Table I. Rates of Inhibition of Trypsin-Like Serine Proteases by Substituted Isocoumarins[a]

	$k_{obsd}/[I]$ (M^{-1} s^{-1})						
inhibitor	bovine thrombin	bovine factor Xa	porcine pancreatic kallikrein	human plasma kallikrein	human factor XIa	human factor XIIa	bovine trypsin
1	4700	5600	12000	280000[b]	44000	39000	32000
2	4900	460	1900	13000	1400	520	3300
3	290000[c]	3100	45000[c]	240000[c]	36000	20000	310000[c]

[a] Enzyme (0.06-2.3 μM) was incubated with inhibitor (0.4-11 μM) in 0.25-0.6 mL of 0.1 M Hepes, 0.01 M $CaCl_2$, pH 7.5, and 8-12% Me_2SO at 25 °C. Aliquots (50 μL) were withdrawn at various intervals, and the residual enzymatic activity was measured as previously described.[4] Residual activity was measured with Z-Phe-Phe-Arg-NA (26 μM) as a substrate for trypsin, Boc-Phe-Phe-Arg-SBzl (18 μM) for thrombin, Z-Gly-Arg-SBu-*i* (73 μM) for factor Xa and porcine pancreatic kallikrein, Z-Trp-Arg-SBzl (89 μM) for factor XIIa and human plasma kallikrein, Z-Phe-Arg-SBu-*i* (83 μM) for factor XIa. The k_{obsd} values were calculated from plots of ln v/v_0 vs. time with $r > 0.98$. [b] Inactivation was extremely rapid, and the $k_{obsd}/[I]$ values were based on the residual enzymatic activity at 0.2 min. [c] Inactivation rate was measured by using the progress curve method.[12]

less reactive toward porcine pancreatic kallikrein, human factor XIa, and human factor XIIa, while the other serine proteases tested were 30-2000-fold less reactive. Compound **1** is equally potent as **3** toward human plasma kallikrein, human factor XIa, and human factor XIIa. Loss of the isocoumarin chromophore of **1** (ϵ_{350} = 3620 M^{-1} cm^{-1}) and **3** (ϵ_{360} = 3650 M^{-1} cm^{-1}) was complete within 0.3 min upon the addition of 1.2 equiv of trypsin. In the case of **2** (ϵ_{350} = 3400 M^{-1} cm^{-1}), complete loss of the isocoumarin absorbance occurred in 10 min. The inactivation of trypsin by compounds **1**, **2**, and **3** occurred concurrently with the loss of the isocoumarin absorbance.

Trypsin (0.9 μM) inactivated by **3** (4.3 μM, $t_{1/2}$ = 44 min for spontaneous hydrolysis) regained only 35% activity after standing for 68 h; however, trypsin (0.9-1.3 μM), inactivated by compounds **1** and **2** (9.8 and 8.6 μM, $t_{1/2}$ = 83 and 252 min for spontaneous hydrolysis, respectively), regained 70-100% activity after 6-68 h. Addition of buffered hydroxylamine (0.29 M) to trypsin inactivated by **3** results in the regeneration of 51% activity after 68 h, while addition of hydroxylamine to trypsin inactivated by **1** and **2** resulted in the recovery of 100% activity ($t_{1/2}$ = 7-9 min). Bovine thrombin (1.8 μM) inactivated by **3** (4.4 μM) regained 11% activity after standing for 47 h, while thrombin inactivated by **2** (8.9 μM) regained 85% activity after standing for 47 h. Addition of buffered hydroxylamine (0.29 M) to thrombin inactivated by **3** results in only 27% recovery of activity after 25 h, even though thrombin maintained 63% of its activity under the same conditions.

