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 (11) The separation was carried out with a Whatman Magnum-9 C-18 reverse phase column eluted with 10% MeCN in 0.1 M KH_2PO_4 at a flow rate of 7 mL/min.
 (12) On silica TLC plates eluted with 40% ethyl acetate in hexane, derivative C had R_f 0.16 and derivative D had R_f 0.43.
 (13) Methoxy- and hydroxyferrocene were synthesized according to A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Tetrahedron Lett.*, **13** (1959).
 (14) Ferrocene- d_{10} was prepared by repetitive treatment of ferrocene with $\text{CF}_3\text{CO}_2\text{D}$. Mass spectral analysis indicated that several such exchanges afforded material of >98% isotopic purity.
 (15) Metabolite A appears to be a sulfate ester of hydroxyferrocene, based on the observation that it is found to contain iron and tritium when rats are given tritiated ferrocene orally, and iron and ^{35}S when rats are given ferrocene orally and $\text{Na}_2^{35}\text{SO}_4$ intraperitoneally.

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Received August 25, 1977

Hemiacetal Buildup during Acetal Hydrolysis

Sir:

During the course of examining solvent effects, solvent isotope effects, and substituent effects on the general and specific acid catalyzed hydrolyses of acetals of benzaldehydes, we noticed a reproducible "induction period" as shown in Figure 1. This was recognized as classic behavior for the kinetic system $A \rightarrow B \rightarrow \text{products}$,¹ wherein it is necessary for B to attain a certain finite concentration prior to observing a first-order appearance of product.² For hydrolyses of acetals of benzaldehydes, where progress of the reaction is followed spectrophotometrically, Scheme I obtains. In principle, of course, the steps are all reversible; however, at the concentrations involved in the spectrophotometric rate studies (10^{-5} M), the v_{-1} and v_{-2} processes are negligible and thus the scheme essentially becomes that for consecutive pseudo-first-order reactions.

In order to determine what seemed to be the unlikely possibility that our observation of an induction period was actually due to the buildup of hemiacetal according to Scheme I, the following experimental procedure was devised, based on the well-known fact that v_1 is acid catalyzed whereas v_2 is both acid and base catalyzed: a known amount of acetal ($20 \mu\text{L}$ of a 10^{-2} M solution in CH_3CN) was introduced into the aqueous acidic solution using a rapid injection syringe;³ after the reaction had proceeded for the desired time (e.g., 10% reaction), the reaction was quenched by rapid injection of base ($150 \mu\text{L}$ of 1 N KOH). Immediately upon injection of base, the absorbance due to benzaldehyde increased because of the rapidity of the v_2 process in aqueous base. A typical experimental result is presented in Figure 2, wherein the absorbance difference labeled A refers to benzaldehyde produced by acid catalyzed hydrolysis via Scheme I by time t_q , absorbance difference B refers to benzaldehyde produced by rapid base catalyzed hydrolysis of the hemiacetal present at time t_q , and the absorbance difference C refers to the benzaldehyde produced in the total hydrolysis of acetal (i.e., A_∞). Thus, $B/(C - A - B) = [\text{hemiacetal}]/[\text{acetal}]$ at the time of quenching t_q . By varying t_q , a plot such as Figure 3 may be constructed and these data may be treated in one of two ways: most directly, the time at which $d[\text{hemiacetal}]/dt = 0$ can be measured (the time corresponding to the maximum in curve B of Figure 3) and at this time, t_{max} , $[\text{hemiacetal}]/[\text{acetal}] = k_1/k_2$. Thus, k_2 may be calculated, since $[\text{hemiacetal}]/[\text{acetal}]$ can be calculated where $t_q = t_{\text{max}}$ (Figures 2 and 3) and k_1 is obtained from the slope of the usual pseudo-first-order semilog rate plot (Figure 1, line A). Alternatively, the data of curve A in Figure 3 can be plotted as in Figure 1 and the difference between the "early" points and the

