Table II. Effect of Solvent on the Quantum Yields of Photosensitized Electron-Relay Isomerization[a]

polym deg (n)	$\Phi_{c\to t}$ CH_3COCH_3[b]	CH_3OH[b]	CH_3CN[b]
c	0.45		
SDS[d]	0.55		
100 ± 50	42		
360 ± 120	47		
1700	61	91	93
2400 ± 500	66		
5100			98

[a] Irradiated at 468 ± 5 nm under argon. Initial concentrations: $[PSS^{n-}/n] = [cis\text{-}Stz^+] = 0.4$ mM; $[Ru(bpy)_3^{2+}] = 6.7$ μM. [b] Solvents containing 10% H_2O. [c] Addition of equimolar HCl in place of PSS^{n-}. [d] SDS (sodium dodecylsulfate) was added in place of PSS^{n-}.

the poly(styrenesulfonate) anion chain and hydrophobic cation BTA^+ form micellelike clusters and their N_A values are in the range of 80–90, irrespective of the degree of polymerization, as depicted in Scheme I. So far, dodecyltrimethylammonium bromide and PSS^{n-} have been reported to form minimicelles, but their N_A values are less than 10.[14] Hence, the present evidence for micellelike clusters is new and quite interesting.

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Effect of Solvents. To our surprise, a similar enhancement of the electron-relay isomerization was also observed in organic solvents such as acetone, methanol, and acetonitrile (Table II). The chain isomerization occurs in organic solvents as efficiently as in water. This suggests that the $PSS^{n-}\cdot(Stz^+)_n$ forms micellelike clusters even in organic solvents. This is in sharp contrast to the case of typical anionic micelles; i.e., micelles do not prevail in 90% aqueous acetone as exemplified by the quantum yield of less than unity in the presence of sodium dodecylsulfate (Table II). It was, however, impossible to measure the aggregation number of $PSS^{n-}\cdot(BTA^+)_n$ in the organic solvents on account of the experimental restriction that 9-methylanthracene quencher is quite soluble in the solvents.

In conclusion, the present results suggest that Stz^+ and PSS^{n-} form a number of divided micellelike clusters, resulting in the electron-relay chain isomerization of *cis*-Stz^+. This may provide an interesting model system for biopolymers and polyions.

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Mechanism of Aromatic Hydroxylation in the Fenton and Related Reactions. One-Electron Oxidation and the NIH Shift

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Abstract: Hydroxylation of substituted benzenes in the Fenton and peroxydisulfate oxidations has been studied mechanistically in relation to the NIH shift. One-electron oxidants such as Fe^{3+}, Cu^{2+}, and quinones increased the shift value effectively in aqueous or acetonitrile solutions. The shift values obtained were as high as 40–50% and dependent on both substituents (i.e., MeO ≪ Me, Cl, MeCO) and solvents. A high shift value was obtained also for the methoxylation, indicating unimportance of the arene oxide intermediate for the NIH shift. Oxygen reduced the shift effectively and sometimes was incorporated into product phenols with selective meta orientation. This means that oxygen abstracts a hydrogen atom from or adds to the oxycyclohexadienyl radical intermediate. It is concluded that the one-electron oxidation of the dienyl radical is the key step for the shift and its rates are dependent on substituents, oxidants, and solvents.

The NIH shift is a rearrangement of a hydrogen atom during enzymic aromatic hydroxylations,[1-3] and significantly large shift values have been reported also in model cytochrome P-450 oxidation.[4] The shift mechanism was originally understood by arene oxide intermediates,[1] but some results not compatible with the arene mechanism have also been reported.[5,6] Recently, a rearrangement via cationic intermediates has been suggested by cytochrome P-450 model study[7] or semiempirical MO calculation.[8]

As a nonenzymatic hydroxylation the Fenton oxidation is well-known and extensively studied.[9,10] Recently developed are the regioselective hydroxylation of alcohols,[11] the nonclassical[12a] or photo-Fenton reaction,[12b] efficient hydroxylation of aromatics