These results are consistent with mechanism shown in Figure 1 where serine proteases inactivated by isocoumarins **1** and **2** form acyl enzymes which deacylate slowly at varying rates or quickly upon the addition of hydroxylamine. However, the acyl enzyme formed from **3** decomposes further probably through a quinone imine methide[8] to give an irreversibly inactivated enzyme by reaction with an active site nucleophile such as His-57. The quinone imine methide intermediate could also react with a solvent nucleophile to give an acyl enzyme which can be reactivated by hydroxylamine.[5,9]

Compound **3** is an effective anticoagulant in human plasma. The prothrombin time[10] was prolonged from 12 s (first appearance of clotting) to 2.8 min in the presence of 33 μM **3**. The general serine protease inhibitor 3,4-dichloroisocoumarin prolonged the prothrombin time to 2 min at 330 μM. The isocoumarin **3** decomposes quite rapidly in human plasma ($t_{1/2}$ = 7 min), and preincubation of the inhibitor in plasma for 3 min resulted only in an 80% increase in prothrombin time.

The isocoumarins **1** and **3** developed in this study are the most potent inactivators yet reported for several of the coagulation enzymes studied, and **3** is the first mechanism-based serine protease inactivator which is active as an anticoagulant in human plasma.[11] Our future efforts will be directed at improving the selectivity and stability of the inhibitors in plasma and further clarifying the mechanism by structural studies of inhibitor-protease complexes.

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Supplementary Material Available: Experimental details for the synthesis of the new isocoumarins (3 pages). Ordering information is given on any current masthead page.

(8) Direct alkylation of the benzylic chloride would yield the same result and cannot be distinguished from a mechanism involving a quinone imine methide. A quinone imine methide mechanism has been postulated to explain the high reactivity of aminobenzyl halides, which decompose rapidly to 4-quinone imine methides and alkylate nucleophiles such as imidazole: (a) Wakselman, M.; Dome, M. *Bull. Soc. Chim. Fr.* **1975**, 571-575. (b) Dome, M.; Wakselman, M. *Bull. Soc. Chim. Fr.* **1975**, 576-582.

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Membrane-Spanning Steroidal Metalloporphyrins as Site-Selective Catalysts in Synthetic Vesicles

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Substrate recognition and binding have long been recognized as a means to induce regioselectivity and stereoselectivity in enzyme-mediated reactions. We have sought to develop synthetic biomimetic approaches to similar selectivity by using the organization intrinsic to phospholipid bilayers.[1] It has been shown by Tsuchida et al.[2] that amphiphilic metalloporphyrins can be encapsulated in synthetic liposomes. More recently, Nolte et al.[3] have demonstrated that hydrophobic membrane-bound metallo-

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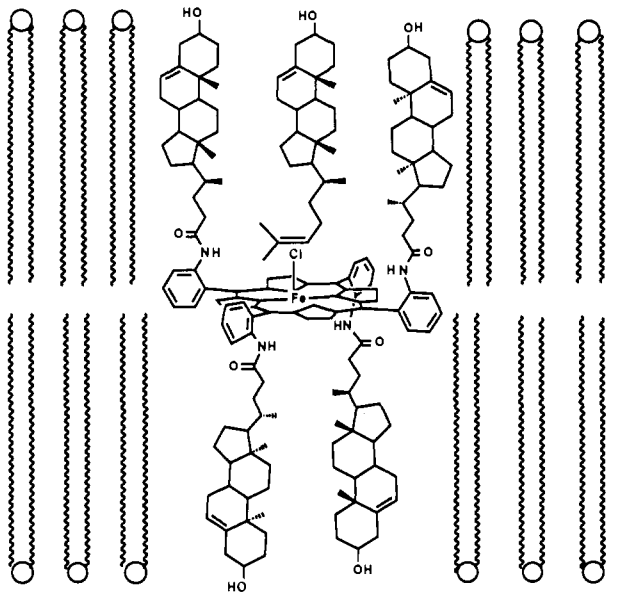

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Figure 1. Idealized molecular assembly of chloro-α,β,α,β-*meso*-tetra(*o*-3β-ol-5-cholenylamidophenyl)porphyrinatoiron(III) [Fe(ChP)Cl], desmosterol, and phospholipid.

