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Steric Effects and Selectivity in the Benzylic Hydroxylation by Metalloporphyrins and by the Fungus *Mortierella Isabellina*

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Abstract: *The role of steric effects in the biomimetic and enzymatic benzylic hydroxylation is assessed by comparing inter- and intramolecular selectivity of these reactions.*

Cytochromes P-450 are a family of isozymes capable of monoxygenase activity leading, among other reactions, to alkane hydroxylation.[1] Since all these isozymes have iron protoporphyrin IX as their prosthetic group,[1] synthetic metalloporphyrins have been widely employed to mimic the enzymatic activity of cytochrome P-450,[1,2] and reactivities comparable to those of the latter have indeed been verified for alkane hydroxylation.[3,4]

The commonly accepted mechanism for cytochrome P-450 and metalloporphyrins-catalyzed aliphatic or benzylic hydroxylation[1,2] is shown in Scheme 1. It involves rate limiting hydrogen atom abstraction from the substrate by a porphyrin iron(V) oxo-complex ($TPPFe^{V}=O$ in Scheme 1), followed by oxygen rebound.

$$ArCH_3 \xrightarrow[-\ TPPFe^{IV}\text{-}OH]{TPPFe^{V}=O} ArCH_2\cdot \xrightarrow[TPPFe^{III}]{TPPFe^{IV}\text{-}OH} ArCH_2OH$$

Scheme 1

However, in spite of the enormous amount of work carried out in this area, only very few systematic studies have concerned problems of steric effects and selectivity, particularly in the oxidation of alkylaromatic compounds. We have began to address this problem, and here we now report on the determination of the *intra*- and *inter*molecular selectivity of hydroxylation of secondary encumbered *vs.* primary benzylic positions under biomimetic and enzymatic catalysis. In particular, we have studied the relative reactivity of hydroxylation of neopentylbenzene (NPB) and of ethylbenzene *vs.* toluene (TOL), and the 2 -C-H *vs* 1 -C-H relative reactivity in the hydroxylation of *p*-neopentyl- toluene and of *p*-ethyltoluene. As oxidizing systems, we have used iron(III)- and manganese(III)tetraphenyl-porphyrin chloride (TPPM; M = Fe or Mn), in the presence of PhIO,[5] and also the fungus *Mortierella Isabellina*, which contains enzymes whose active site is very similar to that of cytochrome P-450.[6] For comparison purposes, some experiments of free radical bromination have also been carried out. All the results are collected in Table 1.

By comparing the columns 2 and 3 in the Table, it clearly turns out that for both the reactions induced by

FeTPP and by MnTPP the 2 C-H/1 C-H reactivity ratios, $k(CH_2R)/k(CH_3)$, determined by the ethylbenzene/toluene and neopentylbenzene/toluene relative rates of oxidation, are significantly higher when R = Me than when R = *t*-Bu (10 *vs* 0.7 with FeTPP and 15 *vs* 0.6 with MnTPP).[7] This clearly indicates the presence of steric interference to the approach of the porphyrin catalyst to the bulky CH_2-*t*-Bu group, which results in a 14-30 fold depression of the reactivity of this secondary benzylic position of NPB with respect to the corresponding more accessible one of ethylbenzene. The fungus *Mortierella Isabellina* exhibits a still larger depression (*ca.* 70), but part of it may be due to differences in the enzyme-substrate complexation constants. Very surprisingly, however, the magnitude of the observed depression in the 2 -C-H/1 -C-H reactivity ratios is not significantly different from that found (*i.e.*, from 25 to 0.5) in the free radical bromination of the same compounds with N-bromosuccinimide in CCl_4, induced by AIBN. Thus, it would appear that the approach of the bulky porphyrin metal oxo-complex to the secondary benzylic position of the substrate is influenced by steric effects to an extent similar to that of the much smaller bromine atom from NBS. As a tentative explanation, a loose interaction between aromatic substrate and the metalloporphyrins oxo-complex in the transition state may be suggested.

