initiators **1** and **2** show comparable efficiencies as do **4** and **5**. In multilamellar vesicles (liposomes) of dipalmitoylphosphatidylcholine (DPPC) at 60.00 °C with a pH 7 buffer, 1.0 mM EDTA, under atmospheric oxygen, all of our initiators show a *pronounced* decrease in efficiency from the value obtained in chlorobenzene.

This result is in contrast to the efficiencies obtained[5] with **5** in liposomes at 50 °C ($e = 0.25$). We suggest that the high escape efficiency exhibited by **5** in bilayers may be attributed to its localization in a region of low microviscosity, e.g., near the terminal methyl groups of the acyl chains.[11] The same reasoning would account for the slightly higher efficiency of **2** in bilayers compared to **1** since the diazene linkage for **2** would be in a region of lower microviscosity than that of **1**.

Of the initiators **1–3**, **3** has the highest escape efficiency. We speculate that the hydrophobic effect[12] provides a driving force for realignment of the lipid radicals once the diazene linkage is broken. This realignment of radicals would shear apart the radical centers and thus retard coupling of radicals during the initial encounter[11] (see Figure 1).

Registry No. *meso*-**1**, 86550-44-9; (±)-**1**, 86550-45-0; *meso*-**2**, 88377-13-3; (±)-**2**, 88377-14-4; *threo*-**3**, 88377-15-5; *erythro*-**3**, 88377-16-6; DPPC, 2644-64-6; chlorobenzene, 108-90-7.

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Copper Ion Mediated Epoxidation of Olefins by Iodosylbenzene

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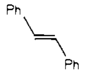
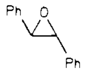
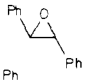
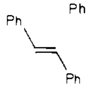
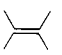
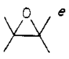
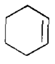
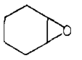
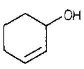
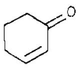
Metalloenzymes that catalyze the incorporation of oxygen atoms derived from dioxygen into organic substrates usually contain either iron or copper. Our understanding of the mechanisms involved in the reactions of the iron-containing heme oxygenases has been substantially advanced by the characterization of high-valent iron porphyrin oxo complexes capable of epoxidation or hydroxylation of organic substrates. Such iron porphyrin oxo complexes have typically been prepared from single oxygen atom sources such as iodosylbenzene,[1,2] peroxy acids,[3] or amine oxides.[4] Similar reactivity has been observed with manganese and chromium porphyrins as well.[5-7] In the case of the copper enzymes, e.g., tyrosinase[8] or dopamine-β-hydroxylase,[9] our understanding is much more limited. It has been suggested that either a (μ-peroxo)dicopper(II) complex or a high-valent copper oxo complex derived from O–O bond cleavage may be the active species.[9,10] The best model system for this reaction is the binuclear cuprous complex of Karlin and co-workers,[11] which reacts with dioxygen to give ligand hydroxylation. The nature of the copper complex that is directly responsible for the hydroxylation is unknown in this case also.

Table I. Products of the Reaction of Copper Nitrate and Iodosylbenzene with Olefins in Acetonitrile[a]

substrate	products	yield,[b,c] %	substrate consumed,[c] %
		76	68
	PhCHO	10[d]	
		28	27
		44	
	PhCHO	28[d]	
	 [e]	28	92
		28	26
		1.8[f]	
		2.6[f]	

[a] See text for experimental procedure. The ratio reactant: copper nitrate:iodosylbenzene = 1:4:8. [b] Percent yields are based on substrate consumed. [c] Rates and yields are somewhat variable and appear to depend on variations in individual preparations of iodosylbenzene. Values reported are typical values obtained after 2-h reactions. [d] Yields of benzaldehyde are calculated based on two benzaldehyde molecules per stilbene. [e] Other products were present in low yield and have not been characterized. [f] Yields of cyclohexenone and cyclohexenol were variable, although always low, and may have been due to competing side reactions.[1]

We have initiated a study of copper-mediated oxygenations using a variety of oxygen atom sources, e.g., dioxygen, superoxide, hydrogen peroxide, iodosylbenzene, etc., in an attempt to observe and characterize some of the intermediates in these reactions and relate them back to the biological systems. We report here an initial success in this endeavor, the observation that olefins can be epoxidized by iodosylbenzene in the presence of copper ions in organic solvents. The occurrence of this reaction leads to the surprising conclusion that porphyrin ligands are not required for metal ion activation of iodosylbenzene, as has recently also been demonstrated by Hecht and co-workers[12] who reported that copper bleomycin could mediate the reaction of iodosylbenzene with olefins in aqueous solution.