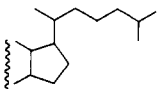
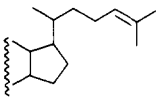
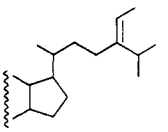
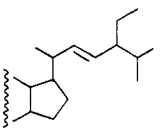
porphyrins can be functionally active oxidation catalysts. We report here the preparation of a *membrane-spanning* metalloporphyrin catalyst designed to provide rigid organization of the catalytic center. The microenvironment provided by this porphyrin in phospholipid bilayer assemblies has been shown to induce a profound regioselectivity for the side-chain epoxidation of sterols. Further, the degree of selectivity for the monoepoxidation of polyunsaturated fatty acids was found to depend on membrane rigidity.[4]

The iron tetra(*o*-cholenylamidophenyl)porphyrin [Fe(ChP)Cl (**1**)] (Figure 1) was prepared by condensing 3β-ol-5-cholenic acid with the α,β,α,β-rotamer of *meso*-tetra(*o*-aminophenyl)porphyrin. The amide linkage was achieved through use of the mixed anhydride method.[5] Subsequently, the free base porphyrin was metalated in the usual manner.[6] The product, α,β,α,β-*meso*-tetra(*o*-3-β-ol-5-cholenylamidophenyl)porphyrin was unambiguously characterized by its spectroscopic properties: ^{1}H NMR at 300 MHz in $CDCl_3$ δ 8.88 (8 H, s, pyrrole) 8.74 (4 H, d, phenyl) 8.00 (4 H, d, phenyl) 7.89 (4 H, t, phenyl) 7.53 (4 H, t, phenyl) 6.70 (4 H, s, amide) δ 5.29 (4 H, d, C_6 steroid) 3.50 (4 H, br s, C_3 steroid) 0.93 (12 H, s, C_{19} steroid) 0.85 (12 H, s, C_{18} steroid) 0.31 (12 H, d, C_{21} steroid) 2.25–0.16 (104 H, m, steroid) −2.64 (2 H, s, pyrrole); VIS (CH_2Cl_2) λ_{max} 422, 516, 549, 590, 645 nm; FABMS on a *m*-nitrobenzyl alcohol matrix gave the molecular ion at *m/z* 2100, 2155 for Fe(ChP)Cl. The iron porphyrin gave VIS (CH_2Cl_2) λ_{max} 420, 510, 584, and 654 nm.

Use of this rotamer and a steroid with a four-carbon side chain has provided a porphyrin with a total hydrophobic length complementary to a dimyristoylphosphocholine (DMPC) or a dipalmitoylphosphocholine (DPPC) bilayer (35–40 Å). The equatorial C-3 hydroxyl groups of adjacent steroidal appendages are arranged such that they can interact with opposing sides of the bilayer membrane. An elongated pocket is formed on both sides of the porphyrin plane, centered in the bilayer, such that a substrate sterol may pass over the active site by lateral diffusion (Figure 1).

Epoxidations of sterols (Table I) and fatty acids (Table II) have demonstrated that this pillared steroidal metalloporphyrin–bilayer assembly is a highly regioselective catalytic system. The sterols that were chosen were cholesterol analogues having two double bonds, Δ^5 in the steroid nucleus and at various positions in the side chain. Several polyunsaturated fatty acids have also been examined. A typical bilayer porphyrin system was assembled by dissolving 10 μmol phospholipid, 1.0 μmol substrate, and 0.1 μmol Fe(ChP)Cl in a minimal amount of chloroform. The solvent was evaporated in a stream of nitrogen to produce a thin film. Unilamellar vesicles were formed by the addition of 4 mL of phosphate buffer (pH 7.4), deaeration with N_2, and ultrasonication

