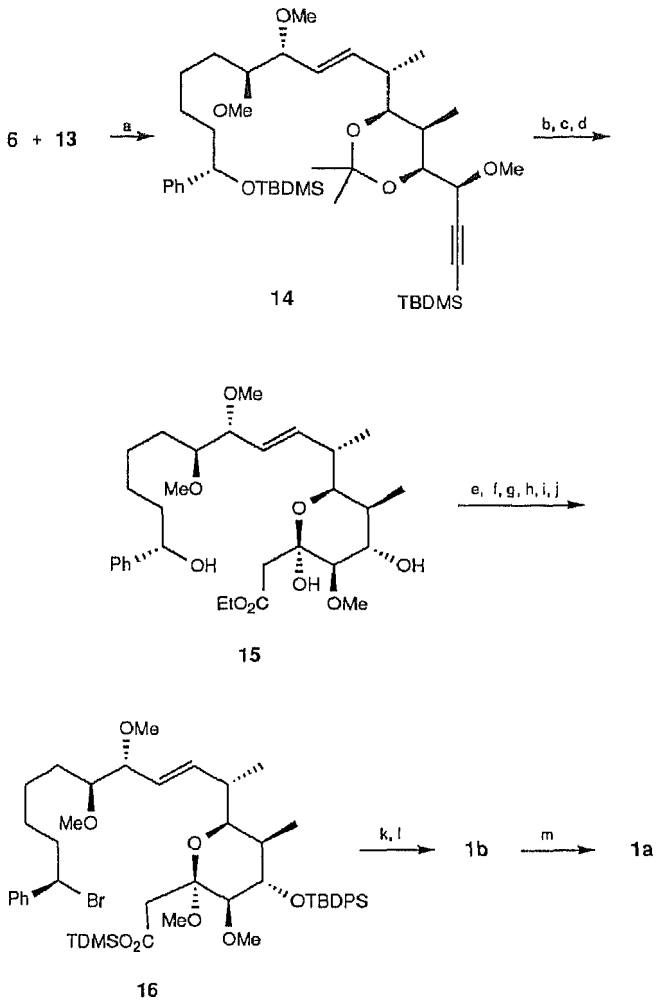

Scheme 4. a) *t*BuLi, THF, 90 min, −78 °C; BzCl, pyridine, 12 h, 20 °C; 5% Na/Hg, 5 h, −20 °C, 35%; b) Bu_4NF, THF, 1 h, 0 °C, 85%; c) *n*BuLi, $ClCO_2Et$, THF, 1 h, −30 °C, 85%; d) morpholine, THF, 2 h, reflux; 60% CH_3CO_2H, 2 h, 50 °C, 75%; e) TBDPSCl, imidazole, DMF, 7 d, −60 °C, 96%; f) Ac_2O, pyridine, 4-dimethylaminopyridine, 30 min, 0 °C, 98%; g) $HC(OMe)_3$, CH_2Cl_2, MeOH, 4 d, 20 °C, 99%; h) $Ti(OiPr)_4$, 2-(trimethylsilyl)ethanol, 3 d, 100 °C, 90%; i) CsF, DMF, 1 d, 20 °C, 98%; j) thexyldimethylsilyl chloride (TDMSCl), CH_2Cl_2, triethylamine, 20 min, 20 °C; $(CH_3)_2C{=}CBr(NMe_2)$, CH_2Cl_2, triethylamine, 1 h, 20 °C, 91%; k) triethylamine, acetone, H_2O, 15 min, RT; Cs_2CO_3, DMF, 1 d, 20 °C, 50%; l) tetrabutylammonium fluoride, THF, 4 h, 0 °C, 1 M HCl, THF, 1 d, 20 °C, 95%; m) 2 equiv of potassium-2,6-di-*tert*-butylphenoxide, DMF, 1 d, 20 °C; MeI, DMF, molecular sieves (4 Å), 30 min, 0 °C; HCl, THF, 12 h, 20 °C, 70%.