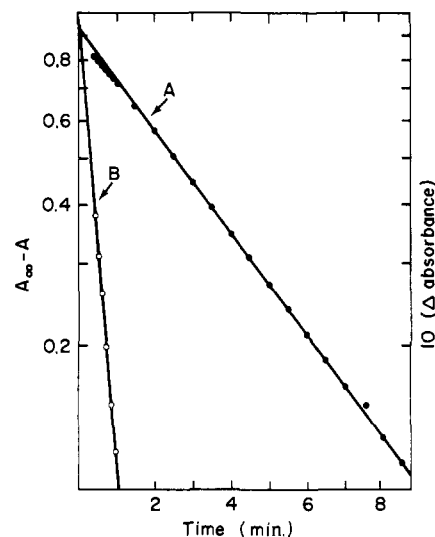


Figure 1. A plot of $\log(A_\infty - A)$ vs. minutes for *p*-methylbenzaldehyde diethyl acetal in acetate buffer ($\mu = 0.5$, KCl) at 25 °C. Line A (●, left ordinate scale) represents experimental data, line B (○, right ordinate scale) represents the difference between line A (based data from the second and third half-lives of reaction time) and the experimental data recorded early in the reaction.

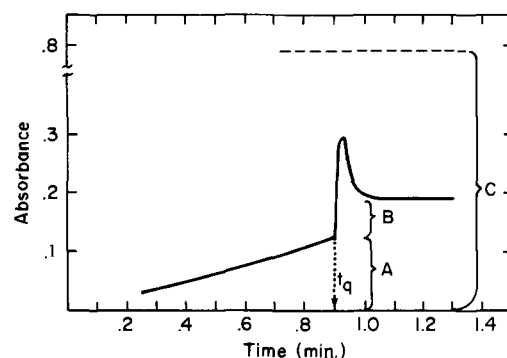


Figure 2. A plot of absorbance vs. minutes for *p*-methylbenzaldehyde diethyl acetal in acetate buffer at 25 °C. The time designated t_q corresponds to the time of injection of $150 \mu\text{L}$ of 1 N KOH. The dashed line represents the absorbance of an acetal solution of equal concentration which was not quenched (i.e., allowed to completely hydrolyze) and thus is the absorbance at $t = \infty$.

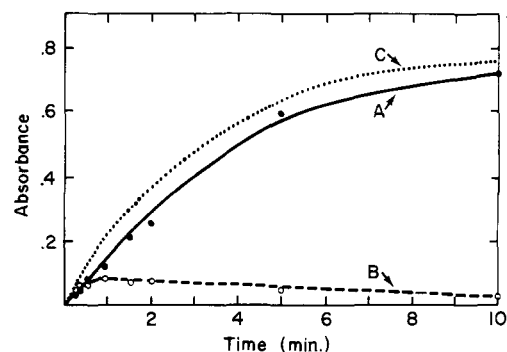


Figure 3. A plot of absorbance vs. minutes for *p*-methylbenzaldehyde diethyl acetal in acetate buffer ($\mu = 0.5$, KCl) at 25 °C. The solid line A, is the appearance of *p*-methylbenzaldehyde, the dashed line B, is the appearance of hemiacetal (measured at various t_q ; cf. Figure 2). The sum of A and B is the dotted line C.

extrapolated line plotted vs. time (line B). The slope of line B produces k_2 . Both procedures produce equivalent values of k_2 as shown in Table I; thus, while an exact kinetic treatment of consecutive first-order reactions is rather complex,^{1a,c} the data can in fact be treated rather simply provided that the competitive reaction rates are different by at least a factor of 2.²

Table I. Values of k_2 Calculated by Independent Methods

X	pH	k_1/k_2^a	$k_1,^b \text{ s}^{-1}$	$k_2,^c \text{ s}^{-1}$
H	4.544	0.18	4.61×10^{-3}	$3.0 \pm 0.5 \times 10^{-2}$
CH ₃	5.288	0.15	4.10×10^{-3}	$3.3 \pm 0.5 \times 10^{-2}$
OCH ₃	5.382	0.21	1.05×10^{-2}	$6.3 \pm 1.3 \times 10^{-2}$

^a Measured directly by the quenching method (cf. Figure 3 and related discussion). The probable error limit is $\pm 15\%$. ^b Mean of replicate determinations carried out in the traditional spectrophotometric manner. Average deviation from the mean $\leq 3\%$. ^c Mean of the values calculated by the direct quench method and the differential kinetic method (cf. Figures 1 and 3 and related text), \pm average deviation.

