

COMPUTER-AIDED MOLECULAR DESIGN OF ALKANE-ACTIVATION CATALYSTS

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Introduction

Methane can provide an abundant source of liquid fuels if an efficient method of conversion can be found. Direct conversion, without an initial steam reforming step to carbon monoxide and hydrogen, offers several significant advantages. These include improved efficiency, reduced capital costs, and more effective resource utilization. The key to success lies in the development of a catalyst that will activate the relatively inert carbon-hydrogen bond in methane. Several approaches are under active investigation, including oxidative coupling, partial oxidation by molecular oxygen at high temperature, photochemical conversion, and biomimetic processes.¹⁻³ Our work focuses on a novel biomimetic approach to the development of catalysts for activation of methane, using computer-aided molecular design (CAMD) techniques.

The biomimetic CAMD methodology consists of several elements: (1) Design activities are guided by the structural and chemical information about naturally occurring biological catalysts that carry out alkane oxidation to alcohols. The macromolecular biological catalysts are investigated to determine the features that need to be designed into a synthetic catalyst in order to mimic the alkane-oxidation function. (2) Molecular mechanics calculations are used to evaluate possible designs for catalysts based on synthetic metalloporphyrins. The metalloporphyrins have been chosen because they occur at the active site of many monooxygenases and other enzymes that catalyze C₁ chemistry. Also, the porphyrin macrocycle provides a platform upon which additional molecular architecture is erected to provide the structural features required to mimic the enzymes. Recent Russian work⁴ has demonstrated methane-to-methanol conversion using an iron-porphyrin catalyst; thus, methane-activation catalysts based on the metalloporphyrins are feasible. (3) The computer designed catalysts are then synthesized. (4) The synthetic catalysts are characterized by various spectroscopic techniques including Raman-difference, transient Raman, FTIR, NMR, and UV-visible absorption spectroscopies. We are also using these spectroscopic probes to further structurally characterize some of the enzymes of interest (methylreductase⁵⁻⁷ and heme proteins⁸). (5) The designed catalysts are tested in alkane-oxidation reactions. The activity test results and results of the structural studies are evaluated to obtain structure-activity relationships that form a basis for making further improvements in the catalyst. This feedback procedure gives an iterative method for optimizing catalytic properties.

The reaction catalyzed by the monooxygenase cytochrome P₄₅₀ uses molecular oxygen to oxidize alkanes at ambient temperatures. The reaction may be amenable to molecular engineering techniques that will result in a synthetic methane-oxidation catalyst. The active site of cytochrome P₄₅₀ contains an iron-porphyrin (heme) prosthetic group. Cytochrome P₄₅₀ uses two equivalents of reduced nicotinamide adenine dinucleotide (NADH) to activate molecular oxygen; the resulting high oxidation-state Fe-oxo intermediate then attacks a C-H bond of the alkane by inserting an oxygen atom.

The protein matrix surrounding the iron porphyrin serves to protect and control access to the catalytic site. Because the X-ray crystal structure of cytochrome P₄₅₀ is known, we can use the structure of the active site of the enzyme to guide the design of a synthetic analog specifically engineered for methane activation rather than oxidation of biological substrate molecules. The

X-ray crystal structure of cytochrome P₄₅₀ of *Pseudomonas putida*⁹ shows several features of the active site that might be engineered into a synthetic porphyrin. First, the enzyme has a hydrophobic pocket of the same size and shape as the substrate (camphor). The pocket promotes selective binding of the substrate molecule without axial coordination to the metal. The pocket also orients the camphor molecule so that only a specific carbon atom of camphor is (regioselectively) hydroxylated. Second, the pocket is rigid, thus maintaining its size and shape in the absence of substrate. The pocket's rigidity prevents the enzyme from self oxidation and probably self destruction. Finally, the asymmetric environment of the iron porphyrin in the protein provides a mercapto-sulfur ligand opposite the substrate binding pocket. The electron donating thiolate ligand is thought to facilitate cleavage of the O-O bond, thus, promoting formation of the active oxo intermediate.