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Table I. Effect of Solvent and Oxidants on the Fenton Reaction of Toluene and Chlorobenzene[a]

run	solvent	added oxidant[b]	products,[c] %			NIH shift,[d] %
			$PhCH_2OH$	PhCHO	phenols (o:m:p)	
		(A) Effect of Oxidants for the Oxidation of Toluene-*4-d* in Water				
1	H_2O		<0.1		8 (56:15:29)	21.1
2	H_2O	Fe^{3+}	*e*		*e*	30
3	H_2O	Fe^{3+} (0.2 M)	*e*		*e*	35
4	H_2O	AQS[f]	*e*		3 (60:11:29)	31.8
5	H_2O	Fe^{3+}/AQS[g]	*e*		7 (57:14:29)	40.1
6	H_2O	Ti^{3+} [h]	*i*		<0.1	
		(B) Oxidation of Toluene-*4-d* in Acetonitrile				
7	MeCN		1	1	5 (38:20:42)	52.9
8	MeCN	Fe^{3+}	1	1	5 (40:23:37)	51.8
9	MeCN	O_2	1	5	12 (37:33:30)	50.0
10	MeCN	Cu^{2+}	5	1	24 (65:15:20)	52.0
11	99.5% MeCN	Cu^{2+}	8	2	32 (68:14:18)	51.8
12	95% MeCN	Cu^{2+}	8	1	41 (61:15:24)	52.9
13	90% MeCN	Cu^{2+}	6	1	23 (59:22:19)	48.2
14	90% MeCN		1	9	12 (53:16:31)	50.5
15	90% MeCN	Fe^{3+}	1	8	4 (53:20:27)	47.5
16	90% MeCN	O_2	0.1	11	6 (51:36:13)	14.8
		(C) Oxidation of Chlorobenzene-*4-d*				
17	90% MeCN				7 (50:37:13)	22.7
18	90% MeCN	Fe^{3+}			10 (53:12:36)	31.3
19	90% MeCN	Cu^{2+}			44 (57:22:21)	42.3
20	90% MeCN	O_2			9 (59:20:21)	1.4

[a] The Fenton oxidation was started by adding slowly (ca. 15 min) 0.1 mmol of H_2O_2 to a 2-mL solution of 1 mmol of substrate and 0.1 mmol each of Fe^{2+} and oxidant in water or MeCN at 25 °C under argon. Reagent concentrations: 0.5 M substrate and 0.05 M each of H_2O_2, Fe^{2+}, or Cu^{2+}. [b] Oxidant concentration is 0.05 M if not noted otherwise. [c] Product yields based on H_2O_2 added. [d] The NIH shift percent for *p*-cresol and *p*-chlorophenol. The shift values were determined three to five times and averaged (±5%). The corresponding ortho-substituted products retained deuterium almost quantitatively (≥97%), while 5–10% of deuterium was eliminated for the *m*-phenols. [e] Not determined. [f] Anthraquinone-2,6-disulfonate. [g] Oxidation of toluene with 1 mM Fe^{3+}, 2 mM AQS, and 20 mM H_2O_2, i.e., in the absence of Fe^{2+} added.[13] [h] Ti^{3+} was added in place of Fe^{2+}. [i] Major product was bibenzyl in 8% yield.

with quinone–Fe^{3+},[13] and the interesting anhydrous system of Fe^{2+}–H_2O_2 in acetonitrile.[14] While the NIH shift in the Fenton hydroxylation was reported to be very low in aqueous solution (e.g., <5%),[10] a Fenton reaction in acetonitrile[15] has been shown to afford remarkably high shift values (e.g., 30–40%), which are close to P-450 systems. However, it is known that ferric ion in dry acetonitrile possesses a high redox potential and could oxidize various types of organic compounds.[16] Then it seems to be hard to assign the true oxidizing species in dry MeCN as $HO^{\bullet}$, Fe^{3+}, or $Fe{=}O^{3+}$.

Herein, we summarize our detailed study on the effect of one-electron oxidants on the NIH shift in aromatic hydroxylations by the Fenton and peroxydisulfate oxidations. One-electron oxidants such as Fe^{3+}, Cu^{2+}, and quinones increase the shift value sharply, while oxygen reduces it effectively. It has been shown that oxygen abstracts a hydrogen atom from or adds to the intermediate dienyl radical, depending on conditions and substituents in aromatics. These results are believed to shed light on the mechanism of enzymatic hydroxylations.

Results

Fenton Oxidation. It is well-known that the Fenton oxidation of toluene yields cresols in addition to small amounts of benzyl alcohol or benzaldehyde.[9,10] We reinvestigated the oxidation under various conditions as shown in Table I. To our surprise, a significant NIH shift was observed in the Fenton oxidation of toluene in water; the percent shift value increased from 21 to over 30% when ferric ion or quinone was added (Table IA). Here, oxidants added or Fe^{3+} formed in situ from H_2O_2 and Fe^{2+} plays an important role in the aromatic hydroxylation. This is because cresols were not obtained in the absence of appropriate oxidants, as when a hydroxy radical was produced from Ti^{3+} and H_2O_2, affording bibenzyl as a sole product (run 6 in Table I).