Table II. Values of k_1 and k_2 for Various Acetals of Benzaldehyde at 25 °C, $\mu = 0.5$ (KCl)

X	Solution	$k_1,^a \text{ s}^{-1}$	$k_2,^b \text{ s}^{-1}$	k_1/k_2^c
<i>m</i> -NO ₂	10 ⁻³ M HCl	8.70×10^{-4}	2.4×10^{-2}	0.036
H	10 ⁻³ M HCl	0.145	0.35	0.41 ^d
H	Acetate buffer, ^e pH 3.601	3.98×10^{-2}	0.11	0.35 ^d
H	Acetate buffer, ^e pH 4.544	4.61×10^{-3}	3.0×10^{-2}	0.15
<i>p</i> -CH ₃	Acetate buffer, ^e pH 5.288	4.10×10^{-3}	3.3×10^{-2}	0.13
<i>p</i> -OCH ₃	Acetate buffer, ^e pH 4.544	7.15×10^{-2}	0.10	0.69
<i>p</i> -OCH ₃	Acetate buffer, ^e pH 5.382	1.05×10^{-2}	6.2×10^{-2}	0.17
<i>p</i> -OCH ₃	phosphate buffer, ^e pH 5.972	2.67×10^{-3}	7.6×10^{-2}	0.035
<i>p</i> -OCH ₃	50% dioxane, acetate buffer, ^e pH 5.216	2.99×10^{-3}	4.3×10^{-2}	0.069

^a Measured in the traditional spectrophotometric manner. Average deviation from these mean values is $\leq 3\%$ for replicate determinations. ^b Measured directly by the quenching method (cf. Figure 3 and related discussion). Probable error limit is $\pm 15\%$. ^c Calculated from listed k_1 and k_2 values. ^d Same value, within the experimental error. ^e 0.02 M buffer.

Our first method of treatment is more direct, but since it corroborates the second method, the latter is preferable because it is less cumbersome.

Table II demonstrates some of our preliminary efforts to establish the scope and substituent effects on the "buildup" of hemiacetals during the course of hydrolysis of acetals in aqueous acidic medium. Several conclusions are evident. (1) The concentration of hemiacetal is *not* trivial, being 40% of the total substrate concentration at t_{max} for *p*-methoxybenzaldehyde. (2) Acid catalyzed hydrolyses of acetals exhibit a larger substituent effect ($\rho = -3.4$) than the acid catalyzed hydrolyses of hemiacetals ($\rho \sim -2$). (3) Acid catalyzed hydrolyses of acetals exhibit a larger solvent effect than the acid catalyzed hydrolyses of hemiacetals. Hydrolysis of hemiacetals are characterized by a large k_{OH^-} term, such that above pH 4–5 the hemiacetal concentration drops sharply because of the contribution of k_{OH^-} to k_2 in Scheme I.

While we are currently in the process of extending the study summarized in Table II, several major trends are already evident. For acetal hydrolyses proceeding through carboxonium ions less stable than those derived from acetals of benzaldehydes, $k_2 \gg k_1$. Thus, for acetals of simple aliphatic aldehydes, hemiacetal buildup probably will be negligible. In cases where k_1 has been decreased relative to k_2 , hemiacetal buildup will be negligible. Thus, the mixed acetals of benzaldehyde (e.g., benzaldehyde methyl phenyl acetal)⁴ will not

Scheme I

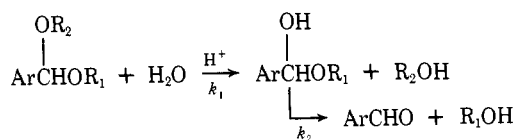


exhibit significant hemiacetal concentrations during the course of hydrolysis. *However*, several cases have been reported where hemiacetals probably do contribute significantly, perhaps predominantly, to the overall substrate concentration. In these cases k_1 is increased relative to k_2 because of steric and/or ring strain. Hydrolyses of cyclic acetals, acetone di(trichloroethyl) acetal,⁵ various rather hindered ketals (e.g., benzophenone ketals),⁶ ortho esters,⁷ and orthocarbonates,⁷ are all examples of reactions which we are examining for buildup of intermediates analogous to hemiacetals. These examples are particularly critical, since several have been shown to exhibit general acid catalysis and it is important to establish whether it is acetal hydrolysis which is general acid catalyzed or hemiacetal hydrolysis (the latter may be either general acid or general base catalyzed).

Several reports have recently shown hemiacetals (or analogues) to be present in significant amounts during hydrolytic processes. However, these systems all possess some "unique" structural feature which has the effect of increasing v_1 relative to v_2 in Scheme I (ring strain, steric crowding, presence of a good leaving group not requiring catalysis). Thus Bruice⁸ and Schaleger⁹ showed that three- and four-membered ring acetals hydrolyze quickly to hemiacetals which more slowly produce aldehydes. Capon¹⁰ recently reported that benzaldehyde di-*tert*-butyl acetal hydrolyzes similarly. These are instances where $v_1 > v_2$ because of ring strain and steric crowding, respectively.

