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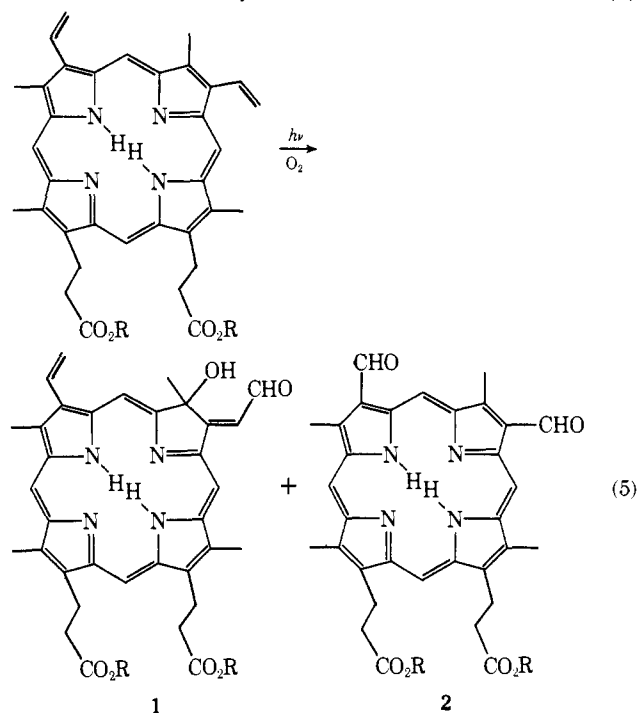
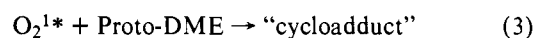
Environmental Effects on Photochemical Reactions: Contrasts in the Photooxidation Behavior of Protoporphyrin IX in Solution, Monolayer Films, Organized Monolayer Assemblies, and Micelles¹

Sir:

There has been considerable recent interest in reactions and photoprocesses occurring in organized media such as micelles, films, and monolayer assemblies and particularly in the effects produced by the relatively organized semirigid environment provided by these media.²⁻⁵ Much of the interest in effect produced by organized media is related to possible analogies between these processes and phenomena occurring in biological systems, particularly in membranes and related structures. A problem of particular interest to photochemists and photobiologists is that of photodynamic deactivation.⁶⁻⁸ Though in many cases it appears probable that this process involves production and subsequent reaction of singlet oxygen, the overall reactions are frequently quite different from those observed with similar substrates in solution.⁶⁻⁸ A substance frequently linked to destructive photobiological processes is protoporphyrin IX; while the iron complex is relatively inert under irradiation in vivo, the presence of excess free base protoporphyrin IX in red blood cells can lead to photohemolysis, presumably by generation and subsequent reactions of singlet oxygen.⁹⁻¹² It has been found that protoporphyrin IX in solution is itself reactive toward photooxidation in a process involving intermediacy of singlet oxygen.^{13,14} Since the mechanism of this process involves several steps that might be influenced by environment, we felt the reaction should be an especially attractive candidate for study in different organized media. In the present paper, we report preliminary results of a study of protoporphyrin IX photooxidation in solution, micelles, and monolayers. These results indicate that environment can produce striking effects in both the rates and products formed in the reaction as well as in quenching processes.

The surfactant protoporphyrin IX derivative selected for

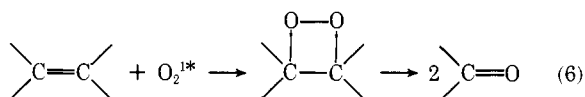
investigation in micelles and monolayers was the bis(dihydrocholesterol) ester (Proto-DHC). The photoreactivities of Proto-DHC and the previously investigated dimethyl ester (Proto-DME)¹⁴ were found to be essentially identical on irradiation in aerated methylene chloride solution. Formation of a green photoproduct having λ_{\max} 670 nm occurred for both derivatives; the products could be separated analytically by TLC or preparatively by medium-pressure liquid chromatography (MPLC). In addition to the green photoproduct **1**, some starting material and two minor products having red-shifted but characteristic "porphyrin-type" spectra were also obtained in each case. Although formation of these products (**2** and **3**) has not previously been noted, details of the formation and structure determination for **1** have been reported by Inhoffen;¹⁴ in line with other photooxidations, the most likely mechanism involves the steps outlined in eq 1-4.¹⁵ The key step in forming hydroxyaldehyde **1** is the cycloaddition of singlet oxygen to a diene unit in the porphyrin consisting of one endocyclic double bond and the vinyl group.



