencher free in solution. This requires a finite time, and singlet oxygen must traverse a finite distance during this time. During this period it may be quenched either by solvent molecules, or by quenchers present in the solution in uncomplexed form. (This is important in the case of anthracene where the rate of reaction with the trap, anthracene, is slower than is the rate of quenching of singlet oxygen by water).[22,24] When the system is micro-organized, singlet oxygen is formed directly in the quenching sphere of the included anthracene, (see Scheme IIc.) In this quenching sphere, the concentration of the quencher is artifically high. The quenching rate of singlet oxygen with quenchers freely dispersed in solution is simply controlled by the rate of diffusion. Microorganization, however, partially negates the rules of diffusion, and artifically enhances the quenching rate.

CONCLUSION:

Rose bengal derivatives of β-cyclodextrin artifically enhance the concentration of both chemical traps and physical quenchers of singlet oxygen by including the non-polar traps in the hydrophobic central sphere of the β-cyclodextrin and in direct proximity to the source. These microorganized systems are characterized by rates of quenching which are greater than that expected for singlet oxygen thermally diffusing to the quenching sphere of the quencher. Microorganizational effects are illustrated with the specific physical quencher β-carotene and the chemical quencher, anthracene.

EXPERIMENTAL SECTION

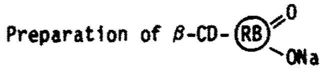
Rose bengal (DyeTel), dye content 92%, was used in all synthetic processes without further purification. Rose Bengal was purified according to the methods of Lamberts and Neckers[9] for photochemical studies. β-Cyclodextrin was purchased from Sigma. 6-Bromohexanoyl chloride, 6-bromohexanoic acid, 11-bromoundecanoic acid, and spectroscopic grade ethanol were purchased from Aldrich. These were used without further purification. All new products were analyzed correctly for iodine content.

Absorption spectra were measured using a Varian-Cary 219. Emission spectra were measured using a Perkin-Elmer MPF-44A fluorescence spectrophotometer.

The proton n.m.r. spectra were recorded on Varian XL-200.

SYNTHETIC PROCEDURES

Preparation of



$\beta\text{-CD-(RB)}\genfrac{}{}{0pt}{}{\text{=O}}{\text{ONa}}$ (III)

β-Cyclodextrin, 5.65g (5 mmole) was dissolved in 75 ml of dry pyridine. To this cold (ice-water bath) β-cyclodextrin solution, 3.2g (15 mmole) of 6-bromo-hexanoyl chloride was added. After one hour the temperature of the reaction mixture was increased to 30-35°C. The reagents were stirred and after four hours II was precipitated with acetone. The product II, was dried in a vacuum oven to final weight of 4.25 g.

II (3.95g; 2 mmole) was dissolved in 50 ml of DMF and rose bengal (2.16 g, 2 mmole) was added. The mixture was stirred at 70°C. After 20 hours the product was precipitated in acetone and twice reprecipitated from DMF-H_2O (3:1) with acetone. The product was dried in a vacuum oven. 2.1 g of the red product III was obtained (IR: (KBr): 1733 cm^{-1}, C=O stretching frequency for esters, λ_{max} in ethanol = 558.5 nm, ε_{max} = 87,500.

Rose Bengal 5-Carboxypentyl Ester, Molecular Form

Rose bengal (1.07 g; 1 mmole) was dissolved in water (10 ml) and a solution of 6-bromohexanoic acid (0.60 g, 3 mmole) in 10 ml of acetone was added. The resulting mixture was refluxed overnight and after cooling to room temperature, the precipitates that had been formed filtered and throughly washed with ether to remove the excess acid. The product was dried overnight in a vacuum. IR (KBr): 1733cm^{-1} (ester C=O), 1700cm^{-1} (acid C=O); H'NMR (DMSO): δ = 1.00-1.25 (6H), 2.07 (-CH_2COOH, 2H), δ = 3.90 (CH_2-OCO-,2H), δ = 7.55(2H, xanthene), δ = 11.12 (1H,-COOH).

Rose Bengal 10-Carboxydecyl Ester, Molecular Form

The same procedure was used as for rose bengal 5-carboxypentyl ester, molecular form, except 0.90g (3 mmole) of 11-bromoundecanoic acid was used. IR (KBr: 1734 cm^{-1} (ester C=O), 1700 cm^{-1} (acid C=O); H^1 NMR (DMSO): δ = 1.06-1.49 (16H) δ = 2.15 (CH_2COOH, 2H), δ = 3.91 (-CH_2OCO-,2H), δ = 7.54 (xanthene, 2H), δ = 11.13 (COOH, 1H).

MEASUREMENT OF EFFICIENCY FOR SINGLET OXYGEN FORMULATION

A solution of β-carotene (3.0×10^{-6} M), 25.4 mg of III, and 23.8 mg of 1,2-diphenyl-p-dioxene (4.0×10^{-3} M) in 25 ml of ethanol was allowed to equilibrate for 48 hours, and the rate of oxidation of 1,2-diphenyl-p-dioxene measured. The solution (2.8 ml) was irradiated in rectangular cell with high intensity mercury source through a monochrometer at 560nm. The solution was stirred, and a continuous flow of oxygen was passed through the solution. The formation of the photo-oxidation product (ethylene glycol dibenzoate) was followed by GLC at 200°C.

The results were compared with three control systems in which (1) rose bengal disodium salt (2.9×10^{-4} M), and 1,2-diphenyl-p-dioxene (4.0×10^{-3} M); (2) rose bengal disodium salt (2.9×10^{-4} M), 1,2-diphenyl-p-dioxene (4.0×10^{-3} M), and β-carotene (9.0×10^{-6} M); and (3) rose bengal disodium salt (2.9×10^{-4} M), 1,2-diphenyl-p-dioxene (4.0×10^{-3} M), CD (2.9×10^{-4} M), and β-carotene (9.0×10^{-6} M).

Similar procedures were used for measurement with various β-carotene concentrations, e.g: 0.2×10^{-6} M, 0.4×10^{-6} M, 0.60×10^{-6} M, 0.75×10^{-6} M, 1.05×10^{-6} M, and 1.20×10^{-6} M.

PHOTOOXIDATION OF ANTHRACENE

A 3.92×10^{-6} M solution of anthracene was prepared by injecting 1 ml of 1.96×10^{-4} M anthracene solution in methanol into 43 ml (water) solutions of: (1) III 50.8 mg; (2) RB (4.36×10^{-6} M) + CD (6.0×10^{-4} M). These solutions were allowed to equilibrate for 24 hours. To the 2.8 ml of solution (1) containing anthracene or (2) in fluorometric cell a corresponding amount of 1.0 M DABCO in water was added using a chromatographic syringe. The solution was irradiated with high intensity monochromator at 560 nm, and a continuous flow of oxygen was passed through the solution. All solutions were initially saturated with oxygen. The photo-oxidation of anthracene was monitored by decay of the fluorescence emission band of anthracene at 402 nm ($\lambda_{ex} = 375$ nm), using the MPF-44A fluorimeter.

The results for all solutions were compared with solution 2 without DABCO, The quantum yield assumed was $\phi^1O_2 = 0.75$ for rose bengal in water.

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