therefore contain larger error.
(7) K. T. Suzuki, H. Yamada, and M. Hirobe, *J. Chem. Soc., Chem. Commun.*, 485 (1978).
(8) Note Added in Proof. After the manuscript was accepted, we measured the ^{13}C NMR spectrum of [$^{15}N_7$]-9-ethyladenine in Me_2SO and found that the C_8 signal appeared as a sharp singlet. This fact establishes that the unassigned coupling constant, 10.4 Hz, in the C_8 signal in [^{15}N]adenosine is $J(C_8N_9)$ (Kainosho, Watanabe, and Kyogoku, unpublished results). Therefore, disappearance of splitting in the C_8 signal of adenine derived from doubly enriched formamide is indeed due to the bond fission and re-formation of C–N bond during the thermal reaction, as Suzuki et al. have suggested.[1]

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Hydroxylation and Epoxidation Catalyzed by Iron–Porphine Complexes. Oxygen Transfer from Iodosylbenzene

Sir:

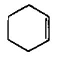
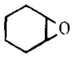
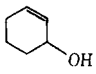
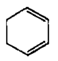
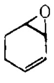
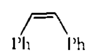
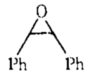
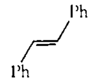
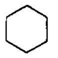
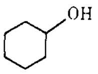
The catalytic cycle of cytochrome P-450 is believed to involve reductive activation of dioxygen at the heme center and subsequent peroxy bond cleavage to give a ferryl ion species as the active oxygen transfer agent.[1,2] Support for an iron–oxo species such as **1** is derived from the fact that a number of single oxygen donors, hydroperoxides, peroxy acids, and iodosylbenzene, effect oxygen transfer in a manner similar in many respects to the fully reconstituted enzyme system.[3-5] As part of our program to evaluate simple iron catalysts as oxygen transfer agents,[6,7] we have found that chloro-$\alpha,\beta,\gamma,\delta$-tetraphenylporphinatoiron(III) (**2**) and chlorodimethylferriprotoporphyrin IX (**3**) catalyze the hydroxylation and epoxidation of hydrocarbons with iodosylbenzene as an oxygen source.

$$\text{P-450}\cdot \text{Fe}^{3+} \xrightarrow[2e^-,\ 2H^+]{O_2} \text{P-450}\cdot \text{Fe}^{3+}\cdot H_2O_2 \longrightarrow \underset{\mathbf{1}}{\text{P-450}\cdot \text{FeO}^{3+}} + H_2O$$

In a typical experiment solid iodosylbenzene was added slowly to a solution of hydrocarbon and catalyst in methylene chloride under nitrogen at room temperature. Results for the oxidation of a representative family of hydrocarbons are given in Table I. Thus, cyclohexene (1 mL, 9.8 mmol) and **2** (0.035 g, 0.049 mmol) were dissolved in 6 mL of methylene chloride. Iodosylbenzene (0.066 g, 0.3 mmol) was added to this mixture over a period of 30 min. The reaction mixture was diluted with ether, washed with sodium sulfite, and analyzed by GLC. The yield of cyclohexene oxide was 55% based on iodosylbenzene. Cyclohexenol (15%) and a trace of cyclohexenone were the only other organic products. Iodobenzene was recovered in quantitative yield. Similarly, cyclohexadiene gave a 74% yield of the corresponding monoepoxide.

The reaction of *cis*- and *trans*-stilbene with iodosylbenzene using **3** as a catalyst gave the corresponding *cis*- and *trans*-stilbene oxides. The complete retention of configuration in this case contrasts with the epoxidation of *cis*- and *trans*-stilbene by tris(acetylacetonato)iron(III) hydrogen peroxide which has been reported to yield the trans epoxide from both starting materials.[8] Surprisingly, **2** catalyzed the conversion of *cis*-stilbene to *cis*-stilbene oxide while the trans isomer was inert. Indeed, a mixture of the two olefins led to efficient isolation of *cis*-stilbene oxide (82%) and recovery of *trans*-stilbene!