When the medium was changed from water to 90 or 100% acetonitrile and an oxidant such as Cu^{2+} was added, the NIH shift and cresol yields increased significantly (Table IB). The shift values here were surprisingly high and constant at 50.8 ± 1.8 for runs 7–15 in 90–100% MeCN. The one exception was the presence of oxygen in 90% MeCN, reducing the shift to only 15% (run 16).

The effect of oxidants was more typical for the case of chlorobenzene-*4-d*. The shift values decreased in the order of Cu^{2+} > Fe^{3+} ≫ O_2, exhibiting again the dramatical inhibition of the NIH shift by oxygen (cf. Table IC).

Substituent Effects. In Table IIA are listed the results for the Fenton oxidation of 4-substituted benzenes-d_1. As noted by Norman,[10] the NIH shift for anisole-*4-d* was not high (runs 21 and 22). However, in the hydroxylation of other substituted benzenes, i.e., toluene, chlorobenzene, and acetophenone, the resulting shift values were ca. 20% in water and as high as 40–50% in 90% acetonitrile. It is now concluded that the NIH shift in the Fenton oxidation is considerably high even in aqueous solution. The exceptionally low shift value for anisole is inconsistent with the reported high value of 30% in acetonitrile.[15] The discrepancy is probably based on the fact that the reported value was determined indirectly from 1,4-benzoquinone and might contain some kinetic isotope effect for the further oxidation of methoxyphenol to the quinone.

Effect of substituents was also examined for the related aromatic oxygenation as shown in Table IIB. It is interesting to note that a considerably high shift value was obtained also for the methoxylation in the Fenton oxidation in the presence of methanol (run 29 in Table II). In contrast, the shift values were much lower or zero for the acyloxylation with benzoyl peroxide and Cu^{2+} [17]

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Table II. NIH Shift in Some Aromatic Substitutions

run	substrate	reagent	solvent	product[a]	percent[a]	(o:m:p)[a]	NIH shift,[b] %
			(A) Hydroxylation by the Fenton Oxidation[c]				
21	p-$MeOC_6H_4D$	$Fe^{2+}/H_2O_2/Cu^{2+}$	H_2O	$MeOC_6H_4OH$	16	(87:2:11)	3.1
22	p-$MeOC_6H_4D$	$Fe^{2+}/H_2O_2/Cu^{2+}$	90% MeCN	$MeOC_6H_4OH$	3	(98:<1:1)[d]	8.0
23	p-MeC_6H_4D	$Fe^{2+}/H_2O_2/Cu^{2+}$	H_2O	MeC_6H_4OH	9	(56:16:28)	19.0
24	p-MeC_6H_4D	$Fe^{2+}/H_2O_2/Cu^{2+}$	90% MeCN	MeC_6H_4OH	12	(58:22:19)	48.2
25	p-ClC_6H_4D	$Fe^{2+}/H_2O_2/Cu^{2+}$	H_2O	ClC_6H_4OH	2	(56:27:17)	22.8
26	p-ClC_6H_4D	$Fe^{2+}/H_2O_2/Cu^{2+}$	90% MeCN	ClC_6H_4OH	44	(57:22:21)	42.3
27	p-$MeCOC_6H_4D$	$Fe^{2+}/H_2O_2/Cu^{2+}$	H_2O	$MeCOC_6H_4OH$	8	(33:42:25)	21.5
28	p-$MeCOC_6H_4D$	$Fe^{2+}/H_2O_2/Cu^{2+}$	90% MeCN	$MeCOC_6H_4OH$	9	(68:21:11)	45.7
			(B) Methoxylation and Acyloxylation				
29	p-MeC_6H_4D	$Fe^{2+}/H_2O_2/Cu^{2+}$	MeOH/MeCN (1:9)	MeC_6H_4OH	2.8	(66:20:14)	51.2
				MeC_6H_4OMe	0.2	(~3:2:5)[d]	40.2
30	p-MeC_6H_4D	BPO/Cu^{2+}[e]	90% MeCN	$PhCO_2C_6H_4Me$	46	(48:17:35)	3.1
31	p-ClC_6H_4D	BPO/Cu^{2+}[e]	90% MeCN	$PhCO_2C_6H_4Cl$	12	(72:<1:28)	1.7
32	p-ClC_6H_4D	electrolysis[f]	AcONa/AcOH	$MeCO_2C_6H_4Cl$		(47:<1:53)	0

