Pure & Appl. Chem., Vol. 65, No. 3, pp. 367–372, 1993.
Printed in Great Britain.

Doing chemistry in the second ring of a fused macrobicyclic ligand – substrate oxygenations by transition metal cyclidenes

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Abstract

The transition metal cyclidene complexes open the possibility of organizing multiple aspects of monooxygenase catalysis by providing specific receptors for both the activated center and the substrate within a second ring of a macrobicyclic ligand. The ability of the Fe, Mn, and Cr cyclidenes to mimic cytochromes P450 closely parallels that of porphyrins, but it is difficult to produce activation within the cavity using surrogate oxidants. The bound O_2 of the cobalt(II) complex is the oxidant in well known phenol oxidations and this has provided further insights into doing chemistry within the cavity of the ligand and into the radical mechanism of that reaction.

INTRODUCTION

A broad gap exists in the level of complexity and intricacy between the natural systems that bioinorganic and bioorganic chemists mimic and the synthetic systems those investigators study. The broadly occurring cytochromes P450 illustrate these relationships.[1] In order for P450 to function (a) the substrate must bind; (b) dioxygen must bind; (c) a cofactor must donate an electron to the dioxygen complex; (d) proton(s) (or alternate electrophile) must be delivered to bound peroxide; (e) the O-O bond must cleave; (f) a hypervalent iron compound must form and then deliver an oxygen atom to the substrate. Attempts to recreate the natural cycle in synthetic systems[2] dramatize the subtlety of the organization of the molecular events in vivo. Each of the steps has been mimicked at some quality level, but it has proven difficult to link them together. Dioxygen and substrate binding are, of course, commonplace; reduction of bound O_2 has produced peroxo-iron(III) complexes;[3] peroxides and other surrogate oxidants have been used to form hypervalent metal ion species and to drive metal promoted substrate oxidations. But, going back to dioxygen activation, in synthetic systems, typically those involving substituted porphyrins, the cofactor that activates the dioxygen also competes as a substrate and, in most cases, the added complication of an axial ligand places that species in competition with substrate and dioxygen. The problem is one of organization, and superstructured macrocycles, e.g., macrobicyclic ligands, have provided a basis for early attempts to organize the various critical events.[4]

OXYGENATIONS BY IRON, MANGANESE, AND CHROMIUM CYCLIDENES

The macrobicyclic cyclidene ligands (**Fig. 1**) have been used for extended studies on O_2 complexes, detailing the relationships between the size of the cavity created by the second ring and reactions.[5] Enlarged cavities have made possible the binding of organic molecules,[4] potential substrates, using the same complexes that bind O_2, and these species have been instrumental in demonstration of a cobalt-based model of the P450 ternary complex

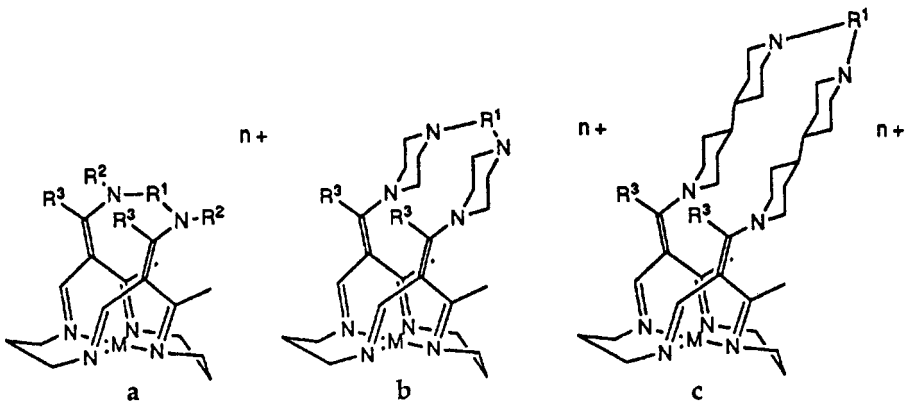

Figure 1. Structures of the cyclidene complexes: a) lacunar; b) vaulted; c) supervaulted.

(enzyme:O_2:substrate). Here we report partially functional cytochrome P450 models based on transition metal cyclidenes. The cyclidenes are particularly attractive models because (1) they are the only well established synthetic non-porphyrin iron dioxygen carriers, (2) a credible cyclidene model for the P450 ternary complex has already been produced, and (3) the cavity of the cyclidene should facilitate highly specific oxygenations.