mate after desilylation.[13] Subsequent addition of water across the triple bond via an enamine intermediate followed by cleavage of the protecting groups resulted in the tetrahydropyran ring structure of **15**. Experiments by G. Höfle et al. on the ring-opened soraphen demonstrated that the lactonization is best effected by a substitution reaction of the cesium salt of the carboxylic acid.[14] Therefore, benzyl alcohol **15** and the bromo enamine reported by Ghosez et al.[15] were allowed to react under mild conditions and yielded bromide **16** with complete inversion. The macrocyclization of the cesium carboxylate of **16** (20 °C, 60% yield) produced the soraphen ring structure also with inversion at the benzyl group. Since the methyl group in soraphen $A_{1\alpha}$ (**1a**), that is in α-position to the lactone occupies the thermodynamically favored configuration,[16] it was introduced in the last step of the synthesis. By using two equivalents of potassium 2,6-di*tert*-butylphenoxide, the hemiketal ring of norsoraphen **1b** was opened and deprotonated to give the potassium enolate. To avoid overmethylation, the enolate ion was quenched with an excess of methyl iodide within 30 min at 0 °C. Subsequent cyclization to the hemiketal in acidic medium gave soraphen $A_{1\alpha}$ (**1a**) in 70% yield.

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[7] M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. When using the magnesium salt of acetylene only the desired D-*glycero* isomer **11** was detected. The formation of the L-*glycero* isomer, however, was favored in a ratio of 8:1 when using the triisopropyloxytitanium salt.
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[16] Upon treatment of soraphen $A_{1\alpha}$ (**1a**) [2] with base (thermodynamic conditions), no change of configuration occurs at the methylated carbon α to the lactone. The crystal structure of **1a** shows that the methoxy group of the tetrahydropyran ring and the methyl group α to the lactone are in a sterically favorable position relative to each other. In the corresponding *epi* form, however, these methyl and methoxy groups are subject to 1,3-diaxial interactions. This might also be the reason why a possible dimethylation of norsoraphen **1b** can be avoided under appropriate reaction conditions.

Novel Bimetallic Model System for Cytochrome P_{450}: Effect of Membrane Environment on the Catalytic Oxidation**

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Cytochrome P_{450} catalyzes a variety of oxidation reactions, including the hydroxylation of alkanes and the epoxidation of alkenes.[1] The active site of this membrane-bound enzyme contains a heme function and a thiolate as axial ligand. The catalytic cycle involves the binding of a substrate, reduction of iron(III) to iron(II), and binding and reductive cleavage of molecular oxygen to generate what is formally an oxoiron(V) complex,

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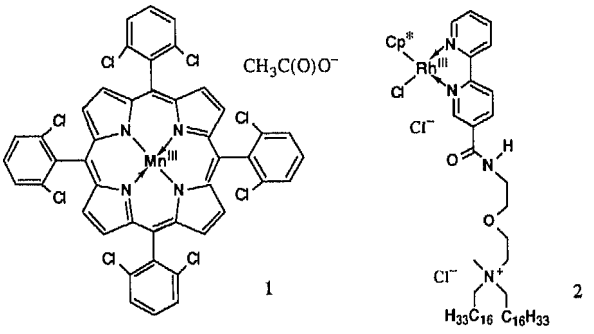
which transfers its oxygen atom to the bound substrate. The iron center accepts the electrons from NADPH, through mediation of a flavoprotein.

Because of its biological importance—this enzyme plays a crucial role in the metabolism of endogeneous 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 P_{450}.[2] 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.[3] All models have the disadvantage of displaying very low catalytic activity.