[a] Product yields in percent based on H_2O_2 added. The values in parentheses show the ratio of ortho, meta, and para isomers. [b] The NIH shift percent shows the deuterium retention percent for para-substituted products. [c] See footnote a in Table I. Initial concentrations: ~0.5 M substrate and 0.05 M each of Fe^{2+}, Cu^{2+}, and H_2O_2 under argon. [d] Product yields were too small to determine the isomer ratio accurately. [e] Benzoyloxylation with 0.1 M benzoyl peroxide (BPO) and 0.1 M $CuCl_2$ at 80 °C under Ar according to the reported method.[17] [f] Acetoxylation by cathodic oxidation (+2.0 V) in the presence of 1 M AcONa in AcOH according to the literature.[18]

Table III. Peroxydisulfate ($S_2O_8^{2-}/Fe^{2+}$) Oxidation and the NIH Shift[a]

run	substrate	oxidant added[b]	$E°$,[c] V	products,[d] % PhCHO[d]	products,[d] % $(PhCH_2)_2$	products,[d] % phenols (o:m:p)	NIH shift,[e] %
33	p-MeC_6H_4D			1	30	0	
34	p-MeC_6H_4D	Cu^{2+}	−0.07	1	2	12 (49:2:49)	40.5
35	p-MeC_6H_4D	O_2	−0.39	3	2	3 (53:7:40)	7.1
36	p-MeC_6H_4D	BQ	−0.50	2	0	10 (53:9:38)	15.2
37	p-MeC_6H_4D	Cu^{2+}[f]		3	0	5 (40:2:58)	16.8
						3[g] (51:3:46)	15.2
38	p-ClC_6H_4D				0		
39	p-ClC_6H_4D	Cu^{2+}	−0.07			3 (37:<1:63)	42.5
40	p-ClC_6H_4D	O_2	−0.39			5 (24:<1:76)	3.1
41	p-ClC_6H_4D	duroquinone	−0.84			1 (29:<1:74)	18.7
42	p-ClC_6H_4D	BQ	−0.50			4 (32:<1:68)	15.9
43	p-ClC_6H_4D	p-chloranil	0.01			23 (26:<1:74)	6.5
44	p-ClC_6H_4D	DDQ	0.51			42 (30:<1:70)	36.7

[a] The reaction was started by the addition of $S_2O_8^{2-}$ to the solution of substrate and Fe^{2+} under argon at 25 °C. Reagent concentrations: 0.5 M substrate and 0.05 M each of $S_2O_8^{2-}$ and $Fe(ClO_4)_2$ in 90% MeCN unless noted otherwise. [b] Oxidant added: 10 mM Cu^{2+} or quinones and ca. 20 mM O_2. BQ = p-benzoquinone, and DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone. [c] Redox potentials of oxidants in volts vs SCE in water for inorganics and in MeCN for organics. The values for quinones from ref 21a and for O_2 from ref 21b. [d] Product yields based on $S_2O_8^{2-}$ added. [e] The NIH shift for para-substituted products (±5% value). [f] The reaction in $MeOH/H_2O/MeCN$ (5:4:1). [g] Methoxylated product, MeC_6H_4OMe.

Table IV. Oxygen Incorporation from O_2 in the Fenton Oxidation

run	substrate	conditions[a]	products[b]	oxygen incorporation[c] ortho	oxygen incorporation[c] meta	oxygen incorporation[c] para
44	chlorobenzene		chlorophenols	2.9 ± 0.3	3.1 ± 1.4	2.0 ± 0.5
45	toluene		cresols	4.0 ± 0.3	29.3 ± 0.4	5.0 ± 0.4
46	toluene	0.05 M Fe^{3+}	cresols	5.3 ± 0.3	16.4 ± 1.5	4.3 ± 1.1
47	toluene	100% MeCN	cresols	3.1 ± 0.2	4.0 ± 0.5	2.0 ± 0.3
48	anisole		methoxyphenols[d]	0.1 ± 0.6	46.4 ± 4.2	
49	anisole	water	methoxyphenol[e]	0.7 ± 0.2	2.9 ± 0.4	0.1 ± 0.4
50	benzene	water	phenol[f]	0.5 ± 0.6		
			benzoquinone[f]	1.0 ± 0.7[g]		

[a] Conditions: $H_2O_2/Fe^{2+}/{}^*O_2$ in 90% MeCN unless noted otherwise. Reagent concentrations are the same as footnote a in Table I. $^*O_2$ means 1 atm of oxygen gas containing 8.4% $^{18}O_2$. [b] Product ratios were approximately the same as those under oxygen in Table I. [c] Percent incorporation of oxygen atom from O_2 gas as calculated from the ^{18}O contents in products. The ^{18}O contents were determined from (M + 2) values in mass spectra. [d] Product ratio is o:m:p = 72:24:4. [e] Product ratio is o:m:p = 87:5:8. [f] Product ratio is PhOH:benzoquinone:biphenyl = 92:2:6. [g] The ^{18}O content of benzoquinone was determined after the conversion to p-dimethoxybenzene; the direct determination was unsuccessful because of variable (M + 2) values.

or the anodic oxidation[18] where one-electron oxidation is surely involved.