In the solvents acetonitrile, acetone, water and mixtures with water, including 1:1:1 acetone:pyridine:water, we have shown that surrogate oxidizing agents do indeed cause the cyclidenes to oxygenate an array of organic substrates, including syrene, 2- and 4-vinyl pyridine, toluene, cyclohexene, cyclohexane and methylcyclohexane. Eleven cyclidenes of various cavity sizes were used, ranging from the highly restricted trimethylene and tetramethylene bridged derivatives, through the vaulted complexes to unbridged species. Referring to **Fig. 1** and using the ligand abbreviation $LR^1R^2R^3$ (where Cn for R^1 refers to the length of a bridging polymethylene chain and L, to a small *lacunar* cavity), the main complexes studied are [Fe(LC3MeMe)Cl], [Fe(LC4MeMe)Cl], Fe(LC6MeMe)Cl], [Fe{L(m-xylene)MeMe}Cl], [Fe{V(3,6-durene)Me] (V stands for the larger *vaulted* cavity, **Fig. 1b**), [Mn{L(m-xylene)MeMe}Cl], [Mn{U(piperidine)Me}Br] (U stands for an unbridged or open structure and R^1 and R^2 are parts of piperidines), [Mn{U(piperidine)Ph}Br], [Cr{V(3,6-durene)Me}Cl], and [Cr{U(piperidine)Me}Cl]. Using iodosobenzene in acetonitrile, all complexes showed some activity toward all substrates with yields ranging from 2% to 4100% based on catalyst concentration;, the latter clearly indicating catalytic activity. The manganese complexes uniformly gave the best overall yields. Since Valentine and associates[6] have shown that simple metal salts are capable of catalyzing epoxidations of olefins in the absence of such elaborate ligands as cyclidenes or porphyrins, styrene was treated with PhIO in the presence of $FeCl_3$ under the same conditions. Both benzaldehyde and styrene oxide were formed but at less that 1% of the yields observed using macrocyclic derivatives.

Cyclohexane oxygenation showed the powerful nature of the activated cyclidene, giving cyclohexanol and cyclohexanone in 2 to 107% yields, along with small amounts of halide. The halogenated products could be increased greatly by addition of a halogen source. With cyclohexane-d_{12}, [Mn(LC4MeMe)Cl], and PhIO, a kinetic isotope effect $k_H/k_D=3.0\pm0.3$ was obtained, much less than the value of 12.9 found for [Fe(TPP)Cl] with cyclohexane, but suggesting C-H bond breaking and hydrogen abstraction.[7] As expected with methylcyclohexane, the tertiary hydrogen was the primary target in all cases, with hydroxylation yields ranging from 62% to 92%, based on products. The unbridged manganese complexes hydroxylate the methyl in sufficient yield to indicate some orienting effect. With styrene and cyclohexene, epoxidation was the dominant reaction (60-97%) with relatively little product from side reactions. The generallly greater selectivity of the manganese complexes is consistent with the "reactivity-selectivity principle".[8]

The occurrence of highest yields of oxygenation products with the catalysts having the smallest cavities clearly shows that the activation by the metal ion site occurs outside the cavity, a result that was not surprising since (1) the solvent (acetonitrile) obviates the hydrophobic driving force for guest binding within the cavity, and (2) the oxygen transfer agent PhIO is polar while the cavity is apolar so that activation probably occurs at the extra-cavity metal ion site.

The oxidation of toluene with H_2O_2 in aqueous solution gives persuasive evidence for reaction within the cavity; the ratio of aromatic vs methyl hydroxylation increased regularly with cavity size. Studies with mixtures of 2- and 4-vinyl pyridines as substrates, using mixed water/acetonitrile and iodosobenzene were made in attempts to force the reaction into the pocket by ligating the external axial site with excess vinyl pyridine, and it was found that increasing the proportion of water in the solvent favored 4-vinyl pyridine oxidation, further supporting intra-cavity reaction.