In a typical experiment, 174 mg (0.791 mmol) of iodosylbenzene[13] was added all at once to a solution of *trans*-stilbene (17.8 mg, 0.0987 mmol) and cupric nitrate,[14a] $Cu(NO_3)_2 \cdot 2.5H_2O$ (91.5

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(12) Murugesan, N.; Ehrenfeld, G. M.; Hecht, S. M. *J. Biol. Chem.* **1982**, *257*, 8600–8603.

(13) Prepared by the method of Saltzman and Sharefkin (Saltzman, H.; Sharefkin, J. G. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 658–659) and stored at −5 °C to retard the spontaneous disproportionation to iodoxybenzene and iodobenzene.

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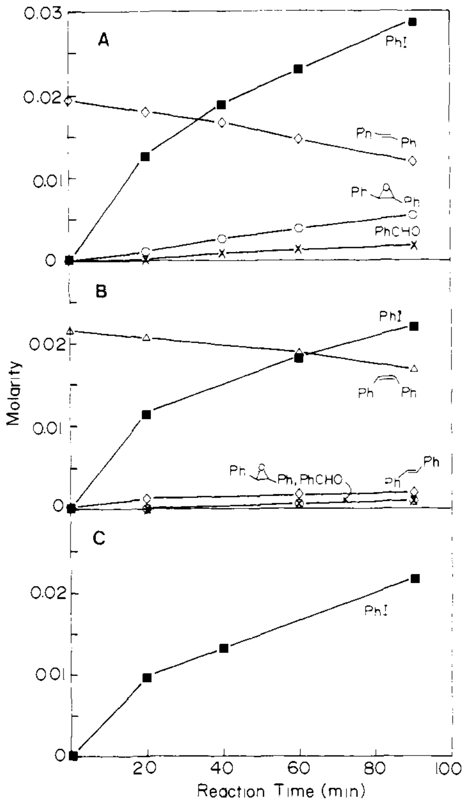


Figure 1. Time course for the reaction of cupric nitrate and iodosylbenzene with (A) *trans*-stilbene, ◇, (B) *cis*-stilbene, △, and (C) no substrate: ○ represents *trans*-stilbene oxide; X represents benzaldehyde; and ■ represents iodobenzene. Experimental details are described in the text.

mg, 0.393 mmol), in 5 mL of acetonitrile. The reaction mixture was stirred continuously at room temperature except when 100-μL aliquots of the solution were taken at periodic intervals for analysis. (The reaction mixture was heterogeneous due to the insolubility of iodosylbenzene in acetonitrile.) Each aliquot was diluted with 2 mL of methanol, filtered through a 0.45-μm filter, and analyzed by either HPLC (stilbenes) or GLC (other olefins). The time course of typical reactions of *trans*- and *cis*-stilbene is plotted in Figure 1A,B. Major products and yields are summarized in Table I.

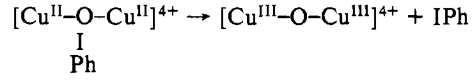
Cyclohexene, 2,3-dimethyl-2-butene, and 1-hexene were also found to give the corresponding epoxides under similar reaction conditions (see Table I). Addition of small amounts of water to the acetonitrile solvent had little effect on the product ratios. The reaction was found to proceed in tetrahydrofuran also but with lower rates and yields.

