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Characteristic Effect of Pyridine on the NIH Shift and Selectivity in the Monooxygenation of Aromatic Compounds Catalyzed by a Nonheme Iron Complex/Hydroquinones/O_2 System

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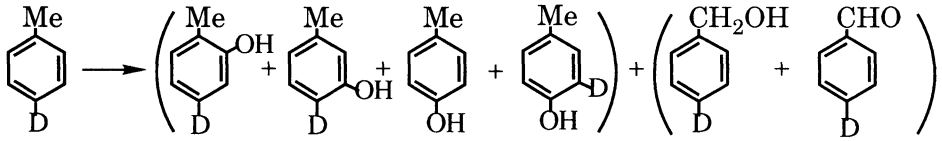
The high values of the NIH and Me-NIH shifts were observed in the hydroxylation of aromatic compounds such as toluene and xylenes with O_2 by the catalytic system in the title. The pyridine concentration greatly affected not only the NIH shift, but the selectivity to form phenols by hydroxylation of the aromatic ring and to form aldehydes by oxidation of the methyl group.

Monooxygenation of hydrocarbons with activation of molecular oxygen is of current interests and very important both in the fundamental and industrial chemistry. Many monooxygenase model systems have been studied in the aim of developing new catalytic systems and of understanding the mechanism of the enzymatic reactions. As seen from the function of methane monooxygenases, nonheme iron systems are expected to give high activity for oxygenation of various inactive hydrocarbons with molecular oxygen, though the identification of the active species may be more difficult than the heme systems. Oxygenations by tri-iron[1] and di-iron[2,3] complexes have been developed in relevance to methane monooxygenases that include two irons, but our interest is to develop the monoiron model systems. Previously we have reported monooxygenation of aromatics[4,5] and saturated hydrocarbons[6] by the catecholatoiron complex/hydroquinone system. Characteristic of the system is the usage of hydroquinones as proton and electron donors, which are essential for the oxygen activation in the similar fashion to monooxygenases. The system exhibits the different reactivity from other systems using Zn/acetic acid,[1] Zn/hexafluoroacetylacetonate,[2] PhNHNHPh/ṖhCOOH.[7] This report is to show the high values of the NIH shift observed in the oxygenation of toluene and xylenes and the remarkable effect of pyridine on the selectivity. The NIH shift is a common feature of aromatic hydroxylation by monooxygenases, but little is studied in the nonheme iron model complexes/O_2 system.[8]

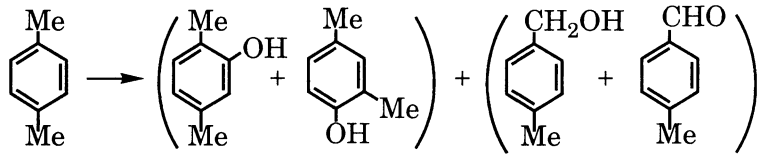
Reaction was performed by stirring $FeCl_3$ (0.1 mmol), pyrocatechol (0.1 mmol), 2,5-di-t-butylhydroquinone (DTBHQ, 6 mmol), pyridine (0.2 mmol), toluene-4-D or xylenes (2.5 cm^3), and acetonitrile (5.0 cm^3) under 1 atm O_2 at 25 °C. The reaction was also performed in pyridine (5.0 cm^3, 620 mmol) in place of acetonitrile. $FeCl_2$ and $Fe(Py)_4Cl_2$ (Py denotes pyridine) were also used in place of $FeCl_3$. Products were quantitatively analyzed by GLC with using a 25 or 50 m capillary column and by GC-MS. The D content in toluene-4-D and p-cresol-3-D was estimated based on the relative peak intensity of m/e=91, 92, 93 for the former and 107, 108, 109 for the latter.

Table 1 shows the results of oxygenation of toluene-4-D and o-, m-, p-xylenes. Toluene gave cresols by hydroxylation of the aromatic ring, and benzyl alcohol and benzaldehyde by the oxygenation of the methyl group

(Eq. 1). Xylenes gave xylenols, methylbenzyl alcohols, and tolualdehydes, as shown by the reaction of p-xylene in Eq. 2. A small amount of benzoic acid was detected only with the reaction in pyridine, but phthalaldehydes were not detected. Hydroxylation of the aromatic ring and oxidation of the methyl group were promoted in the low and high pyridine concentration, respectively. The oxidation of the methyl group to give benzaldehyde proceeds highly selectively in pyridine. This reaction is useful as the convenient synthetic method of aldehydes. The total yield of the oxygenation products was much higher when the reaction was performed in pyridine than in acetonitrile.



(1)



(2)

The NIH shift value is often referred as an important indication of the enzyme-like oxygenation. The NIH shift from toluene-4-D compares the extent of the migration of deuterium to the meta position with that of the elimination in the formation of p-cresol. The content of the p-cresol-3-D in the total p-cresol (p-cresol-3-D and -3-H), not in the total cresols, was high in the acetonitrile solution and the value (55%) is close to 70% obtained in the Fe(TFPP)Cl/PhIO[9] and to 54% in the rat liver microsome/NADPH/O_2 systems.[10] The NIH shift value observed in pyridine was lower than that in acetonitrile.