Extensive studies have shown that oxygenation catalysis by cyclidene complexes is limited by oxidative destruction of the ligand, a result anticipated by earlier electrochemical studies[9] and by parallel autoxidation studies on the complexes.[10] A general indication is the fact that manganese complexes give the greatest yields whereas the reactivity should vary in the series Fe>Mn>Cr. Further, the yield of oxidation products decreases monotically with the decrease in reactivity of the substrate. Proof has come through isolation and characterization of both major fragments of the cyclidene destruction, which occurs by oxidative cleavage of the vinyl substituents.

Finally, no substantial success has come from dedicated efforts to autoxidize organic substrates, beginning either with dioxygen or with the peroxo complexes that can be formed from the dioxygen adducts. Tantalizing traces of products and irreproducible results have been encountered. Varieties of solvents, reducing agents and nucleophiles have been used in the studies.

In conclusion, the cyclidene complexes of iron, manganese, and chromium are competent catalysts for the oxygenation of the full range of substrates recognized for cytochromes P450 and its porphyrin-based mimics. The same surrogate oxidants are effective for these complexes and the products are consistent with the presence of a hypervalent metal ion in the activated state. Under a variety of conditions, the reaction appears to occur within the cavity, but that aspect of the system is not fully under control. Yields are limited by the decomposition of the activated complex, a matter under investigation with a view toward extending catalyst life. Oxygenations via the native oxidants remain elusive.

OXYGENATIONS BY COBALT CYCLIDENES

Cobalt cyclidene dioxygen adducts oxygenate phenols in accord with a radical mechanism that has been much studied.[11] The usual mechanistic model provides an excellent opportunity to test for the effects of cavities on substrate oxidation reactions, and reciprocally, the influence of the cavity on the reaction provides tests of the mechanism. Figure 2 summarizes the mechanism, indicating the points of entry of the dioxygen adduct into the process: (1) the initiating 1-electron oxidation occurs between the O_2 adduct and the phenol, possibly in the rate determining step, and (2) a second mole of O_2 adduct captures the phenoxy radical in a peroxo complex. Heterolytic cleavage of the O-O bond in the peroxo complex gives the quinone and a cobalt(III) complex that also participates in the redox reactions. 2,6-Di-t-butylphenol served as substrate for most of the studies and the catalysts included [Co(MeV(2,6-durene))], [Co(LMeMeMe)], [Co(LC4MeMe)], [Co(LC5MeMe)], [Co(LC6MeMe)], [Co(LC7MeMe)], and [Co(LC8MeMe)]. Product analysis shows that closing down the O_2 binding site by decreasing the cavity size leads to increased relative yields of the radical coupling product (tetra-t-butyldiphenoquinone), confirming that the participation of the

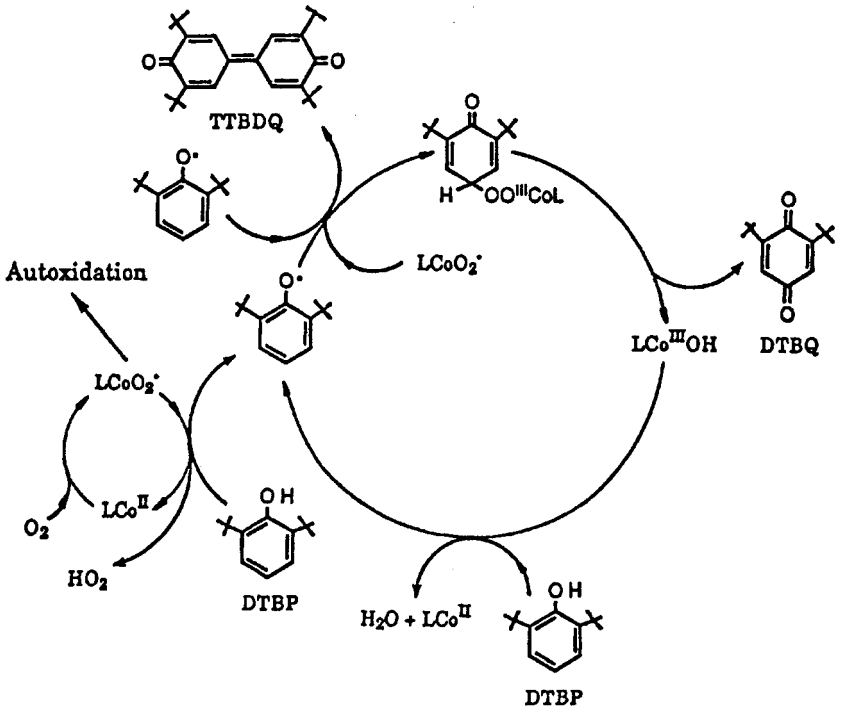

Figure 2. Reaction mechanism for oxygenation of 2,6-di-*t*-butylphenol by the dioxygen adducts of cobalt cyclidenes.