Peroxydisulfate Oxidation. Peroxydisulfate has been applied to many useful reactions[19,20] and involves a one-electron oxidation by sulfate radical ion $SO_4^{\bullet-}$. The hydroxylation of aromatic rings is known to proceed by way of aromatic cation radicals followed by the addition of water.[20] When toluene was oxidized with $S_2O_8^{2-}$–Fe^{2+} alone at 25 °C, cresols were not obtained and bibenzyl was the major product (run 33 in Table III). The hydroxylation of an aromatic ring was attained when effective oxidants such as

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Cu^{2+}, O_2, or quinones were added. The accompanying NIH shift was of the maximum value of 41% with Cu^{2+} and the lowest with O_2.

Similar results were obtained for the peroxydisulfate oxidation of chlorobenzene-*4-d*; the NIH shift was 43% with Cu^{2+} and only 3% with O_2. As for the effect of quinones, the phenol yields increased with the increasing oxidizing power, i.e., duroquinone < 1,4-benzoquinone < *p*-chloranil < DDQ. But, the corresponding NIH shift values were somewhat different, i.e., in the order of *p*-chloranil < 1,4-benzoquinone < duroquinone < DDQ.

Oxygen Incorporation. In order to clarify the oxygen effect on the present NIH shift, an ^{18}O tracer study on the Fenton oxidation has been done with regard to the oxygen incorporation in phenols produced. The results as summarized in Table IV indicate that the oxygen incorporation from O_2 is dependent on substituents and conditions. While the NIH shift for chlorobenzene was efficiently reduced by O_2, the oxygen incorporation in chlorophenols was negligibly small (run 44). On the other hand, in the cases of toluene and anisol, oxygen atom from O_2 was incorporated significantly for the reaction in 90% MeCN (run 45 and 48). The oxygen incorporation decreased when the Fenton oxidation was carried out in 100% MeCN or water (cf. runs 45, 47, and 49). The most interesting in Table IV is the selective oxygen incorporation at the meta position of toluene and anisol. Mechanistic features of these results are analyzed in the discussion section.

In Table IV is listed the result on the Fenton oxidation of benzene, which indicates that oxygen from O_2 was incorporated into neither phenol nor 1,4-benzoquinone. This is not consistent with a recently reported result that just one oxygen atom in benzoquinone was incorporated from O_2 in the oxidation of benzene.[22] Since the direct mass spectral analysis, as reported, was unsuccessful because of variable (M + 2) peak for benzoquinone, it was converted to 1,4-dimethoxybenzene,[23] which afforded reproducible mass spectral data. The discrepancy is probably caused on the mass spectral analysis of benzoquinone, which sometimes affords a high (M + 2) peak corresponding to hydroquinone. At any rate, oxygen incorporation was negligible under the present conditions in water.[24]

Discussion

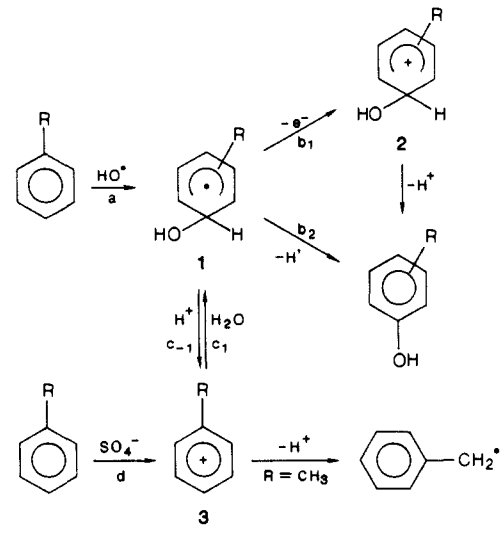
The NIH shift in the enzymatic aromatic hydroxylation approaches as high as 70–80% and has often been explained by arene oxide intermediates. Similarly, high shift values have also been reported in nonenzymatic hydroxylations, e.g., 77% with HOF.[25]

The present study deals with the effect of oxidants and other conditions for the aromatic hydroxylation with $HO^\bullet$ and $SO_4^{\bullet-}$. Important features obtained are as follows. (i) One-electron oxidants such as Cu^{2+}, Fe^{3+}, and quinones lead to large NIH shift. (ii) Substantially high shift values have been obtained in aqueous solvent, indicating that an aprotic environment is not always necessary for the high NIH shift. (iii) A high shift has been observed likewise for the methoxylation, denying arene oxides as an inevitable intermediate. (iv) Similar results on the shift were obtained for the oxidation with $SO_4^{\bullet-}$, i.e., by starting from arene cation radicals. (v) Oxygen reduces the NIH shift effectively and sometimes is incorporated into product phenols with selective meta orientation.