To design a homogeneous metalloporphyrin-based catalyst for methane activation, two major problems must be addressed. First, a catalytic center capable of hydroxylating methane with high catalyst-turnover rates is required. This property is determined by the choice of metal, axial ligands, and electronic properties of the porphyrin macrocycle. We are addressing this problem by examining a variety of metalloporphyrin catalysts with a range of alkanes of decreasing molecular weights. The idea is to identify the porphyrins with high activity for the harder-to-oxidize gaseous hydrocarbons, methane in particular. The second major problem is to control which species have access to the active site. Because alkanes bind only via weak van der Waals interactions, detection of alkane binding itself presents a formidable obstacle to experimental studies aimed at determining what species can enter the cavity. One approach is to use comparative studies of the hydroxylation of various alkanes to determine which alkanes can enter the pocket. These studies also provide information about such properties as the size and shape of the pocket and the ability to select the carbon atom at which hydroxylation occurs (regioselectivity).

Here, we report on recent efforts to design, synthesize and test a regioselective alkane-to-alcohol catalyst based on the carboranyl porphyrins. The bulky carboranyl units attached to porphyrins like the one shown in Figure 1 provide a means of controlling the chemistry at the site of O₂ activation and C-H bond addition. By varying the structure of the porphyrin macrocycle and the nature of the connectors between the carborane units and the phenyl rings, a cavity was designed that controls access of various substrates, oxidants, products, and solvents to the reactive metal center. In this way, these porphyrins are being engineered to mimic the active site of cytochrome P₄₅₀.

Experimental Procedures

Materials. The catalysts used in this work include manganese(III) tetra(pentafluorophenyl) porphyrin (MnTpFPPX), where X represents an axial ligand, manganese(III) tetra(2'-carboranylphenyl-anilide) porphyrin chloride (MnTCBPPCl), and the manganese(III)-chloride derivative (MnTDNPPCl) of tetra(2',6'-dinitrophenyl) porphyrin free base (H₂TDNPP). H₂TpFPPCl was obtained from Porphyrin Products and converted to the Mn(III) derivative. The icosahedral carboranyl porphyrin, which was synthesized at the University of California at San Francisco by Stephen Kahl¹⁰ using the Rothmund condensation, was converted anaerobically to the Mn(III)Cl derivative by dissolving it in methanol containing MnCl₂ at room temperature. Isomerization of the carboranylphenyl substituents is not expected under these conditions. H₂TDNPP was synthesized¹¹ using a modification of the method recently reported by Lindsey.¹² Methylene chloride (99+%) was used as the solvent in the activity tests. Methylene bromide or methylene chloride were used in imidazole titration experiments. The oxidant was either O₂ or iodosylbenzene (IOB) prepared from the reaction of iodosobenzene

diacetate with NaOH.¹³ The alkanes used for various tests were cyclohexane (99+%), and n-hexane (99%). Sodium borohydride (NaBH₄) was used as a reductant (analogous to NADH in the cytochrome P₄₅₀ reaction) when O₂ was used as the oxidant. NaBH₄ was obtained commercially and used without further purification. Imidazole (Im) was obtained commercially and purified by distillation.

Reaction Conditions. Reactions with cyclohexane and hexane were performed in the solution phase in an argon atmosphere glove box. Methylene chloride was the solvent. The ratio of reactant:oxidant:catalyst was 1100:20:1 on a mole basis. These reactions were carried out at ambient temperatures (about 30° C) and at atmospheric pressure. Reactants were stirred at 1000 rpm. Reaction times were 2 h. For the run with MnTDNPP, a solution of 3.98 μmoles of the porphyrin and 17.57 mg of iodobenzene in 1.1 ml of methylene chloride and 0.5 ml of cyclohexane was stirred in a glove box for two hours. Product yields were 2 and 9 μmoles of cyclohexanone and cyclohexanol, respectively.

Product Analysis. Oxidation products were identified using gas chromatography/mass spectrometry techniques and quantified using capillary column gas chromatographic techniques with commercially available compounds as standards. Product yields are reported as the number of catalyst turn-overs during the 2 h run. Typically, however, the reaction stops after only 30 min, because the supply of oxidant is exhausted.