cobalt complex is critical to selective formation of the quinone. Increasing the concentration of the catalyst also increases the yield of quinone, while adding a strong axial base decreases the yield, as expected on the basis of competition between catalyst oxidation of the radical and radical coupling.

Reaction of [Co{MeV(2,6-durene)}O_2] with the spin trap phenyl-N-butylnitrone produced the characteristic ESR spectrum of the species [Co{MeV(2,6-durene)}OOPBN], thereby establishing the ability of the cobalt-bound dioxygen to enter into radical reactions, even though the reactive center is within the cavity. The most dramatic result from O_2 uptake measurements is the failure of dioxygen in small cavities (C4) to participate in the catalytic process. Further, the next larger cavity (C5) shows only meager catalysis before catalyst autoxidation terminates the reaction, in accompanyment to the evolution of the excess bound O_2. Further increases in cavity size lead to increased yields of the catalysis products, a result that is generally traceable to the competition between catalytic oxidation of the substrate and irreversible oxidation of the catalyst itself. This is strongly supported by comparison of rate data for the vaulted complex [Co{MeV(2,6-durene)}O_2] and the completely open structure [Co(MeMeMe)]. The initial rates of dioxygen uptake are the same, within experimental error, for the two complexes, 7.1×10^{-3} and 6.0×10^{-3} mmole/min respectively, but the ratio of the yields of catalysis products (4.3) is very close to the ratio of the rates of autoxidation[12] of the two catalysts (4.0).

Kinetic studies on the rate of O_2 uptake show simple first order dependence on the concentration of the cobalt catalyst, but the dependence on substrate concentration obeys saturation kinetics with $k_{cat} = 0.27$ min^{-1} and $K_m = 0.023$ M, in accord with a Menton-Michaelis model for the catalytic process. The dependence on the dioxyen pressure gave a tentative and unexpected 3/2 order dependence, a result that may suggest a more complicate rate determining process. The experimental rate law is given in the equation below.

$$d[O_2]/dt = \{k_{cat}\,[CoMeVD][DTBP](P_{O_2})^{3/2}\}/(K_m + [DTBP])$$

The results of molecular mechanics[12] and NMR relaxation[4] studies strongly suggest that the encounter complexes of the dioxygen adduct with the phenol will favor approach of the oxidant to the aromatic **PI** system, rather than to the phenolic hydrogen atom. Further, estimation of the ionization potentials[13] of phenols having 2,6-disubstitutents lead to the sequence H>MeO>Me>t-Bu, as expected on the basis of electronic properties,[14] and consistent with the selectivity of the present catalyst system. The cobalt cyclidene complexes fail to produce catalytic autoxidation of 2,6-dimethylphenol and only traces of product with 2,6-dimethoxyphenol. The OH bond energies for the substituted phenols do not anticipate much selectivity.[15,16] The suggestion that the primary oxidation event is electron transfer is also consistent with the results of electrochemical studies[17] and spin density calculatio-ns.[16]

Summarizing, the study of cobalt cyclidenes of various cavity sizes as catalysts for the autoxidation of phenols provides strong confirmation of the participation of the dioxygen adduct at (1) the initial oxidation step and (2) in the oxidation of the phenoxy radical to the quinone. Alterations in cavity size can moderate or even stop either or both functions. The catalysts are highly selective, reacting with 2,6-di-t-butylphenol while showing little or no reactivity toward 2,6-dimethyoxyphenol and 2,6-dimethylphenol. This selectivity and a number of other considerations are consistent with electron transfer as the initial oxidation event. Overall product yield is limited by destruction of the catalyst. The rate law is generally compatible with the commonly proposed mechanism, but additional complexity is suggested by the apparent order with respect to $[O_2]$.

Acknowledgement

The support of the National Science Foundation and The National Institutes of Health is gratefully acknowledged.

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