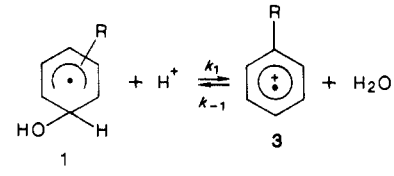
These results may be understood by the hydroxylation mechanism as outlined in Scheme I and discussed in the following.

Comparison of the Oxidation with $HO^\bullet$ and $SO_4^{\bullet-}$. Major reaction of benzenes with the $HO^\bullet$ radical is the addition to the nucleus,[26] while the one-electron oxidation is predominant with

Scheme I. Hydroxylation of Benzenes



sulfate radical ion $SO_4^{\bullet-}$, its redox potential being as high as 2.84 V vs SCE.[27] As apparent in Tables I and III, product distributions with $HO^\bullet$ are different from those with $SO_4^{\bullet-}$. The difference in product ratios is understood by the different product-determining steps, i.e., the addition of $HO^\bullet$ to aromatics (step a in Scheme I) and the addition of water to cation radical **3** (step c_1). For the latter case, the product selectivity is governed mostly by the distribution of cationic charge in **3**,[20,28] resulting in the ortho–para orientation. The equilibrium between cyclohexadienyl radical **1** and cation radical **3** (eq 1) have been suggested from



(1)

product analysis[9,10] and pulse radiolysis,[26,29] Under the present conditions (i.e., from neutral to 0.1 M $HClO_4$), however, the equilibrium is not attained since product ratios are quite different between the $HO^\bullet$ and $SO_4^{\bullet-}$ oxidations.

For the case of toluene, the deprotonation of cation radical **3** (R = Me) to yield benzyl radical occurs as an alternative reaction as shown in Scheme I. Thus, bibenzyl was obtained as a major product from the $SO_4^{\bullet-}$ oxidation in the absence of any effective oxidant (cf. run 33), while cresols were obtained predominantly in the presence of oxidants via the pathway **3** → **1** → cresols. This fact indicates that the addition of water to **3** (path c_1 in Scheme I) is much faster than the deprotonation to yield benzyl radical. After the formation of dienyl radical **1**, the chemistry is just the same with the Fenton case. Thus, the large NIH shift of ca. 40% was similarly observed for the $SO_4^{\bullet-}$ oxidation in the presence of efficient one-electron oxidant (see runs 34, 39, and 44 in Table III). This is natural since the oxidation step of dienyl radical **1** is equally involved in the hydroxylation step as discussed in the following.

Conditions for the NIH Shift. Effect of Oxidants. It is long known that phenol yields are significantly improved by the oxidation of hydroxycyclohexadienyl radical **1** with oxygen[9,30] or metallic salts.[9,31] The efficiency of metallic oxidants is reported

(22) Kunai, A.; Hata, S.; Ito, S.; Sasaki, K. *J. Am. Chem. Soc.* **1986**, *108*, 6012.
(23) 1,4-Benzoquinone was reduced to hydroquinone with sodium dithionite, followed by the methylation with dimethyl sulfate.
(24) The Fenton oxidation of benzene in 90% MeCN was carried out similarly, but the yield of benzoquinone was too low (i.e., <0.4%) to obtain reliable mass spectral data.
(25) Appelman, E. H.; Bonnett, R.; Matean, B. *Tetrahedron* **1977**, *33*, 2119.
(26) Sehested, K.; Corfitzen, H.; Christensen, H. C.; Hart, E. J. *J. Phys. Chem.* **1975**, *79*, 310.
(27) Balej, J. *Electrochim. Acta* **1984**, *24*, 1239.
(28) Eberhardt, M. K. *J. Org. Chem.* **1977**, *42*, 832.
(29) Christensen, H. C.; Sehested, K.; Hart, E. J. *J. Phys. Chem.* **1973**, *77*, 983.
(30) Dorfman, L. M.; Taub, I. A.; Buhler, R. E. *J. Chem. Phys.* **1962**, *36*, 3051.
(31) (a) Baxendale, J. H.; Smithies, D. *J. Chem. Soc.* **1959**, 799. (b) Eberhardt, M. K.; Martinez, M. I. *J. Phys. Chem.* **1975**, *79*, 1917. (c) Eberhardt, M. K. *Ibid.* **1975**, *79*, 1913; **1977**, *81*, 1051.

to be in the order of $Fe(CN)_6^{3-} > Cu^{2+} > Fe^{3+}$,[31b] which is not the order in their reduction potentials.