During the course of our studies on novel supramolecular catalytic systems, we found that the rhodium complex [$Rh^{III}(\eta^5$-Cp*)(bpy)Cl_2] (Cp* = pentamethylcyclopentadienyl, bpy = 2,2'-bipyridine) is an efficient catalyst for the reduction of manganese(III) porphyrins by sodium formate.[4] We report here on a membrane-bound cytochrome P_{450} mimic that epoxidizes alkenes with good turnover numbers. The system is composed of vesicles containing an α-(aceto)-[5,10,15,20-tetrakis(2,6-dichlorophenyl)-porphyrinato]manganese(III) catalyst ([$Mn^{III}t_{2,6}$-diClPP] **1**),[5] *N*-methylimidazole as axial ligand, and an amphiphilic rhodium(III) complex (**2**)[6] 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)[7] and negatively charged dihexadecylphosphate (DHP)[7] vesicles by the ethanol injection method.[8] 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 H_2-$t_{2,6}$-diClPP in both DODAC and DHP vesicles ($T = 70\,^{\circ}C$) 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.[9] The addition of water-soluble quenchers (NaI and $CuSO_4$ in the case of DODAC and DHP vesicles, respectively) to the system did not change the fluorescence spectrum of the vesicle-bound H_2-$t_{2,6}$-diClPP. Most likely the porphyrin is situated in the inner part of the vesicle bilayer. EPR studies, using [$Cu^{II}(t_{2,6}$-diClPP)] instead of **1** revealed that for both vesicle systems the orientation of the porphyrin molecules was parallel to the vesicle surface.[10] 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(III) porphyrin. To this end the

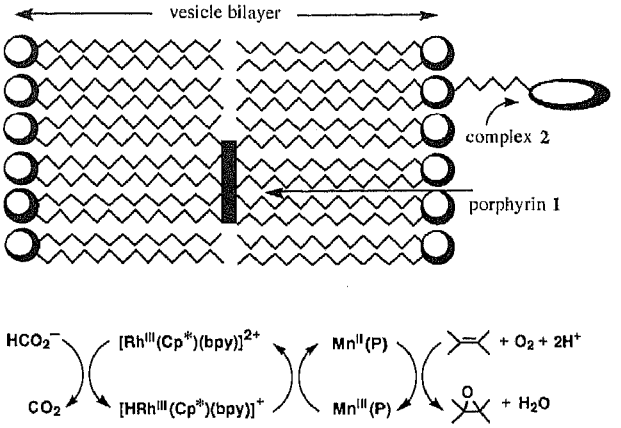


Fig. 1. Schematic representation of the cytochrome P_{450} mimic and the catalyzed reaction.

decrease in the absorption at 660 nm (Mn^{III} porphyrin) and the increase in absorption at 448 nm (Mn^{II} porphyrin) in the UV/VIS spectrum was followed as a function of time, both under an argon atmosphere and in air. The rhodium complex manganoporphyrin ratio was varied from 0.5 to 10. Under argon in DODAC as well as in DHP vesicles, the Mn^{III} porphyrin was reduced at all Rh/Mn ratios tested. The reduction rate was found to increase linearly with the Rh^{III} concentration. At a fixed Rh/Mn ratio the reduction was faster in DODAC vesicles than in DHP vesicles ([Rh]/[Mn] = 1; k_0 (DODAC) > 100 nmol $L^{-1}s^{-1}$, k_0 (DHP) = 20 ± 2 nmol $L^{-1}s^{-1}$). The reduction of Mn^{III} 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 Mn^{II} was observed. In the absence of the Rh^{III} complex or formate no reduction took place. These results indicate that the rhodium-formate system is capable of reducing the membrane-bound Mn^{III} porphyrin and presumably, as observed previously,[4] the rhodium complex acts as a redox-active phase transfer catalyst in this process. The reduction of Mn^{III} 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 Mn^{II} 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 P_{450} 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.[4] They are in the same range as those observed for the natural system (1 nmol product per nmol P_{450} per min).[1] 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)[11] 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-

Table 1. Epoxidation of alkenes by the membrane-bound cytochrome P_{450} mimic [a].