The reaction with *trans*-stilbene was also carried out using conditions identical with those described above except that the cuprous complex $[Cu(CH_3CN)_4](NO_3)$ was substituted for cupric nitrate. Epoxide and benzaldehyde were produced but in low yield and with poor material balance. Moreover, a considerable induction period was observed (>20 min) during which time iodobenzene but no epoxide or benzaldehyde was formed. The likely explanation for this induction period is that it represents the time required for oxidation of enough Cu(I) to Cu(II) to cause the reaction to occur at an observable rate, suggesting that the reaction requires copper(II).

Addition of excess solid iodosylbenzene to blue-green solutions of cupric nitrate (~0.1 M) in acetonitrile caused the solutions immediately to turn dark green. After stirring briefly, aliquots were removed, filtered to remove unreacted iodosylbenzene, diluted with methanol, and analyzed by HPLC. These methanolic solutions were found to contain substantial quantities of the same product that was formed from direct reaction of iodosylbenzene with methanol, presumably iodobenzene dimethoxide, $C_6H_5I(OMe)_2$.[15] Since iodosylbenzene itself is insoluble in acetonitrile, this result suggests that the product we are forming is an iodosylbenzene complex of copper(II). The ESR spectrum of this green solution shows traces of the starting copper nitrate spectrum, but otherwise there is no signal, indicating that the product we are forming is ESR silent. Since it is highly unlikely that the addition of a strong oxidizing agent to copper(II) would cause a reduction to copper(I), we believe that the product formed is either a diamagnetic Cu(III) complex or, more likely, an iodosylbenzene-bridged complex of copper(II) that is ESR silent because of the proximity of the Cu(II) centers. The solutions of the (iodosylbenzene)copper(II) complex are themselves unstable, even in the absence of added substrate, and the formation of iodobenzene is observed (see Figure 1C). In the presence of excess solid iodosylbenzene, as in the case of the experiments with the stilbenes described above, a substantial amount of iodobenzene is formed, in excess of the amount of stilbene consumed.[16]

At this point in our studies, we can only speculate about the mechanism of the reactions forming epoxide and benzaldehyde. We do know that benzaldehyde is not formed from epoxide because we find both *cis*- and *trans*-stilbene oxides to be stable under our reaction conditions and because benzaldehyde is formed at an appreciable rate even at the beginning of the reaction. Any mechanism must also account for the observation that the reaction of *trans*-stilbene proceeds at a greater rate and with better material balance than the reaction of *cis*-stilbene. We also note that *cis*-stilbene is at least partially isomerized to *trans*-stilbene under the reaction conditions. The observation that *cis*-stilbene gives only *trans*- rather than *cis*-stilbene oxide could be due to this isomerization or to the involvement of a diradical intermediate that can rotate prior to ring closure, similar to intermediates proposed for the manganese porphyrin catalyzed reaction of stilbenes with iodosylbenzene.[6]

Iodosylbenzene itself is known to be a nucleophilic reagent and to react slowly with electron-deficient olefins to give epoxidation.[1,17] The oxygen atom in iodosylbenzene might be expected to be "oxene"-like[18] if it were coordinated to two Cu(II) ions, and consequently it might be reactive with electron-rich olefins. Alternatively, iodobenzene might dissociate from such a complex leaving a (μ-oxo)dicopper(III) species that could be the active reagent.



$$[Cu^{II}\text{–}\underset{\underset{\displaystyle Ph}{\displaystyle I}}{O}\text{–}Cu^{II}]^{4+} \rightarrow [Cu^{III}\text{–}O\text{–}Cu^{III}]^{4+} + IPh$$

It is also possible that the reaction occurs through activation of water by a high oxidation state metal ion. Our future studies will be directed toward elucidating the mechanism of this novel reaction.

Acknowledgment. Financial support from the National Science Foundation is gratefully acknowledged.