Table I. Epoxidation of Sterols

substrate	bilayer assembly Fe(ChP)Cl/DMPC[a] epoxide prod.	yield[c] (%)	homogeneous solution FeTpTPCl/CH_2Cl_2[b] yield[c] (%)	rel reactvty Δ^5/side chain[d]
 cholesterol		0	31.2	
	5,6	0 (0)[e]	26.2	3.6
 desmosterol	24,25	32 (27.1)[e]	7.3	
	5,6	0	26.4	3.2
 fucosterol	24,28	22.2	8.3	
	5,6	0	28.7	18
 stigmasterol	22,23	trace	1.6	

[a] Reaction conditions: 1.0 μmol substrate, 0.1 μmol Fe(ChP)Cl, 10 μmol DMPC, 1 μmol PhIO as 20 mM solution in 1/1 methanol/water in 4 mL of phosphate buffer (pH 7.4), 30 °C, time 2 h. [b] Reaction conditions: 2.0 μmol substrate, 0.2 μmol Fe(TpTP)Cl, 70 μL CH_2Cl_2, 4.0 μmol PhIO as a solid, room temperature, time 2 h. [c] Yields as based on starting sterol. Epoxides were analyzed as silyl ethers by glpc vs. authentic samples; 30 m. SPB-1 column, e.g., for desmosterol: 5β,6β-epoxide, 28.6 min; 5α,6α-epoxide, 30.54 min; 24,25-epoxide, 29.09 min. [d] Ring epoxidation gave a 3/1 ratio of 5β,6β/5α,6α-epoxide. [e] Reaction done with DPPC in place of DMPC.

Table II. Epoxidation of Fatty Acids

substrate	bilayer assembly Fe(ChP)Cl[a] yield[c] (%)	ratio mono-epoxides[d]	homogeneous solution FeTpTPCl/CH_2Cl_2[b] yield[c] (%)	ratio mono-epoxides
9,12-(*Z*,*Z*)-octadecadienoic acid	32	1.7	7.5	1
9,12-(*Z*,*Z*)-octadecadienoic acid	28[e]	1.9		
9,12-(*E*,*E*)-octadecadienoic acid	8	1.4	2.5	1
11,14-(*Z*,*Z*)-eicosadienoic acid	16	1.3	8.1	1
9,12-(*Z*,*Z*)-octadecadienoic methyl ester	25	1.5	9	1
9,12-(*Z*,*Z*)-octadecadienoic acid cholesterol[f]	24	6.7		

[a] Reaction conditions: 1.0 μmol substrate, 0.1 μmol Fe(ChP)Cl, 10 μmol DMPC, 1.0 μmol PhIO as 20 mM solution in 1/1 methanol/water in 4 mL of phosphate buffer (pH 7.4), 30 °C, time 2 h. [b] Reaction conditions: 2.0 μmol substrate, 0.2 μmol Fe(TpTP)Cl, 2 μmol PhIO as a solid, 70 μL of CH_2Cl_2, room temperature, time 2 h. [c] Yields based on starting fatty acid. [d] Ratio of hydrophobic end/hydrophilic end epoxide. [e] Reaction done with DPPC in place of DMPC. [f] Cholesterol (0.5 μmol) added during bilayer preparation.

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(Heat Systems; Microson; 80% power) for 5 min at ambient temperature. The vesicular solution thus obtained was equilibrated at 30 °C, and reactions were initiated by addition of 1.0 μmol iodosylbenzene[7] (50 μL of a 20 mM solution in 1/1 methanol/water). After 2 h the reactions were quenched by addition of ether and vigorous shaking to destroy the vesicles. The substrate and product were purified by passing the organic phase over a dry alumina column, and the resulting mixture was analyzed by GLPC and GC-MS. Fatty acids were methylated with diazomethane prior to purification.

The results of the steroid epoxidations (Table I) show that the steroidal porphyrin Fe(ChP)Cl-bilayer assembly is indeed a site selective catalytic system. All the sterols were epoxidized *exclusively on the side chain*, while epoxidations with iodosylbenzene in a homogeneous methylene chloride solution with chloro-*meso*-tetra-*p*-tolylporphyrinatoiron(III) [Fe(TpTP)Cl] showed that the Δ^5 double bond in the steroid nucleus was considerably more reactive.[8] Desmosterol was found to be slightly more reactive than fucosterol, possibly because the approach to the double bond in the latter is more hindered. Significantly, stigmasterol with a Δ^{22}-double bond only two bond lengths closer to the hydrophilic end (approximately 11 carbon-carbon bonds vs. 13 for desmosterol and fucosterol) was found to be unreactive under these conditions as was cholesterol. This evidence indicates that the catalytic-bilayer assembly is very rigid, and a "perfect fit" is necessary for successful epoxidation.