Acylals are substances similar to acetals but possessing a good leaving group (e.g., acetoxy) not requiring acid catalysis. Capon¹¹ has recently used α -acetoxy- α -methoxytoluene (an acylal) as a precursor for the hemiacetal derived from benzaldehyde dimethyl acetal. At 15 °C ($\mu = 0.05$) the observed rate constant contains the terms k_{H^+} , $k_{\text{H}_2\text{O}}$, and k_{OH^-} ($261 \text{ M}^{-1} \text{ s}^{-1}$, $5.18 \times 10^{-3} \text{ s}^{-1}$, and $6.87 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, respectively). These quantities produce a break in the pH-rate plot at pH 4.5–5, corroborating the behavior that we observed (Table II). The acylals produce hemiacetal quickly because of the facility with which acetate leaves, producing the carboxonium ion (i.e., $k_{\text{H}_2\text{O}} \gg k_{\text{H}^+}(\text{H}^+)$). This type of reaction is one where the *non-acid-catalyzed* v_1 process is made faster than v_2 in Scheme I.

Acyloxy ortho esters¹² and cyclic ortho esters¹³ also were shown recently to hydrolyze more quickly to hydrogen ortho esters (hemiacetal analogues) than the hydrogen ortho esters hydrolyze to esters. In these cases, as in all those reported to date, the intermediate builds up in solution only in those cases where $v_2(\text{OH}^-) < v_2(\text{H}^+)$. That is, as the pH increases, the likelihood of hemiacetal or hydrogen ortho ester buildup decreases. Thus, for a given hydrolytic process, hemiacetal buildup may be avoided by carrying out the hydrolysis at a rather neutral pH.

In summary, it may no longer be legitimately assumed that hemiacetals are present at a low steady-state concentration and that v_1 (Scheme I) is the rate-controlling step in acetal hydrolysis or analogous hydrolytic processes. It appears that hemiacetal buildup is a rather common feature of acetal hydrolysis and that ketals, ortho esters, and orthocarbonates may hydrolyze with buildup of analogous intermediates. The purpose of this report is to present an easy experimental procedure for the detection of these intermediates (cf. Figure 2) and to briefly summarize the effects of solvent, structure, and pH which control their buildup.

Acknowledgments. This work was supported by grants from the CSULB Research Foundation and the National Science Foundation.

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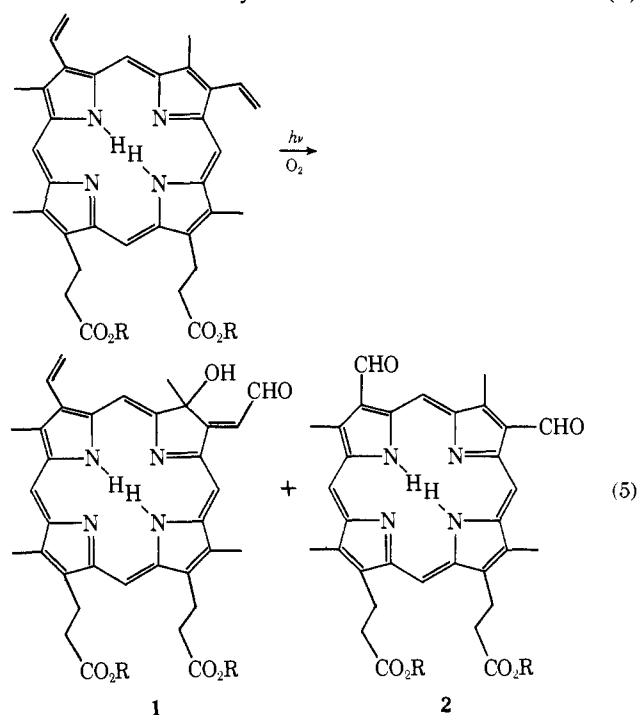
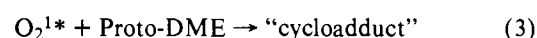
Environmental Effects on Photochemical Reactions: Contrasts in the Photooxidation Behavior of Protoporphyrin IX in Solution, Monolayer Films, Organized Monolayer Assemblies, and Micelles¹

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