When the $k(CH_2R)/k(CH_3)$ reactivity ratios have been obtained by *intra*molecular experiments, once again a decrease in these ratios has been obseved as we move from R = Me (*p*-ethyltoluene) to R = *t*-Bu (*p*-neopentyltoluene) (compare columns 4 and 5 in Table 1). However, whereas for the reaction with NBS the magnitude of this reduction (from 21 to 0.5) is almost identical to that determined in the related competitive *inter*molecular experiments (from 25 to 0.5), the variations are significantly smaller for the *intra*molecular biomimetic and enzymatic reactions, the $k(CH_2R)/k(CH_3)$ ratios for the change R = Me $\Rightarrow$ *t*-Bu going from 8 to 1.5 with FeTPP, from 6 to 1.3 with MnTPP, and from 5 to 1.3 with the fungus *M. Isabellina*. It is really remarkable that, when determined by intramolecular selectivity studies, the effect of the steric requirements of R on the reactivity of a benzylic CH_2R group in biomimetic and enzymatic oxidations turns out to be quite small in absolute, and in particular with respect to what is found in the intermolecular competition experiments. It is likely that in these reactions the role of steric hindrance to the approach of the reagent is reduced by some compensating factor, which reveals itself only in intramolecular selectivity studies. We suggest that this factor is represented by the *remote steric effects* exerted by the neopentyl or by the methyl group when *p*-NPT approaches the reactive species, being parallel to the perferryl group.[3] Accordingly, when this approach takes place with the methyl group pointing toward the oxygen of the iron oxo-complex, so to allow H-abstraction (see Figure 1), the bulky neopentyl group is in a position where non-bonded interactions with the porphyrin ring and/or substituents are likely to be significant. *Vice versa* the opposite approach, with the secondary C-H bonds of the neopentyl group pointing toward the metal oxo-complex, would position the methyl group backwards, resulting in less severe steric interactions with the porphyrin ring. This would cause shape recognition of the *p*-NPT molecule, so to "enhance" the functionalization at the secondary encumbered position with respect to the methyl group, even in the presence of an *intrinsic* steric hindrance to its reactivity, as manifested by the intermolecular selectivity experiments. Of course, the model shown in Figure 1 essentially holds for the oxidations promoted by the synthetic metalloporphyrins. With the enzyme the situation might be different, even though the very close values of the intramolecular selectivity of enzymatic and biomimetic oxidations indicate that the two systems may exhibit comparable features.

Table 1. Selectivity Determinations (2°CH/1°CH) for Benzylic Positions from Various Reactions.[a]

	intermolecular selectivity[b] $^{k}C_6H_5CH_2R/^{k}C_6H_5CH_3$		**intramolecular selectivity**[c] $^{k}p\text{-}MeC_6H_4CH_2R$	
reaction	R=*t*-Bu	R=Me	R=*t*-Bu	R=Me
FeTPPP[d]	0.7	10	1.5	8
MnTPP[d]	0.6	16	1.3	6
NBS[e]	0.49	25[f]	0.51	21[g]
M. Isabellina[h]	0.06	4	1.3	5

[a] Corrected for the number of equivalent H-atoms. Typical errors: ±4%; GLC determinations.
[b] Determined from competition experiments by the relative amounts of $PhCHOHR$ and $PhCH_2OH$.
[c] Reckoned by the relative amounts of $p\text{-}MeC_6H_4CHOHR$ and $p\text{-}HOCH_2C_6H_4CH_2R$.
[d] Hydroxylation by metalloporphyrins with PhIO in benzene.
[e] Bromination in CCl_4.
[f] From ref 8.
[g] From ref 9.
[h] Enzymatic hydroxylation in water.

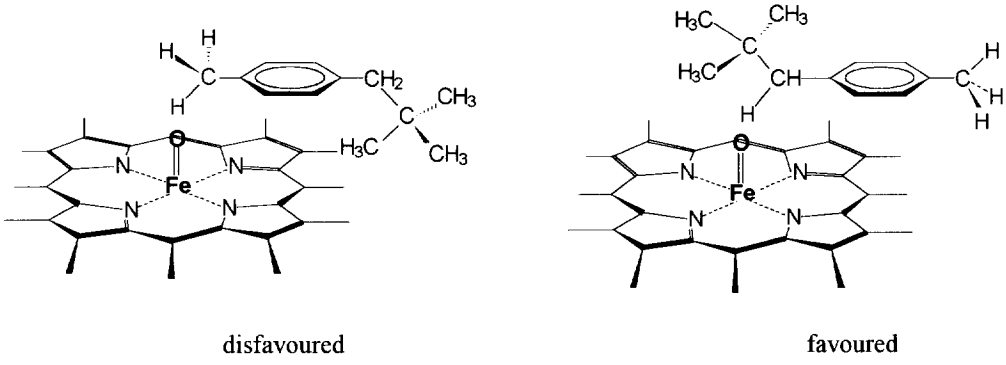

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Figure 1. Proposed effect of remote substituents.

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