Molecular Modeling. CAMD was carried out on an Evans&Sutherland PS390 graphics work station using a MicroVAX II host computer. Three dimensional graphical display and molecular energy-optimization and dynamics calculations were performed using BIOGRAF software (BioDesign).

Results and Discussion

A Mn(III)-carboranyl porphyrin that has some of the structural features of cytochrome P₄₅₀ is shown in Figure 1. The porphyrin (α⁴-MnTCBPP) has all four ortho substituents on the phenyl rings oriented toward the same side of the porphyrin plane (α⁴ isomer). For the α⁴ isomer, the bulky carborane groups at the ends of the 3-atom chain, which links them to the phenyl rings, form a pocket adjacent to the Mn atom in the macrocycle. A possible cavity can be seen in the graphical display of the carboranyl porphyrin (Figure 1). The energy-minimized structure with van der Waals surfaces displayed (not shown) best shows that the pocket exists and is large enough to contain methane and molecular oxygen. Further, the cavity is small enough to prevent other test-system components (e. g. solvent, promoters) from reaching the reactive center. Thus, the carboranyl porphyrin shows potential for providing the size-recognition features required for selective substrate binding. Moreover, molecular dynamics calculations in the presence of model organic solvents (e. g. pentane) show that it is energetically favorable for methane to bind in the pocket of the oxo intermediate. Two features that we would like to tailor into the porphyrin are not yet incorporated. First, the dynamics calculation shows that the carboranyl-porphyrin pocket is not as rigid as we think is required based on the enzyme's X-ray crystal structures.⁹ And, second, P₄₅₀'s thiolate ligand has not been provided, although we have been able to mimic the thiolate ligand with a nitrogenous base (imidazole). Although these two features are not incorporated in an optimum way into the catalyst, nevertheless, experimental studies of the catalyst provide information on how well the cavity controls reactions occurring at the protected site, and, the experimental results obtained using the carboranyl porphyrin can be compared to predictions of the molecular modeling.

One prediction of the molecular modeling studies is that a nitrogenous ligand such as imidazole is too large to coordinate to the metal on the hindered

side of the porphyrin because it sterically cannot fit into the methane binding pocket. Imidazole can still coordinate at the open face of the α^4 isomer, however. In contrast, for porphyrins that are not sterically hindered, such as Mn(III) tetraphenyl porphyrin (MnTPP) and MnTpFPP, both faces of the macrocycle are available for axial ligation of imidazole. Indeed, changes in the uv-visible absorption spectrum of MnTPP and MnTpFPP, obtained as a function of imidazole concentration, show that two imidazole molecules successively coordinate (equilibrium association constants for MnTpFPP with Im in methylene bromide, $\log K_1 = 2.0$; $\log K_2 = 3.1$). On the other hand, the spectral changes for the Mn(III) α^4 -carboranyl porphyrin indicate that only one imidazole molecule binds and that this one-to-one complex is completely formed at 0.1 M imidazole (in methylene chloride, $\log K = 2.5$). For the unhindered porphyrins very little (~20%) of the 1:1 complex is formed before subsequent formation of the 2:1 complex.

One consequence of the lack of coordination of imidazole on the hindered face of the carboranyl porphyrin is that we have successfully mimicked the single axial ligand of the iron in cytochrome P₄₅₀. In the protein, only one thiolate ligand binds because only one ligand is available from the heme's asymmetric protein environment; in the carboranyl porphyrin case only one ligand can bind because of imidazole's lack of access to the small cavity formed by the carborane units. The mimicry of the thiolate ligand of cytochrome P₄₅₀ by an imidazole is good since a single imidazole ligand is known from our work and that of others^{14,15} to promote the catalytic activity of manganese porphyrins.

