was quenched with an excess of methyl iodide within 30 min at 0°C. Subsequent cyclization to the hemiketal in acidic medium gave soraphen A1 (1a) in 70% yield.

Received: July 20, 1994 [Z.7140]

German version: Angew. Chem. 1994, 106, 3521

COMMUNICATIONS

Figure 4: Scheme 4. a) BuLi, THF, 90 min, –78°C; BzCl, pyridine, 12 h, 20°C; 5% NaOH, 5 h, –20°C, 35%; b) Ba(NF)$_2$, THF, 1 h, 0°C, 85%; c) nBuLi, CECO$_2$Et, THF, 1 h, –30°C, 85%; d) morpholine, THF, 2 h, reflux; 60% CH$_3$CO$_2$H, 2 h, 50°C, 75%; e) TBDPSI, aminopyridine, 30 min, 0°C, 96%; f) Cs$_2$CO$_3$, DMF, 1 d, 20°C, 50%; g) HC(OMe)$_2$, CH$_2$Cl$_2$, MeOH, 4 d, 20°C, 20%; h) TBDPSI, imidazole, DMF, 7 d, –60°C, 96%; i) CsF, DMF, 1 d, 20°C, 90%; j) Ti(0/Pr)$_4$, 2-(trimethylsilyl)ethanol, 3d, 100°C, 90%; k) Ti(0/Pr)$_4$, 2-(trimethylsilyl)ethanol, 3d, 100°C, 90%; l) TBDPSI, imidazole, DMF, 7 d, –60°C, 96%; m) Ac$_2$0, pyridine, 4-dime...
which transfers its oxygen atom to the bound substrate. The iron center accepts the electrons from NADPH, through mediation of a flavoprotein.

Because of its biological importance—this enzyme plays a crucial role in the metabolism of endogenous chemicals and xenobiotic compounds—and also because this archetype oxidation catalyst may serve as a model for a new generation of synthetic catalysts, a great deal of research is currently focused on mimicking the action of cytochrome P₄₅₀.

Until now only a few models have been described that incorporate the important features of the natural system, namely molecular oxygen as the oxidant, a metalloporphyrin as catalyst, an electron donor, and a membrane system holding these components. All models have the disadvantage of displaying very low catalytic activity.

During the course of our research on novel supramolecular catalytic systems, we found that the rhodium complex [Rh(n^2-dicyclopentadiene)(bpy)Cl] (Cp* = pentamethylcyclopentadienyl, bpy = 2,2'-bipyridine) is an efficient catalyst for the reduction of manganese(II) porphyrins by sodium formate. We report here on a membrane-bound cytochrome P₄₅₀ mimic that epoxidizes alkenes with good turnover numbers. The system is composed of vesicles containing an a-(acetoc)-5,10,15,20-tetrakis(2,6-di-chlorophenyl)-porphyrinato)manganese(III) catalyst (MnIIICp*,IIIdClPPP) 1). N-methylimidazole as axial ligand, and an amphiiphilic rhodium(II) complex (2) in combination with sodium formate as electron donor. We found that the type of membrane has a dramatic effect on the catalytic activity of the mimic.

The manganese porphyrin 1 and the rhodium complex 2 were incorporated into positively charged dimethyl-dioctadecylammonium chloride (DODAC) vesicles and negatively charged dihexadecylphosphate (DHP) vesicles by the ethanol injection method. Gel permeation chromatography and electron microscopy were used to show that the porphyrin and the rhodium complex were bound to the bilayers of the vesicles and that the vesicle structure was not destroyed by the incorporation procedure. The diameters of the vesicles of both amphiphiles amounted to about 4000 Å. The fluorescence spectra of H₂-t₂ 6-diClPP in both DODAC and DHP vesicles (T = 70 °C) showed no effects of self-quenching when the porphyrin to lipid ratio was lower than 0.005. This indicates that below these ratios the porphyrin molecules are not aggregated. The addition of water-soluble quenchers (NaI and CuSO₄) in the case of DODAC and DHP vesicles, respectively, to the system did not change the fluorescence spectrum of the vesicle-bound H₂-t₂ 6-diClPPP. Most likely the porphyrin is situated in the inner part of the vesicle bilayer. EPR studies, using [CuIIICp*,IIIdClPPP] instead of 1 revealed that for both vesicle systems the orientation of the porphyrin molecules was parallel to the vesicle surface. The structure of the model system is depicted in Figure 1.