Proto-DHC readily forms stable monolayer films in mixtures (1:5) with arachidic acid; these films can be incorporated into monolayer assemblies containing several monolayers by the usual techniques.²⁰ Both Proto-DHC and Proto-DME can be incorporated into micelles formed from cetyltrimethylammonium bromide (CTAB).²¹ The porphyrins exist as dimers in both monolayer assemblies and CTAB micelles as evidenced by characteristic absorption spectra and the measured pressure-area relationships in monolayer films. Although micelles richer in Proto-DHC could be obtained, for the solutions used in this work the average number of porphyrin molecules/micelle for both esters was 2. Irradiation of both porphyrins in the micelles and Proto-DHC in monolayer assemblies open to air led to a decrease in the porphyrin absorptions and a concurrent increase at wavelengths where **1** absorbs. However, relative rates were quite different for the

various media; compared to Proto-DME in toluene ($\phi = 0.006$), relative rate = 1, initial rates for dry monolayer assemblies, Proto-DHC-CTAB micellar solutions, and Proto-DME-CTAB micellar solutions are 0.35, 0.004, and 0.061, respectively. Photooxidation of Proto-DHC also occurs readily in spread films of the pure porphyrin or porphyrin-arachidate mixtures. The reaction in the assemblies occurs about as rapidly when the assemblies are dry or in contact with water, and the rate of reaction is not measurably retarded when layers of Proto-DHC are covered by several outer layers of cadmium arachidate. However, exclusion of oxygen from the assemblies by evacuation results in loss of photoreactivity.

Separation of irradiated porphyrins by TLC and MPLC indicated that **1** and **2** are the major products obtained but that the **2:1** ratio is much higher in films, micelles, and assemblies. The similarity of the spectra of **2** and **3** to those reported for diformyldeuteroporphyrin IX and 2(4)-monoformyl-4(2)-monovinyldeuteroporphyrin IX²² together with known examples of singlet oxygen addition to olefins to form labile 1,2-dioxetanes (eq 6) suggested that **2** and **3** might be



formylporphyrins formed via 1,2 addition of oxygen to the protoporphyrin vinyl groups. Preparation of the diformyldeuteroporphyrin could be accomplished by OsO₄²³ or permanganate²⁴ oxidations of Proto-DHC; the identity of **2** as the diformyl derivative shown in eq 5 was established by comparison of spectra and chromatographic *R_f* values. In solution, **1** is by far the most prominent product on the basis of absorption spectra; relative absorbances at 670 (**1**) and 648 nm (**2**) obtained on photooxidation of Proto-DHC in CH₂Cl₂ are 1 and 0.015, respectively. However, the differences in ϵ values indicate the actual **2:1** ratio obtained in solution is 0.24. Thus, although not previously detected, **2** is an appreciable but minor product in solution; in sharp contrast **2** becomes the major product in monolayer films, micelles, and assemblies. Spread films of 1:5 Proto-DHC-arachidate mixtures on water give a **2:1** ratio of 2.24 while dry assemblies of the same composition give a value of 13.6 or 93% **2**. The **2:1** ratios in micelles have been less precisely established; however, the values measured to date are intermediate between those obtained in spread films and assemblies.

The rather striking effects obtained on rates and product distribution can be at least partially understood in terms of environmental factors. The relatively high net reactivities in monolayer films and assemblies are in agreement with expectation that oxygen can move readily through the assemblies and that moderately high concentrations should exist. The much lower reactivity in micelles is somewhat surprising; however, results of Thomas²⁵ suggest low equilibrium concentrations of O₂ in CTAB micelles even though rapid in-out diffusion evidently occurs. Given the small size of the CTAB micelles,²¹ it appears possible that singlet oxygen is readily generated by micelle bound porphyrin but escapes from the micelle before subsequent reaction can occur. Other mechanisms, including quenching by the CTAB bromide ion, could also be responsible for the observed results; the 15-fold difference in rates favoring the hydrophobic (Proto-DME) over the surfactant (Proto-DHC) would be in accord with a lower net reactivity when the chromophore is near the ionic region of the micelle. The preferential formation of **2**, the product of 1,2 addition, over the preferred 1,4 addition produce **1** in micelles, films and assemblies is probably best explained in terms of a greater difficulty in achieving the necessary geometry for the 1,4 addition in the organized media, probably due to part to the tight packing into dimeric units and in part to the high

effective viscosity.²⁶ The importance of the latter is exemplified by the large increase in the **2:1** ratio on going from spread films to the more rigid dry assemblies with the same porphyrin concentration.