Registry No. Iodosylbenzene, 536-80-1; *trans*-stilbene, 103-30-0; cupric nitrate, 3251-23-8; *cis*-stilbene, 645-49-8; cyclohexene, 110-83-8;

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(14) (a) The choice of nitrate as a counterion for copper in this reaction was made after it was observed that $Cu(BF_4)_2 \cdot 2H_2O$ reacts with iodosylbenzene in acetonitrile. The yellow product contains no copper and lacks the I–O stretch in the IR spectrum characteristic of iodosylbenzene. Its elemental analysis most closely resembles $C_6H_5IF_2$, and we believe it is probably a decomposition product derived from that species. Reactions of *trans*-stilbene with iodosylbenzene in the presence of cupric tetrafluoroborate or $Cu(CH_3CN)_4BF_4$ gave considerably more benzaldehyde than *trans*-epoxide and low yields overall. Since $C_6H_5IF_2$ and $C_6H_5ICl_2$ are known to react with olefins,[14b] we chose thereafter to avoid copper salts with halide anions. (b) Banks, D. F. *Chem. Rev.* **1966**, *66*, 243–266.

(15) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563–1565.

(16) The solid remaining at the end of this reaction was found to contain substantial amounts of iodoxybenzene, $PhIO_2$, identified by IR and elemental analysis. Similar observations have been made for the reactions of iodosylbenzene catalyzed by iron porphyrins: Nappa, M. J.; Tolman, C. A., paper presented at the 186th ACS National Meeting, Washington, D.C., Sept. 2, 1983.

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2,3-dimethyl-2-butene, 563-79-1; 1-hexene, 592-41-6; cyclohexene epoxide, 286-20-4; 2,3-dimethyl-2-butene epoxide, 5076-20-0; 1-hexene epoxide, 1436-34-6; *trans*-stilbene epoxide, 1439-07-2; 2-cyclohexen-1-ol, 822-67-3; 2-cyclohexen-1-one, 930-68-7; PhCHO, 100-52-7; [Cu($CH_3CN)_4](NO_3)$, 14057-91-1.

Washout Effects in Pumped Tank Reactors

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Studies of multiple steady states in continuous-flow stirred tank reactors (CSTR) typically depend on the systematic variation of reactor residence time or some other system constraint such as reactant concentration. The concentration of an intermediate species is usually monitored as a function of time at a particular residence time until a steady state is established; the flow rate is then changed to give a new residence time and the next steady state concentration is determined. At short reactor residence times, the reaction mixture composition approaches the composition of the combined reactant streams; at long residence times, the composition approaches that corresponding to a batch reaction at thermodynamic equilibrium. For most chemical reactions, the steady-state concentration of a particular species is a continuous, smooth function of residence time between the extremes of zero and infinity. However, in a number of autocatalytic reactions,[1-8] the branch of steady states asymptotic to the reactant stream composition and the branch asymptotic to the equilibrium composition do not connect in a continuous fashion, but instead overlap one another. Thus, when a system constraint such as residence time is varied, a hysteresis effect is observed as the system moves from one branch of steady states to the other and back again. The system may exist in either of two steady states in the overlap region, i.e., the system is bistable.

The familiar pattern of steady-state multiplicity is dramatically altered when a minor modification is made in pumping the CSTR. A simple model system recently proposed by Gray and Scott,[9] which combines third-order autocatalysis with a first-order decay of the autocatalytic species, exhibits a second hysteresis region and may even give rise to an isolated branch of steady states. We recognized that a first-order decay of all species in a tank reactor can be provided by supplying a constant flux of solvent to the CSTR in addition to the flux of reagents.[10] In addition, the bistable iodate–arsenous acid reaction exhibits third-order autocatalysis[11] and, therefore, is an ideal chemical system for testing the model predictions. In this communication we report the first experimental characterization of a mushroom (two connected hysteresis regions) and an isola (an isolated branch of steady states) exhibited by a chemical system in an isothermal CSTR.

