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Communications

Mechanisms in a Biomimetic Hydroxylation of a Chemical Probe: 5-Nitroacenaphthene[1]

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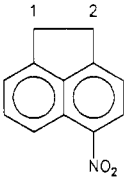
Summary: 5-Nitroacenaphthene is hydroxylated by oxometalloporphyrin complexes of chromium, iron, and manganese via hydrogen atom abstraction pathways with charge separation in the transition state dependent on the electrophilicity of the oxygen atom in these model oxygenases.

Cumulative evidence strongly suggests the intervention of free radicals in hydroxylation (oxidation) reactions catalyzed by the enzyme cytochrome P450[2] as well as by oxometalloporphyrin complexes[3] of iron,[4,5] manganese,[6,7] and chromium,[8,9] but debate continues over the mode of formation of these intermediates.[10,11] Radical cations seem to be logical precursors for substrates with low oxidation potentials[12,13] (reaction 1), whereas hydrogen atom abstraction by the well-characterized oxometal species (M^{V}=O) may be the preferred pathway for others[14] (reaction 2; $P^{\bullet+}$ stands for a porphyrin or protein radical cation).

$$P^{\bullet+}Fe^{IV}{=}O + RH \rightarrow PFe^{IV}{=}O + RH^{\bullet+} \rightarrow PFe^{IV}OH + R^{\bullet} \quad (1)$$

$$P^{\bullet+}Fe^{IV}{=}O + RH \rightarrow PFe^{IV}OH + R^{\bullet} \quad (2)$$

In an effort to distinguish between the two mechanistic alternatives as well as to quantitatively assess the significance of charge transfer in the transition states of these hydroxylation reactions, we have examined the reactions of a chemical probe, 5-nitroacenaphthene (1), with several oxometallotetraphenylporphyrin chlorides, O=M(TPP)Cl (M = Cr, Fe, Mn; TPP = tetraphenylporphyrin), generated by the reaction of corresponding M^{III}(TPP)Cl with iodosobenzene (PhIO).



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The regioselectivity in reactions at the side chain of 1 reflects the mechanism involved in the activation pathway. We find that electrophilic radicals abstract hydrogen atoms preferably from carbon 1, whereas deprotonation from the radical cation of 1 occurs preferentially from carbon 2. This is evident from the fact that photochlorination of 1 with *t*-BuOCl in presence of trichloroethylene (added to suppress chlorine atom chains[15]) yields 1-chloro-5-nitroacenaphthene (1-RCl) and 2-chloro-5-nitroacenaphthene (2-RCl) in the ratio 1-RCl:2-RCl = 1.6. Apparently rate-determining hydrogen atom abstraction by the electro-

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Table I. Oxidation of 5-Nitroacenaphthene[a]

catalyst	% yield[b] 1-ROH	2-ROH	1-RCl	2-RCl	S[c]
Cr(TPP)(Cl)	52.8	17.7	16.5	4.6	3.11
Fe(TPP)(Cl)	50.3	22.0	14.3	5.5	2.35
Mn(TPP)(Cl)	22.1	11.4	34.3	20.6	1.76

[a] Reaction in 10 mL of CH_2Cl_2 with 0.25 M 5-nitroacenaphthene, 0.05 M PhIO and 5.0 mM M^{III}(TPP)(Cl) under argon at 37 °C for 30 min was followed by ether precipitation. [b] Yields based upon recovered 5-nitroacenaphthene. [c] Selectivity parameter, S = [1-ROH] + [1-RCl]/[2-ROH] + [2-RCl].

philic[16] t-BuO• is preferred from carbon 1 possibly due to a greater stabilization of the positive charge at this position in the polar transition state.[17,18] In contrast, one-electron photooxidation of 1 with ceric ammonium nitrate (CAN)[19] yields a mixture of 1-$RONO_2$ and 2-$RONO_2$ which upon reduction with $LiAlH_4$ (LAH) affords 1-hydroxy-5-nitroacenaphthene (1-ROH) and 2-hydroxy-5-nitroacenaphthene (2-ROH) in the ratio of 2-ROH:1:ROH = 5.8. This suggests that rate-determining deprotonation from the initially generated radical cation of 1 occurs preferably from carbon 2. Thus the regioselectivity in hydroxylation of this probe by oxometalloporphyrin complexes should reflect the mechanism involved in these reactions.