If the reaction proceeds via singlet oxygen generation as outlined in eq 1-4,^{15,26} the photooxidation should be quenchable by several species including quenchers of the porphyrin triplet, singlet oxygen, and singlet oxygen scavengers. Several differences have been observed between the effectiveness of various quenchers in the organized media compared to solution; these will be reported in detail in a full paper. However, it is worth noting that cholesterol, a probable singlet oxygen substrate in erythropoietic protoporphyria,^{12,27} is a relatively effective quencher of the photooxidation in micelles, spread films and monolayer assemblies. In the latter, it is found that assemblies containing cholesterol and Proto-DHC in the same layer (2:1:3 mixture with arachidate as the third component) or adjacent layers with hydrophilic-hydrophilic contact show reduced rates (factors of ca. 50 and 35%, respectively) while separation of the porphyrin from the cholesterol by one or more layers of arachidate (~26 Å)²⁸ results in no detectable quenching; in addition, we find the spacing of porphyrin layers also produces no effect on the rate of reaction in the absence of quenchers. The two results suggest that diffusion of oxygen within the assemblies is slow and that the effective range of singlet oxygen within assemblies may be quite small.²⁹

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oxide¹⁷⁻¹⁹). A consideration of redox potentials indicates electron transfer from triplet protoporphyrins to oxygen should be slightly exothermic. However, the observation that porphyrins behave as "normal" sensitizers in other oxidations¹⁸ may suggest that singlet oxygen is the predominant intermediate.

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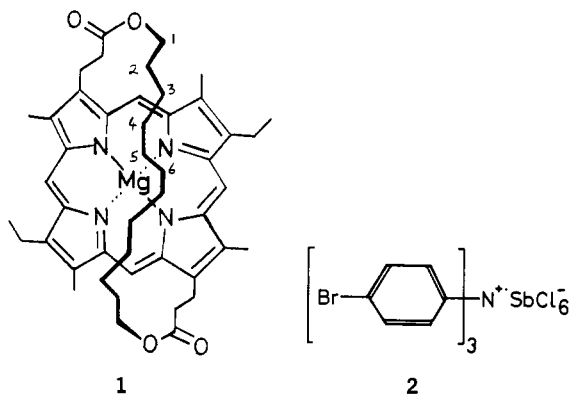
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Radical-Induced Pseudocontact Shifts

Sir:

Paramagnetic species can induce two kinds of NMR chemical shift.¹ Contact shifts arise directly from delocalization of unpaired spin density and are useful probes of covalent bonding. Pseudocontact shifts are geometrically determined by dipolar field effects and are therefore probes of stereochemistry. Contact shifts caused by metal ions² and by organic free radicals³ are well known, as are metal-induced pseudocontact shifts,⁴ but radicals are generally thought not to cause significant pseudocontact effects.⁵ We now report results which appear to disprove this last belief.

The bridged metalloporphyrin **1** (prepared from the free base⁶ with $\text{Mg}(\text{ClO}_4)_2$ in pyridine) can be oxidized to its radical cation $\mathbf{1}^+$ by the crystalline aminium salt **2**.⁷ Slight ox-



idation ($\ll 1\%$) leads to NMR exchange broadening of the peripheral, hyperfine-coupled protons in the usual way.^{8,9} The relative broadenings of these signals agree with those observed for normal disaggregated metalloporphyrin radical cations.^{8b} Further oxidation causes downfield shifts of the resonances of the alkyl methylene bridge protons (Figure 1). The ring current shifted resonance at $\delta -0.72$ is paramagnetically shifted downfield by an amount corresponding to at least 20 ppm in pure $\mathbf{1}^+$. Other alkyl bridge resonances are similarly shifted downfield by an amount proportional to the original upfield aromatic shift (see Table I).