In the reaction of xylenes, the products obtained by the methyl migration were found in the cases of o- and p-xylenes, but not of m-xylene. The Me-NIH shift, defined as the percentage of the methyl migration products in the total xylenols, is very high (38%) compared with the shift (5%) reported recently.[11] It is noticeable that the elimination of the methyl group hardly occurs as shown in the absence of p-cresol in the products from p-xylene. Figure 1 shows the effect of the pyridine concentration on the reactivity of p-xylene. The Me-NIH shift is higher at the higher pyridine concentration, different from the NIH shift in the case of toluene. Compared with p-xylene, o-xylene gives much lower values than those expected from the decrease in the shift sites due to two adjacent methyl groups. The migration may be sensitive to the steric and electronic effects of the substituents. The absence of the Me-NIH shift in the case of m-xylene is reasonable because the hydroxylation proceeds by the ortho and para orientation and the two meta carbons are not attacked by the electrophilic oxygen species.

The remarkable effect of the pyridine concentration on the selectivity suggests the formation of different active oxygen species. The reaction in acetonitrile proceeds without the induction period, and the activity is depressed by using $FeCl_2$ in place of $FeCl_3$ and by the absence of pyrocatechol. This indicates that the active species is directly formed form the catecholatoiron(III) complex. On the other hand, the reaction in pyridine starts after a fairly long induction period. This induction period is not observed when $Fe(Py)_4Cl_2$ is used in place of $FeCl_3$/pyrocatechol, and the reactivity is little affected by the absence of pyrocatechol. This suggests that the Fe(II) species without the catecholate ligand is initially formed by the reaction of Fe(III) with hydroquinones, followed by the formation of the active oxygen species by the reaction with oxygen.

The hydroxyl radical, ·OH, is believed to be an active species for the hydroxylation by the Fenton system, but the selectivity change depending on the pyridine concentration is not explained by ·OH. The high values of the NIH and Me-NIH shifts compared with the low values in the Fenton system[8] suggest an iron-oxygen

species such as $Fe^{V}=O$ as proposed in the iron-porphyrin systems.[10] In addition, we have observed k_H/k_D=2.6-3.2 for the kinetic isotopic effects in the formation of phenol from anisole and [Me-D_3]-anisole.[12] Since $k_H/k_D \approx 1$ is expected in the hydroxyl radical process,[13] this also supports the non-hydroxyl radical process.

Table 1. Oxygenation of toluene-4-D and xylenes by the nonheme iron complex/DTBHQ/O_2 system[a]

Aromatics	Iron[b]	Solvent	Yield	Composition of products/mol %[d]			NIH shift	Me-MIH shift
			10^2%[c]	Me(R)-PhOH(Isomer)	R-$PhCH_2OH$	R-PhCHO	%[e]	%[f]
Toluene-4-D	$FeCl_3$	CH_3CN	4.1	62.7 (64:5:31)	21.1	16.4	55	
	$FeCl_3$	pyridine	6.9	9.0 (46:10:44)	0.3	90.7	20	
1,2-Xylene	$FeCl_3$	CH_3CN	5.1	42.4 (33:7:60)	41.1	16.4		7
	$FeCl_3$	pyridine	12.7	4.3 (28:3:69)	0.5	95.3		3
1,3-Xylene	$FeCl_3$	CH_3CN	5.1	59.8 (67:32:1)	25.4	14.7		0
	$FeCl_3$	pyridine	12.7	13.4 (79:14:7)	0.3	86.3		0
1,4-Xylene	$FeCl_3$	CH_3CN	5.9	41.1 (18:82)	38.4	20.5		18
	$FeCl_3$	pyridine	13.3	3.4 (35:65)	0.4	96.2		35
	$FeCl_2$	CH_3CN	3.6	41.1 (16:84)	34.9	23.9		17
	$Fe(Py)_4Cl_2$	CH_3CN	1.8	37.8 (16:84)	28.7	33.5		16
	$Fe(Py)_4Cl_2$	pyridine	13.6	3.5 (35:65)	1.2	95.3		35

a) Reactions were performed as described in the text. Products were analyzed after 24 h. b) Iron species used for preparation of catalysts. c) Yield based on [Fe]. d) Product composition. R corresponds to Me, H, and D. Isomer compositions in parenthesis are; o-:m-:p-Me-PhOH from toluene, 2,3-:2,6-:3,4-Me_2-PhOH from o-xylene, 2,4-:2,6-:3,5-Me_2-PhOH from m-xylene, 2,4-:2,5-Me_2-PhOH from p-xylene. e) NIH shift is mol % of 4-Me-PhOH-3-D in the total 4-Me-PhOH. f) Me-NIH shift is mol % of the shifted Me_2-PhOH in the total Me_2-PhOH. Me-PhOH isomers were hardly detected.