Entry	Surfactant	Substrate	Product [b]	Turnover number [c]
1	DHP	α-pinene	α-pinene oxide	360
2	DHP	*cis*-stilbene	*cis*-stilbene oxide	45
3	DHP	limonene	limonene oxide	50
4	DHP	styrene	styrene oxide [d]	55
5	DHP [e]	styrene	styrene oxide	5
6	DODAC	styrene	-	0
7	DODAC [e]	styrene	-	0

[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]/1 per hour, calculated from the initial part of the conversion/time plot. α-Pinene oxide was converted (>90%) into pinocamphone 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.

trons become available due to the higher concentration of rhodium centers. As a result a side reaction can take place which produces water (the so-called non-productive pathway[11]).

In summary, we have developed a bimetallic membrane-bound cytochrome P_{450} 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 film. This film was solubilized in 100 μL ethanol/tetrahydrofuran (1:1, v/v) and injected in 1.25 mL water at 75 °C. The suspension was purged with argon for 30 min and injected in a cuvette containing 1.25 mL of an ethylmorpholine/sodium formate buffer at 75 °C. Final conditions: 2.4 μM of **1**, 2.4 × *n* μM of **2** (*n* = Rh/Mn molar ratio), 3.95 μM of *N*-methylimidazole, 910 μM 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 buffered solution at 75 °C. Substrate was added and the reaction mixture was analyzed from time to time by taking a 0.2 mL aliquot to which was added 0.1 mL diethyl ether containing mesitylene as an internal standard. This mixture was shaken vigorously (vortex apparatus) and centrifuged. After phase separation, a 5 μL sample was taken from the diethyl ether layer and analyzed by GLC (column Chrompack, WCOT/CP-SIL5CB, temperature program 70 °C (2 min), 10 K min^{-1} 200 °C (2 min)).

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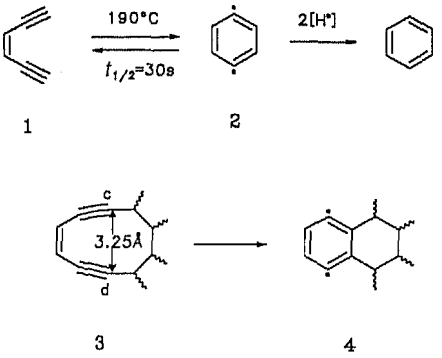
1,4-Didehydrobutadiene: The Intermediate in a New Class of Thermally Induced Intramolecular Alkyne Couplings**

Rolf Gleiter* and Joachim Ritter

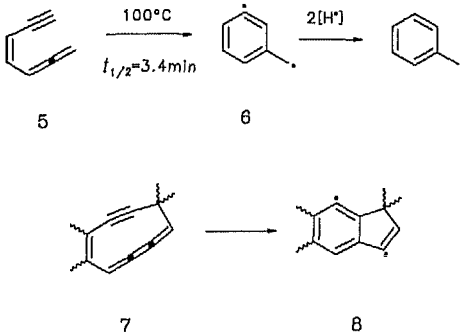
Dedicated to Professor Heinz Dürr on the occasion of his 60th birthday

More than twenty years ago Bergman and co-workers discovered that enediynes such as (*Z*)-hexadiyn-3-ene (**1**) cyclize to give the corresponding 1,4-didehydrobenzenes (**2**) as short-lived intermediates.[1] This reaction occurs at 200 °C with an activation energy of 28 kcal mol^{-1} (Scheme 1).[2a] The recent discovery of the natural antitumor antibiotics calicheamicin, esperamicin, and dynemicin, which contain the cyclic enediyne unit **3**, led to an enormous increase in publications on enediyne chemistry in the last seven years.[3] A common feature in the mechanism of action of these antibiotics is the cycloaromatization of the enediyne unit **3** to give the bicyclic 1,4-didehydrobenzene **4**.



Scheme 1. Cycloaromatization of enediynes.

In the case of neocarzinostatin, the electrocyclization of an initially generated cyclic (*Z*)-cumulene-enyne **7** is proposed as the key step.[4] In related work Myers et al. found that the surprisingly facile cyclization of the open-chain cumulene **5** gives α,3-dehydrotoluene **6** and is an example of a new type of a 1,4-biradical generating reaction (Scheme 2).[5a]



Scheme 2. Cycloaromatization of cumulene-enynes.

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