In a typical oxidation, 2.5 mmol of 5-nitroacenaphthene and 0.05 mmol of M^{III}(TPP)Cl were stirred with 0.5 mmol of PhIO in 10 mL of CH_2Cl_2 under argon at 27 °C for 30 min, and the reaction mixture was quenched by addition of 30 mL of diethyl ether to precipitate metal complexes and unreacted PhIO. Under our conditions, oxidation of 5-nitroacenaphthene yielded 1-ROH, 2-ROH, 1-RCl, and 2-RCl with >90% mass balance. The product yields, based upon recovered 5-nitroacenaphthene and estimated by GC, are listed in Table I. The reported yields are averages of several different runs under identical conditions.

The selectivity parameter:

$$S = [1\text{-ROH}] + [1\text{-RCl}]/[2\text{-ROH}] + [2\text{-RCl}]$$

gives the relative reactivity of the two side chain carbon atoms of 1 and is >1 in all the runs, suggesting a hydrogen atom abstraction pathway through a polar transition state (vide supra) in the reactions of this high oxidation potential substrate with all the metalloporphyrins (reaction 3).[20]

Oxygen rebound from the metal-coordinated hydroxyl "radical" to the substrate radicals (reaction 4) may yield the hydroxylated products. Though hydroxylation occurs predominantly in the reactions with iron and chromium porphyrins, chlorination is preferred with manganese porphyrin (1-RCl + 2-RCl = 54.9%). Halogenated products have been observed previously[21] in oxidation reactions of cyclohexane, isobutane, and *tert*-butylbenzene with oxomanganeseporphyrin complexes and may result from cage escape leading to free alkyl radicals in solution[22] (reaction 5). Oxygen rebound from the iron coordinated hydroxyl "radical" is known[13] to occur very rapidly with rates of the order of 10^8 s^{-1} and thus it is not surprising that hydroxylation is the major pathway for this porphyrin complex. Apparently oxygen rebound from the manganese coordinated hydroxyl "radical" is considerably slower and thus cage escape competes effectively.

$$RH + (Cl)(TPP)M^{V}{=}O \rightarrow [R^{\delta+}\cdots H\cdots{}^{\delta-}OM(TPP)(Cl)] \rightarrow [R^{\bullet}, HOM^{IV}(TPP)(Cl)] \quad (3)$$

$$[R^{\bullet}, HOM^{IV}(TPP)(Cl)] \rightarrow ROH + M^{III}(TPP)(Cl) \quad (4)$$

$$[R^{\bullet}, HOM^{IV}(TPP)(Cl)] \rightarrow R^{\bullet} + HOM^{IV}(TPP)(Cl) \rightarrow RCl + ROH \quad (5)$$

The selectivity parameter, S, is a measure of the difference in free energies of activation for atom abstraction from carbon 2 and carbon 1. Since this difference should be dependent on charge separation in the transition state (large separation of charge in the polar transition state would result in a large difference in the free energies of activation), S should also reflect the degree of polarity in the transition states of these atom abstraction reactions. The value of S decreases from S = 3.11 for M = Cr to S = 2.35 for M = Fe and S = 1.76 for M = Mn. This suggests that the electrophilicity of the oxygen atom in these model oxygenases decreases in the order $Cr^{V}{=}O > Fe^{V}{=}O > Mn^{V}{=}O$, which is in accord with the order of force constants of the M=O bonds, K_{MO} (m dyne/Å) = 7.58 (Cr), 5.21 (Fe), 4.15 (Mn), determined from the resonance Raman M=O stretching frequencies[23] for these complexes.

These results and concusions may explain the observed differences in reactivity and selectivity in the oxidation and epoxidation reactions catalyzed by these model oxygenases[23] as well as different biological functions associated with cytochrome P450 in mammals and the chloroplast photosystem in plants[24]. We are currently developing other chemical probes (e.g. 5-methoxyacenaphthene, 5-cyanoacenaphthene, 4-nitrobibenzyl, etc.) to further explore the structure–activity relationships in these biomimetic systems.

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