The present study revealed that the higher NIH shift values were obtained with one-electron oxidants such as Cu^{2+}, Fe^{3+}, and quinones, while oxygen reduced the shift dramatically. Although the oxidation potential of dienyl radical **1** is not determined directly, the $E_{ox}°$ value of −0.26 V vs NHE has been estimated for **1** (R = H) from electrochemical sequences.[32] Then it is quite natural to assume that the observed high NIH shift is due to the smooth one-electron oxidation of dienyl radical **1** to cation **2** with Cu^{2+} and Fe^{3+}, their redox potentials being positive.[33] The dramatic reduction of the NIH shift by oxygen may indicate that the reduction potential of O_2 (e.g., $E°$ = −0.39 V vs SCE)[21b] is lower than the $E°$ of **1**.

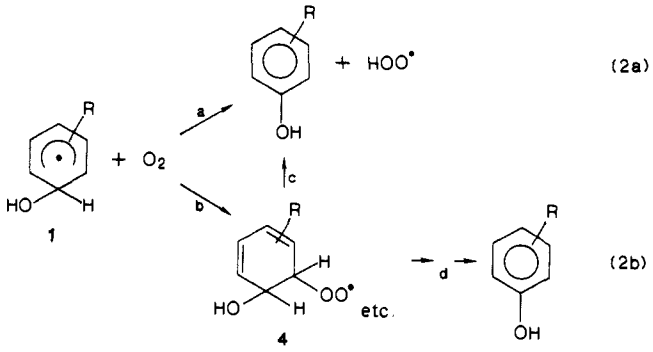
Solvents play an important role in determining product yields and the NIH shift. The oxidizing power of Fe^{3+} or Cu^{2+} is expected to be enhanced significantly by changing the solvent from water to 90 and 100% MeCN.[14,16] In fact, the redox potentials in water, 90% MeCN, and 100% MeCN are 0.78, 0.85, and ~1.2 V for $Fe(ClO_4)_3$ and 0.16, 0.82, and ~1.1 V vs SCE for $Cu(ClO_4)_2$, respectively, as determined by CV at 25 °C. The effect of oxygen in Table I could be explained on the basis of the solvent-dependent redox potentials. Thus, for the Fenton oxidation of toluene-*4-d*, the one-electron oxidation of dienyl radical **1** by Fe^{3+} formed in situ from H_2O_2 and Fe^{2+} is much faster in 100% MeCN (i.e., run 9) but becomes comparable to the reaction with oxygen in 90% MeCN (i.e., run 16).

Since the oxidation potential of **1** with R = Cl from chlorobenzene is certainly higher than that of toluene (R = Me) on the basis of the electron-attracting chlorine group, one-electron oxidation of **1** (R = Cl) becomes much slower compared to the reaction with O_2, and hence the resulting NIH shift is reduced as low as 1%. The shift value under oxygen was only 4.3% even in the presence of 0.1 M Fe^{3+} in 90% MeCN; this suggests that the relative reactivity of Fe^{3+} and O_2 is approximately 1:31 for **1** (R = Cl). The apparent NIH shift thus reflects the delicate balance on the competitive one-electron and radical oxidations, which change by substituents and solvents.

The effect of quinones on the phenol yields and the NIH shift is somewhat complex as apparent in Table III for the $SO_4^{\bullet-}$ oxidation of chlorobenzene (runs 41–44). The yields of phenols increase linearly with the increasing redox potentials of quinones, e.g., 1 and 42% yields with duroquinone and DDQ, respectively. However, the accompanying NIH shift does not depend on the reduction potentials, e.g., 37% shift with DDQ but only 6.5% with chloranil. Thus, quinones seem to act as a one-electron reagent as well as radical oxidant (i.e., H• abstract) for **1**, their balance being very delicate. The reaction of dihydroxycyclodienyl radicals (**1**, R = HO) with quinones has been reported as a one-electron oxidation.[34] But the present study suggests that hydrogen atom abstraction by quinone is also feasible.