Table I. Hydrocarbon Oxidation with **2** and Iodosylbenzene

substrate	products	yield, %[a]
		55
		15
		74
		82
	*trans*-stilbene oxide	trace
		8
adamantane	1-adamantanol	12
	2-adamantanol	1

[a] Yields based on iodosylbenzene consumed. Preliminary results indicate that the lower yields with the less reactive hydrocarbons was due to competing destruction of the catalyst.

Table II. Intermolecular vs. Intramolecular Oxidation of Octyl Esters

	octanediol isomers					
	1,2	1,3	1,4	1,5	1,6	1,7
octyl acetate	<2	17	15	21	22	24
4	<2	15	28	30	13	14

Such a dramatic change in selectivity with changes in the substitution pattern on the porphyrin suggests that the catalyst is intimately involved in the oxygen transfer step.[9] The nature of this selectivity is not clear, however. Space-filling models indicate that the approach of the double bond of *cis*-stilbene to the iron center of **2** is relatively unencumbered by phenyl-phenyl interactions between the catalyst and the substrate. By contrast, significant phenyl-phenyl nonbonded interactions develop between **2** and *trans*-stilbene for any geometry except parallel approach to the porphyrin plane directly from above. This apparent requirement for a restricted mode of approach could reasonably be explained by (a) the need to avoid the creation of a molecular void as the two molecules approach, (b) the specific presence of iodobenzene as oxygen transfer takes place, or (c) the stereoelectronic requirements for such an oxygen transfer. The generality of this specificity was further indicated by the observation that *cis*-2-butene was six times more reactive than the trans isomer in a competitive oxidation with **2** and iodosylbenzene.[10]

Unactivated aliphatic centers were found to be oxidized by **2** and iodosylbenzene to give alcohols. Thus, cyclohexane afforded cyclohexanol in 8% yield. Although this transformation was relatively inefficient, the lack of significant further oxidation to cyclohexanone is exceptional.[11] Adamantane gave a 13% yield of adamantanols with a strong preference (48:1, statistically corrected) for hydroxylation of the tertiary center. Hydroxylation of *cis*-decalin gave *cis*- and *trans*-9-decalol (5:1) indicating predominant retention of configuration at the oxidized center.

Reaction of chlorodioctylferriprotoporphyrin IX (**4**) with iodosylbenzene led to significant oxidation of the aliphatic side chains. Subsequent cleavage of the ester linkages with lithium aluminum hydride and GLC analysis of the product octanediols as the bistrifluoroacetates revealed a pronounced regioselectivity for C_4 and C_5 of the octyl chain (Table II). Similar oxidation of excess octyl acetate with **3** and iodosylbenzene gave a mixture of product diols with a modest selectivity for hydroxylation toward the end of the chain after identical workup and analysis.[12]

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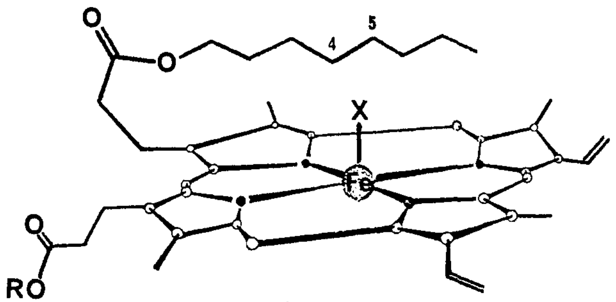

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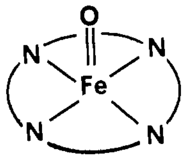
The regioselectivity observed for the side-chain hydroxylation of **4** is most easily accommodated by intramolecular oxygen transfer from the locus of the porphyrin-bound iron. Two general mechanisms consistent with this regioselectivity are (a) oxygen rebound[6a] from iodosylbenzene to the substrate via an iron-oxo intermediate (**5**) and (b) oxygen activation by coordination of iodine to the porphyrin (**6**).