First we investigated the influence of the membrane matrix on the reduction of the manganese(II) porphyrin. To this end the decrease in the absorption at 660 nm (MnIII porphyrin) and the increase in absorption at 448 nm (MnII porphyrin) in the UV/VIS spectrum was followed as a function of time, both under an argon atmosphere and in air. The rhodium complex manganese-porphyrin ratio was varied from 0.5 to 10. Under argon in DODAC as well as in DHP vesicles, the MnIIIporphyrin was reduced at all Rh/Mn ratios tested. The reduction rate was found to increase linearly with the RhIII concentration. At a fixed Rh/Mn ratio the reduction was faster in DODAC vesicles than in DHP vesicles ([Rh]/[Mn] = 1; kₐ (DODAC) > 100 mmol L⁻¹ s⁻¹, kₐ (DHP) = 20 ± 2 mmol L⁻¹ s⁻¹). The reduction of MnIII in DODAC vesicles also took place when the reactions were carried out in an air atmosphere. A similar result was obtained for DHP except when the Rh/Mn ratio was equal or less than 1, under which conditions reoxidation of MnIII was observed. In the absence of the RhIII complex or formate no reduction took place. These results indicate that the rhodium-formate system is capable of reducing the membrane-bound MnIII porphyrin and presumably, as observed previously, the rhodium complex acts as a redox-active phase transfer catalyst in this process. The reduction of MnIII is faster in the positively charged vesicles than in the negatively charged ones because the formate concentration is higher at the bilayer/water interface of the former aggregates. The fact that in DODAC vesicles in general and in DHP vesicles with a Rh/Mn ratio higher than 1 no reoxidation of MnIII takes place, indicates that the reduction of manganese is much faster than its reoxidation.

In a second series of experiments we investigated whether our membrane-bound cytochrome P₄₅₀ mimic was able to epoxidize alkenes. The results are listed in Table 1. All substrates tested were epoxidized by the catalytic system based on DHP vesicles. The turnover numbers are higher than those obtained with the two-phase system previously published by us. They are in the same range as those observed for the natural system (1 nmol product per nmol P₄₅₀ per min). Remarkable is the high stability of the catalyst during the reaction, which is in contrast with the two-phase system. The effect of the membrane environment on the catalytic epoxidation became clear when the DHP vesicles were replaced by the DODAC vesicles. In the latter membrane system no epoxidation of alkenes was observed (last two entries of Table 1). Presumably, the concentration of protons is too low to allow the formation of the catalytically active oxomanganese(v) species at the positively charged interface. When the Rh/Mn ratio was increased from 1 to 10 the turnover number of the reaction decreased considerably (Table 1, entry 5). This phenomenon is possibly caused by the fact that more elec-

Fig. 1. Schematic representation of the cytochrome P₄₅₀ mimic and the catalyzed reaction.
Table 1. Epoxidation of alkenes by the membrane-bound cytochrome P450 mimic [a].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Substrate</th>
<th>Product [b]</th>
<th>Turnover number [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DHP</td>
<td>α-pinene</td>
<td>α-pinene oxide</td>
<td>360</td>
</tr>
<tr>
<td>2</td>
<td>DHP</td>
<td>cis-stilbene</td>
<td>cis-stilbene oxide</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>DHP</td>
<td>limonene</td>
<td>limonene oxide</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>DHP</td>
<td>styrene</td>
<td>styrene oxide [d]</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>DHP [e]</td>
<td>styrene</td>
<td>styrene oxide</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>DODAC</td>
<td>styrene</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>DODAC [e]</td>
<td>styrene</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] For reaction conditions see Experimental Procedure. The reaction was followed by GLC for 1 h. No destruction of the catalyst was found after that period. [b] The only product of the reaction was epoxide, which was gradually decomposed into other products. The decomposition processes were independent of the Rh/Mn ratio. No epoxide was formed without vesicles or when any of the components of the catalytic system were omitted. [c] Turnover number [epoxide]/l per hour, calculated from the initial part of the conversion/time plot. α-Pinene oxide was converted (> 90%) into pinoctanone within a period of one hour. Limonene oxide decomposed (≤ 50%) into as yet unidentified products. [d] Styrene oxide and stilbene oxide were stable under the experimental conditions. [e] Rh/Mn molar ratio = 10.