The epoxidations of polyunsaturated fatty acids (Table II) showed considerably less regioselectivity. Epoxidations under conditions identical with those used for sterols showed that the epoxidation of the double bond closer to the hydrophobic terminus in the bilayer was favored but by a ratio of less than 2:1. C_{20} fatty acids showed only slightly less site selectivity than C_{18} fatty acids. Esterification of the carboxylic acid had little effect on the results, and, as expected, trans isomers gave lower yields.[7] The reduced site selectivity may be due to the fact that phospholipid bilayers become less rigid upon addition of polyunsaturated fatty acids, as is born out by the significant decrease in the phase transition temperature, T_p.[9] For example, the T_p of a DMPC vesicle is 24 °C, but the T_p of an egg yolk lecithin bilayer (partially unsaturated) is −15 °C. Loss of rigidity would enable free motion in the bilayer and lead to the decreased regioselectivity of the epoxidation reaction. Addition of cholesterol to the bilayer (Table II, last entry) resulted in a significantly more selective fatty acid epoxidation as expected for a more rigid system.[10] The results of the fatty epoxidation also show that yields are higher for the vesicular reactions than in homogeneous organic phases of comparable concentration. We attribute this to a favorable orientation effect in the bilayer. One must note that this comparison cannot be made for the sterol epoxidations since the double bonds are not of equal reactivity.

To summarize, a cholesterylmetalloporphyrin has been synthesized which upon intercalation into a synthetic biomembrane catalyzes the regioselective epoxidations of polyunsaturated sterols and fatty acids at the double bond closest to the hydrophobic terminus of the molecule. The characterization of this membrane-spanning porphyrin and generality of this lipid-induced specificity are now being explored.

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The Catalytic Activation and Functionalization of C-H Bonds. Aldimine Formation by the Insertion of Isonitriles into Aromatic C-H Bonds

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Many examples of the activation of aromatic and aliphatic carbon-hydrogen bonds by homogeneous transition-metal complexes have appeared over the past few years, offering attractive new routes to organometallic species.[1] While several of these reports involve oxidative addition of low valent metal complexes to alkanes or arenes, these new adducts have not proven to be useful for the generation of functionalized hydrocarbon products.[2] Reports of successful metal-based alkane functionalization include free radical oxidations,[3] intramolecular cyclizations of alkyl carbenoid species to give cyclopentanones,[4] aromatic isonitrile insertion to give indoles,[2b] and alkane dehydrogenation to produce olefins.[5] Arene functionalization reactions commonly depend upon the presence of teathering groups,[6] although the production of benzaldehyde,[7] benzoic acid,[8] styrene,[9] and phenylsiloxane[10] insertion products have been recently reported.[11] We report here a new type of iron catalyzed insertion of isonitrile into the C-H bond of arenes to produce aldimines (eq 1).

$$RNC + C_6H_6 \xrightarrow[\Delta G^\circ \approx -11\ \text{Kcal/mol}]{[Fe]} C_6H_5\text{—}CH{=}NR \quad (1)$$

In 1975, Muetterties[12a] and Karsch and Klein[12b] reported the preparation of $Fe(PMe_3)_4$ by the reduction of $FeCl_2$ with magnesium in the presence of PMe_3.[13] We have found that reaction of a THF solution of this complex with ~3 equiv of isocyanide results in the formation of orange, air-sensitive crystals of Fe-

† A.P. Sloan Fellow, 1984-86. Camille and Henry Dreyfus Teacher Scholar, 1985-87.

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