We can also exploit the formation of the 1:1 imidazole complex with the carboranyl porphyrin to block alkane-activation reactions at the open face of the porphyrin and force the reaction to occur in the cavity. We wish to block the open face because the reaction at this site is not expected to show significant regioselectivity for primary carbons. The bars in Figure 2 illustrate the relative yields of alcohols under various reaction conditions. The first bar on the left shows the yield of hexanols for an unhindered porphyrin, in this case MnTpFPP. The MnTpFPP result is shown for comparison with the α^4 -MnTCBPP tests. (In this case, we have circumvented the use of molecular oxygen as the oxidant by using a single oxygen donor (iodosylbenzene) to generate the active intermediate directly without the use of reductants. The iodosylbenzene oxidant system is more stable and chemically less harsh than the reductant-O₂ system.) When imidazole is absent (second bar in Figure 2), the open face of α^4 -MnTCBPP is available to cyclohexane, which is hydroxylated with a yield comparable to the unhindered porphyrin. The molecular modeling work indicates that the reaction primarily occurs on the open face because neither cyclohexane nor iodosylbenzene have access to the metal site on the sterically blocked face of the carboranyl porphyrin.

The third bar in Figure 2 illustrates that when imidazole is added (0.1 M) the yield is greatly reduced demonstrating that the coordination of imidazole effectively blocks the alkane-oxidation reaction. This result is consistent with our studies of the yield as a function of imidazole concentration for unhindered porphyrins. Such studies show that the complex with imidazole blocking both axial ligand sites is inactive. In the case of the carboranyl porphyrin, one axial position is sterically blocked and the other has imidazole bound; therefore, little activity is observed. A small amount of substrate oxidation might still occur at the open face because of rapid equilibrium of imidazole association and dissociation at the manganese.

The fourth bar illustrates that when hexane rather than cyclohexane is used as the substrate only a trace amount of hexanol is produced. Less hexane is oxidized than cyclohexane (third bar, Figure 2) partly because hexane has two

primary carbons, which are harder to oxidize than the carbons of cyclohexane. However, it is not clear why so little hexanol is produced relative to cyclohexanol. One might have expected some hexane oxidation since CAMD techniques show that the end of the hexane molecule could reach the protected metal site. However, molecular modeling also suggests that the oxo intermediate cannot be formed in the pocket because iodocyclohexane cannot readily reach the manganese atom.

Finally, if molecular oxygen, which can enter the pocket, is used as the oxidant, then we might expect some hydroxylation of hexane with regioselectivity for the primary alcohol. The fifth bar in Figure 2 shows the yield of hexanols obtained when O_2 is used as the oxidant. In this test sodium borohydride is used to reduce the catalyst, which then binds O_2 . This species is subsequently reduced again yielding the active manganese-oxo intermediate. The total yield of hexanols is minute primarily because the $NaBH_4-O_2$ system rapidly destroys the catalyst,¹⁶ as shown by the rapid bleaching of the porphyrin absorbance during the reaction. Another reason for the low yield is that it is statistically unlikely for the end of the hexane molecule to work its way into the cavity. Nevertheless, some activity is observed. Preliminary results (not shown) indicate that the yield of primary alcohol (1-ol) increases relative to the secondary alcohols (2-ol and 3-ol) when compared to an unhindered porphyrin (first bar). A less harsh O_2 activation reaction than the $NaBH_4$ system is necessary to increase the yield. Preliminary estimates of the primary regioselectivity for the $MnTCBPP$ -imidazole- $NaBH_4-O_2$ system appears to compare favorably with hydroxylation of hexane by the bis-pocket porphyrin, $Mn(III)$ tetra(triphenylphenyl) porphyrin,¹⁷ also a size selective catalyst. The primary regioselectivity of the latter porphyrin is better than for some cytochromes P_{450} ,¹⁸⁻²⁰ showing that a synthetic catalyst can be as regioselective as the enzyme itself.

One way to solve the problem of protecting the open face of the carboranyl porphyrins is to synthesize a porphyrin having no open faces. One possibility is the *di-ortho-phenyl* analog of the carboranyl porphyrin, which is shown in Figure 3. Recently, we have succeeded in synthesizing the precursor of this class of bis-deep-pocket porphyrins, namely H_2TDNPP and its diamino derivative.¹¹ Efforts are underway to synthesize several bis-deep-pocket porphyrins based on H_2TDNPP .