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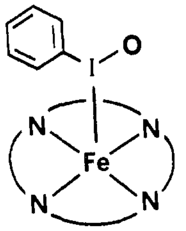

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While the details of this reaction remain to be elucidated, path a is preferred on the basis of the observed cis olefin selectivity. Molecular models indicate little opportunity for substrate-porphyrin nonbonded interactions with **6**. The scope and mechanism of this porphyrin-catalyzed oxygen transfer, the exact constitution of the catalyst, and the relevance of this oxidation to the mechanism of cytochrome P-450 action are under continued study.

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(9) Substitution of cumene hydroperoxide or *tert*-butyl hydroperoxide for iodosylbenzene gave only cyclohexenol and cyclohexenone as reaction products. These reactions are probably related to previously reported porphyrin-initiated free-radical autoxidation processes. Cf. ref 7f–i.

(10) Under similar conditions, *cis,trans,trans*-1,5,9-cyclododecatriene gave a 2:1 mixture of the trans and cis monoepoxides. We thank Professor L. M. Stephenson for an initial sample of pure cis,trans,trans triene. High selectivity for trans epoxidation has generally been observed for the peroxy acids and alkyl hydroperoxides with this olefin. (a) Y. Kobayashi, *Tetrahedron Lett.*, 5093 (1972); (b) W. Stumpf and K. Rombush, *Justus Liebigs Ann. Chem.*, **687**, 136 (1965).

(11) N. C. Deno and L. A. Messer, *J. Chem. Soc., Chem. Commun.*, 1051 (1976).

(12) The distribution of octanediols in this *intermolecular* oxidation was similar to that observed for the oxidation of octanol by trifluoroperoxyacetic acid; cf. ref 11. GLC analyses of the reaction products were conveniently carried out as described in N. C. Deno and D. G. Pohl, *J. Am. Chem. Soc.*, **96**, 6680 (1974).

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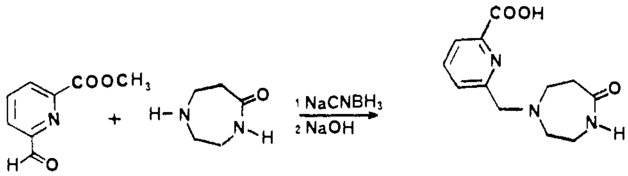
Rapid Amide Hydrolysis Mediated by Copper and Zinc

Sir:

The catalytic role of divalent metal ions in metallohydrolases such as carboxypeptidase A and thermolysin has resisted unambiguous elucidation.[1] Although spectacular rate enhancements have been observed in model systems for ester hydrolysis[2] and nitrile hydration,[3] there has been no demonstration of significant catalysis of amide bond cleavage[4] except those involving Co(III).[5] Either the metal plays only a minor role in enzymic proteolysis or the model systems have failed to achieve some important criterion for catalysis. As part of a program to evaluate geometrical factors in metal catalyzed acyl transfer reactions, we have found very large rate enhancements for amide hydrolysis in copper and zinc complexes in which the metal is forced to lie perpendicular to the amide plane.

The requisite ligand (**3**) for these studies was prepared by reductive amination of aldehyde **1**[6,7] with azalactam **2**. The spectral and analytical properties of **3** were completely in accord with the assigned structure.[8]



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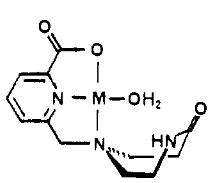
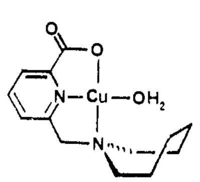


4a: M = Cu^{2+}
b: M = Zn^{2+}
c: M = Co^{2+}
d: M = Ni^{2+}



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Lactam **3** was found to bind readily to divalent cations to form 1:1 complexes (**4**). Titrimetric formation constants (K_f) were found to be $>10^7$ (Cu^{2+}), 1.41×10^5 (Zn^{2+}), 1.23×10^4 (Co^{2+}), and 4.73×10^4 (Ni^{2+}).[9]

Titrations of the metal-amide complexes were consistent with tridentate coordination of the metal by the ligand and ligation of at least one additional water molecule. For the copper complex (**4a**), the pK_a of the metal-bound water was found to be extraordinarily low (7.6). In contrast, complex **5**

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