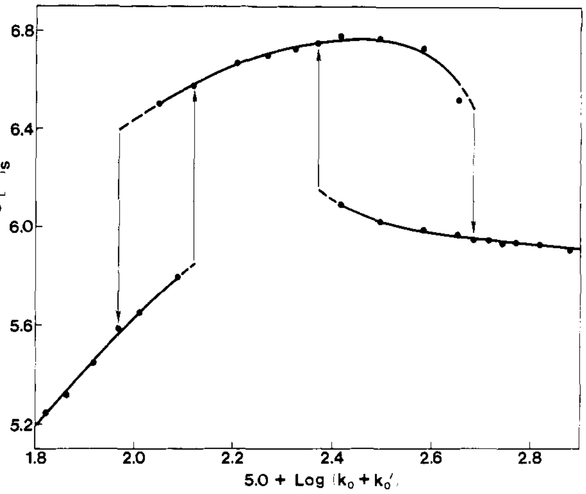

Figure 1. Steady-state iodide concentration (M) as a function of reciprocal residence time (s^{-1}). Concentrations in combined reactant streams: $[KIO_3]_0 = 1.01 \times 10^{-3}$ M; $[KI]_0 = 8.40 \times 10^{-5}$ M; $[H_3AsO_3]_0 = 4.98 \times 10^{-3}$ M. Solvent stream, $k_0' = 4.91 \times 10^{-4}\ s^{-1}$; temperature, 25.0 ± 0.1 °C. Buffer in reactant streams and in solvent stream prepared with $NaHSO_4$ and Na_2SO_4 to yield a reaction mixture of pH 2.23.

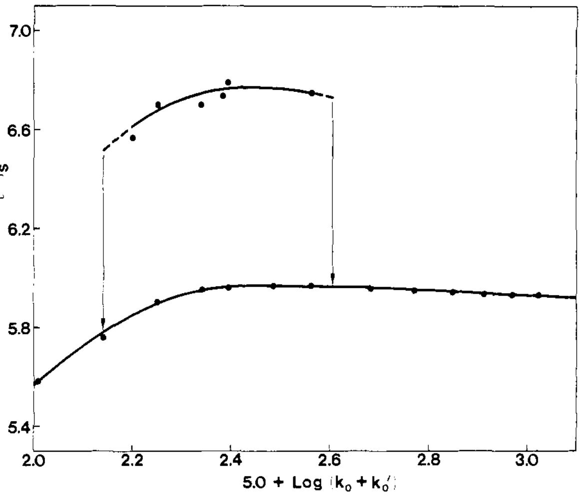

Figure 2. Same concentrations and conditions as in Figure 1 except $k_0' = 6.20 \times 10^{-4}\ s^{-1}$ for solvent stream.

Our investigation utilized a bistable iodate–arsenous acid system with arsenous acid in stoichiometric excess. An additional constant flow of solvent, consisting of a buffer solution identical with that in the reactant stream, was introduced to the CSTR. Figure 1 shows steady-state iodide concentrations as a function of reciprocal residence time (volume flow rate/tank volume). Here, the reciprocal residence time is given by the sum ($k_0 + k_0'$), where k_0 corresponds to the reactant stream and k_0' corresponds to the constant flow of buffer solution. We see that as reciprocal residence time is increased, a discontinuous increase in iodide concentration is found at a reciprocal residence time of $1.32 \times 10^{-3}\ s^{-1}$, and a discontinuous decrease occurs at $4.84 \times 10^{-3}\ s^{-1}$. As reciprocal residence time is decreased, the iodide concentration again increases at $2.34 \times 10^{-3}\ s^{-1}$, and it again decreases at $9.44 \times 10^{-4}\ s^{-1}$. The double hysteresis gives rise to a mushroom-shaped curve.

An important difference between the experiment reported here and earlier studies of bistability can be seen in Figure 1. For nonzero values of k_0', corresponding to a finite flux of additional solvent, the concentrations of all species approach zero as the value of reciprocal residence time approaches k_0'. This "washout" is evident in Figure 1 at low reciprocal residence times. As reciprocal residence time is increased to the first hysteresis limit, iodide

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(7) Orbán, M.; Epstein, I. R. *J. Am. Chem. Soc.* **1982**, *104*, 5918–5922.

(8) Orbán, M.; Epstein, I. R. *J. Phys. Chem.* **1983**, *87*, 3212–3219.

(9) (a) Gray, P.; Scott, S. K. *Chem. Eng. Sci.* **1983**, *38*, 29–43; (b) *J. Phys. Chem.* **1983**, *87*, 1835–1838.

(10) A first-order decay of all species gives rise to the same patterns of multiple steady states as those predicted by the model system of Gray and Scott;[9] however, the systems differ in their stability properties.[13]

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