The manganese(III) derivative of $H_2TDNPPCl$ is interesting in its own right as a potential methane-activation catalyst because (1) it provides shallow cavities at the metal on both faces of the macrocycle and (2) the iron derivative of the related mono-nitro-phenyl-porphyrin has recently been reported to activate methane.⁴ We have not yet tried to oxidize methane with $MnTDNPP$, but we have demonstrated that $MnTDNPPCl$ has catalytic activity for converting alkanes to alcohols as demonstrated by the oxidation of cyclohexane. Turnover numbers for the 2-h run were 0.5 for cyclohexanone and 2.2 for cyclohexanol. Uv-visible absorption spectra at the end of the run showed the presence of a $Mn(IV)$ or $Mn(V)$ porphyrin intermediate species, thus, indicating that the reaction had probably not run to completion.

Conclusions

We have shown that the chemistry occurring at the open face of the deep-pocket porphyrin can be controlled by axial ligation, which forces the reaction to take place in the cavity. Preliminary tests indicate regioselectivity of alkane oxidation by a manganese(III) deep-pocket porphyrin in a reaction using O_2 as the oxidant.

MnTDNPP, a precursor in the synthesis of deep-pocket porphyrins with the pockets on both faces of the porphyrin, has been synthesized and its manganese derivative was shown to be active in alkane oxidation. MnTDNPP may also be interesting from the point of view of methane and ethane activation.

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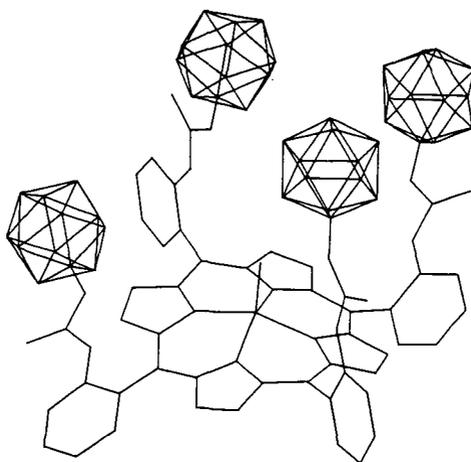


Figure 1. Oxo-metallo- α^4 -tetra(2'-carboranylphenyl-anilide) porphyrin. Energy minimized BIOGRAF structure (not global minimum).

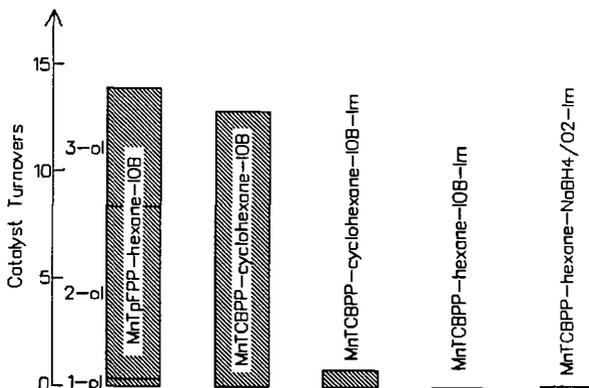


Figure 2. Alkane hydroxylation by designed Mn(III)- α^4 -tetra(2'-carboranylphenyl-anilide) porphyrin catalyst.

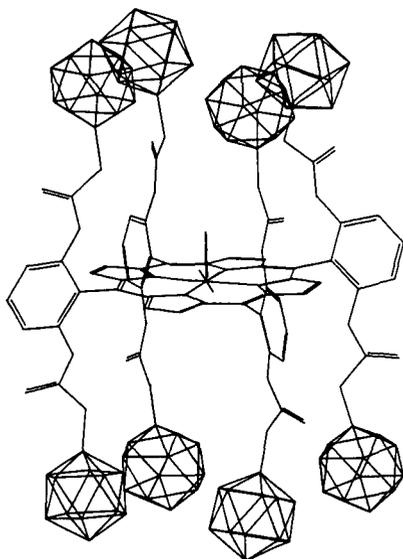


Figure 3. Example of a bis-deep-pocket carboranyl porphyrin that can be synthesized from tetra(2',6'-dinitrophenyl) porphyrin. BIOGRAF structure not fully energy minimized.