We conclude that in the radical cation $\mathbf{1}^+$, the protons of the alkyl bridge experience a magnetic field which has effectively the same geometrical properties as the aromatic ring current¹⁰ but which is 10 times larger and has the opposite sense.^{11,12} The magnesium ion carries no unpaired spin, and therefore we suggest that this is due to g -tensor anisotropy of the unpaired electron, i.e., a pseudocontact shift. The expected temperature dependence of this shift cannot be readily mea-

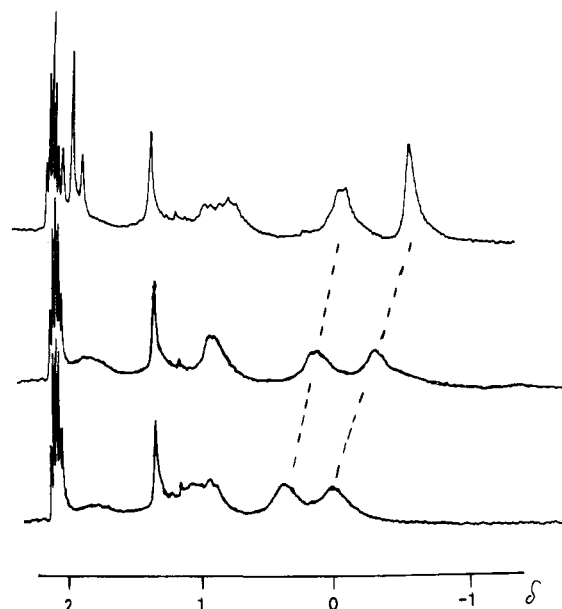


Figure 1. 100-MHz ^1H NMR spectra of **1** in acetone- d_6 . Top: in absence of $\mathbf{1}^+$. Below: after partial oxidation (middle, $\sim 1.5\%$; bottom, $\sim 3.0\%$) to $\mathbf{1}^+$. The triplet at $\delta 2$ is due to the ethyl group of the porphyrin; other protons of the periphery are more severely broadened on oxidation and are not shown. Impurity at $\delta 1.3$.

Table I. Shifts of Bridge Protons in **1** and $\mathbf{1}^+$.

Proton	δ (1) ^a	δ ($\mathbf{1}^+$) ^b	Relative aromatic shift ^c	Relative paramagnetic shift ^c
H-1	3.75, 3.69	8.3	0.19	0.23
H-2	0.72	9.1	0.38	0.42
H-3,4	-0.16	16.2	0.76	0.82
H-5	-0.65	~ 19	0.98	1.0
H-6	-0.72	~ 19	1.0	1.0

^a 0.03 M in acetone- d_6 , 310 K, 270 MHz. Chemical shifts are in δ units (parts per million) from Me_4Si . ^b Calculated by extrapolation from partially oxidized solutions. ^c Relative to H-6.

sured as $\mathbf{1}^+$ gives a diamagnetic dimer at low temperatures.¹³

Although it is believed that radicals cannot induce pseudocontact shifts, we feel that they have simply not been searched for under suitable conditions for these reasons.

(i) In a pure organic radical, the long electron T_1 leads to broad lines even for protons which are not hyperfine coupled. In our system which is undergoing exchange via electron transfer, the line widths can be controlled by varying the mole fraction of paramagnetic molecules.

(ii) Simple nitroxides undoubtedly do have small g -tensor anisotropies.⁵

(iii) Assuming axial symmetry, the pseudocontact shift, ΔH_i , is given by

$$\frac{\Delta H_i}{H} = -\frac{\beta^2 S(S+1)}{9kT} (g_{\parallel}^2 - g_{\perp}^2) \cdot \frac{3 \cos^2 \theta - 1}{r^3}$$

where θ is the angle between the magnetic axis and the vector connecting the unpaired spin and the proton H_i , and r is the length of that vector. For planar, delocalized radicals a proton in the plane of the π system is close to only a very small part of the unpaired spin density and the r^{-3} dependence renders distant centers ineffective. In order to be in the plane and close enough for a pseudocontact effect to be observable, the proton would normally be covalently bound so that hyperfine interaction dominates both shift and broadening.¹⁴ However, a proton held above the plane of the radical as in $\mathbf{1}^+$ is close to all the unpaired spin without the possibility of hyperfine in-