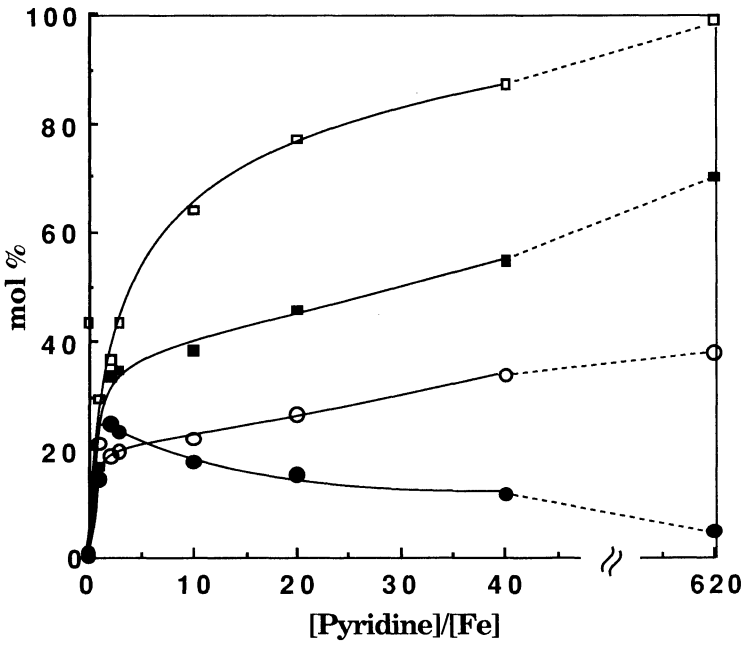
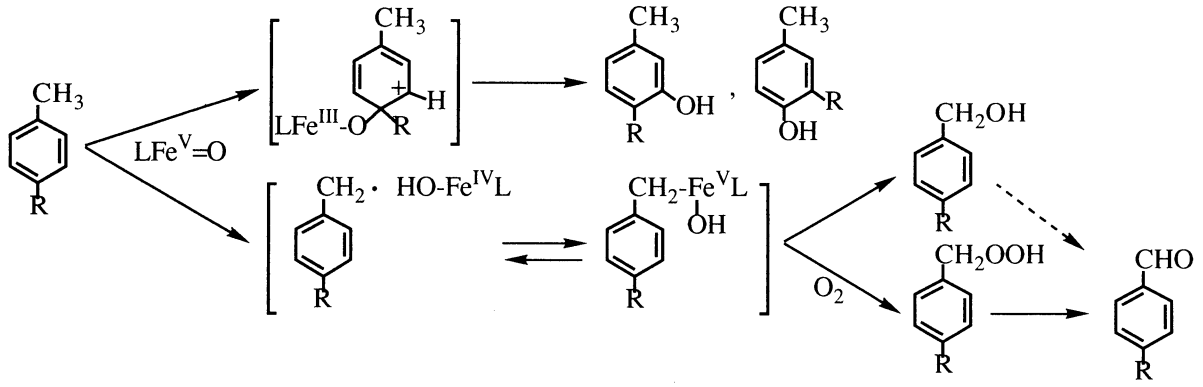


Fig. 1. Effect of the pyridine concentration on the composition and yields of products.
[Fe]=0.1 mmol, [Fe] : [pyrocatechol] : [DTBHQ]=1:1:60, p-xylene=2.5 cm^3, CH_3CN=5.0 cm^3 at 25 °C, 1 atm O_2. [Pyridine]/[Fe] =620 corresponds to the reaction in pyridine without CH_3CN. ○: Me-NIH shift:, *i.e.* 2,4-Me_2-PhOH/(2,4- + 2,5-Me_2PhOH); ●: Total yield of Me_2PhOH, based on [Fe]; □: Me_2-PhCHO/(Me_2-PhCHO + Me_2-$PhCH_2OH$); ■: Total yield of (Me_2-PhCHO + Me_2-$PhCH_2OH$), based on [Fe].

The results obtained here are explained by the following scheme, in which L and R denote ligands and the deuterium or methyl substituent, respectively. As proposed previously,[1,2] Fe^{V}=O is supposed as an active species without any direct evidence. The reactivity of the complex depends greatly on whether the complex is a catecholate complex or a pyridine complex. The ligand effect on the electrophilicity of LFe^{V}=O controls the hydroxylation of the aromatic ring which is favored by the more electrophilic oxygen species. The ligand effect on the radical character of LFe^{V}=O, *i.e.* the LFe^{IV}-O· character, is also important for the homolytic abstraction of hydrogen in the monooxygenation of the methyl group. Benzylalcohol may be formed by the direct reaction of an alkyl radical with ·OH in a solvent cage or by the ligand coupling of a σ-alkyliron complex.[1] If benzaldehyde is formed by the addition of oxygen to the alkyl radical or the σ-alkyliron complex, the reaction depends on the the stability of the σ-alkyliron complex. Although we have observed the oxidation of benzylalcohol to benzaldehyde in the present system, we prefer the oxygen addition process for the formation of benzaldehyde.[6] Effect of pyridine as a deprotonating reagent is also important. The lower NIH value in pyridine than in acetonitrile is ascribed to the enhanced deprotonation of the deuterium ion before migration. The effect is not observed in the Me-NIH shift, which is not accompanied by the elimination of the methyl group and rather promoted in pyridine.



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