In summary, we have developed a bimetallic membrane-bound cytochrome P450 mimic which catalyzes the epoxidation of alkenes with good turnover numbers. Current work is aimed at developing catalytic systems that display substrate selectivity.

Experimental Procedure

Reduction experiments: The desired amounts of stock solutions of 1, 2, N-methylimidazole, and DHP or DODAC in chloroform were mixed in a test tube. The solvent was evaporated under a stream of nitrogen to leave a homogeneous suspension. A-methylimidazole, and DHP or DODAC in chloroform were mixed in a test tube. The solvent was evaporated under a stream of nitrogen to leave a homogeneous suspension. A 5 μL of 1,2, N-methylimidazole, and DHP or DODAC in chloroform were mixed in a test tube. The solvent was evaporated under a stream of nitrogen to leave a homogeneous suspension.

Epoxidation experiments: Final conditions as above, except Rh/Mn molar ratio = 1 and [substrate] = 200 μM. Now the 100 μl solution was directly injected in a 2.5 mL cuvette containing 1.25 mL of an ethylmorpholine/sodium formate buffer at 75 °C. Final conditions: 2.4 μl of 1, 2, 3, 4 μl of 2 (n = Rh/Mn molar ratio), 3.85 μl of N-methylimidazole, 910 μl DODAC or DHP in ethylmorpholine (50 mM)/sodium formate (250 mM) buffer (pH = 7.0), T = 70 °C. Epoxidation experiments: Final conditions as above, except Rh/Mn molar ratio = 1 and [substrate] = 200 μM. Now the 100 μl solution was directly injected in a 2.5 mL cuvette containing 1.25 mL of an ethylmorpholine/sodium formate buffer at 75 °C. Substrate was added and the reaction mixture was analyzed by GLC (columns: Chrompack, WCOT/CP-SIL8CB, temperature program 50 °C (2 min), 10 K min⁻¹ to 200 °C (2 min)).

Scheme 1. Epoxidation of alkenes.

Scheme 2. Epoxidation of alkenes by the membrane-bound cytochrome P450 mimic [a].

1,4-Dihydrobutadiene: The Intermediate in a New Class of Thermally Induced Intramolecular Alkyne Couplings [2]

Rolf Gleiter* and Joachim Ritter

Dedicated to Professor Heinz Döbr on the occasion of his 60th birthday

More than twenty years ago Bergman and co-workers discovered that endiynes such as (Z)-hexadiyn-3-ene (1) cyclize to give the corresponding 1,4-dihydrobenzenes (2) as short-lived intermediates.1 This reaction occurs at 200 °C with an activation energy of 28 kcalmol⁻¹ (Scheme 1).1[a] The recent discovery of the natural antitumor antibiotics calicheamicin, esperamicin, and dynemicin, which contain the cyclic endiynyl unit 3, led to an enormous increase in publications on endiynyl chemistry in the last seven years.2 A common feature in the mechanism of action of these antibiotics is the cycloaromatization of the endiynyl unit 3 to give the bicyclic 1,4-dihydrobenzene 4. In the case of neocarzinostatin, the electrocyclization of an initially generated cyclic (Z)-cumulene-enzyme 7 is proposed as the key step.3 In related work Myers et al. found that the surprisingly facile cyclization of the open-chain cumulene 5 gives 1,6-dihydrobenzene 6 and is an example of a new type of 1,4-biradical generating reaction (Scheme 2).4

Scheme 1. Epoxidation of alkenes.

Scheme 2. Epoxidation of alkenes by the membrane-bound cytochrome P450 mimic [a].

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the BASF Aktiengesellschaft (Ludwigshafen). J. R. thanks the Studienstiftung des deutschen Volkes for a doctoral fellowship.

Received: May 2, 1994 [Z 6891 IE]

German version: Angew. Chem. 1994, 106, 2387