Reaction of 1 with Oxygen. In the above discussion oxygen is simply stated as a radical oxidant leading to H• abstraction. The detailed mechanism for the reaction of dienyl radical **1** with oxygen is more complex.[35-37] It is an open question whether the reaction is a direct H• abstraction (path a, eq 2a)[36] or the alternative addition–elimination mechanism (path c, eq 2a).[30,37] The latter pathway via adduct radical **4** and the regeneration of H_2O_2 from HOO• have been suggested by ^{18}O tracer studies.[22,37] Present ^{18}O tracer experiments indicate that the oxygen incorporation from O_2 changes by substituents and conditions as shown in Table IV.

While the NIH shift for chlorobenzene was efficiently reduced by O_2, the oxygen incorporation in chlorophenols was negligibly small. This means that oxygen abstracts a hydrogen atom effectively from the cyclohexadienyl radical **1** (R = Cl) according to eq 2a. In contrast, oxygen atom from O_2 was incorporated significantly for the cases of toluene and anisole. The oxygen incorporation decreased when the Fenton oxidation was carried out in 100% MeCN or in water (cf. runs 47 and 49). This apparently inconsistent effect of solvents could be explained on the basis of the competitive oxidation of **1** with Fe^{3+} and O_2 and the fact that the oxidizing power of Fe^{3+} in 100% MeCN is much higher and the solubility of O_2 in water is only one-tenth of those in organic solvents.

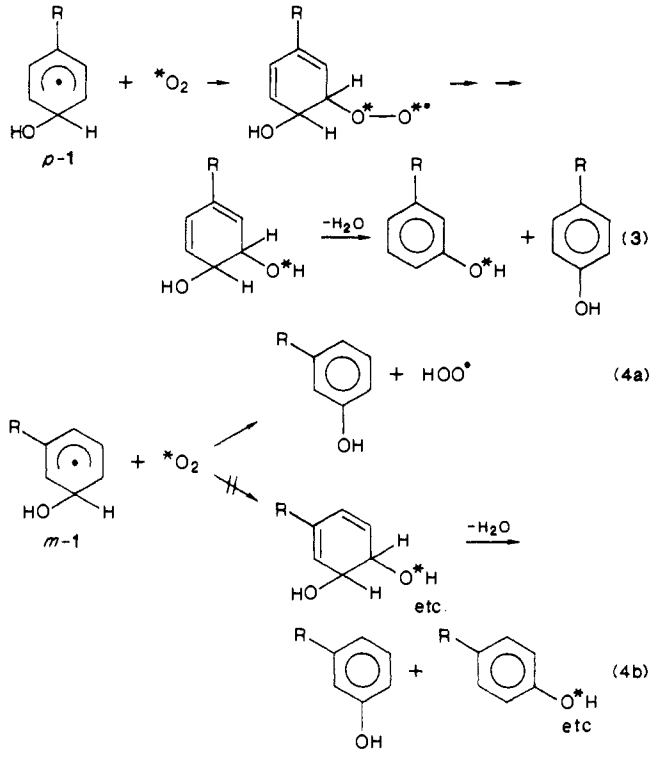


Most interesting here is the selective incorporation of an oxygen atom into the meta position of toluene and anisole.[38] So far, oxygen incorporation from O_2 has been explained by the Dorfman mechanism[30] or the recycle pathway (i.e., $O_2 \rightarrow HOO^{\bullet} \rightarrow H_2O_2 \rightarrow HO^{\bullet}$).[22,37] The latter scheme is based on a reported result that just one oxygen atom was incorporated in benzoquinone for the Fenton oxidation of benzene in water.[22] As stated in the Results section, this was not substantiated by our hands. At any rate, the recycle mechanism predicts an equal distribution of ^{18}O in products and hence cannot explain the selective meta insertion.

To account for the oxygen effect on the NIH shift and the selective meta incorporation in phenols, one feasible mechanism is a delicate competition between the H• abstraction from **1** (path a, eq 2a) and the addition to **1** (paths b and d, eq 2b), where the latter reaction is favored by electron-donating substituents much more in comparison to the former one. This assumption seems to be reasonable since it is known that the addition of oxygen to carbon radicals is faster for radicals of lower ionization potentials.[39] Thus, the substituent effect of MeO > Me ≫ Cl for the oxygen incorporation is readily understood. The competition mechanism can also explain the meta selectivity if the O_2 addition occurs only for *o*- and *p*-**1** (eq 3) and solely H• abstraction for *m*-**1** (eq 4a). The assumption is probably true since the oxidation potential for *m*-**1** (R = electron-donating group) is much higher than that for the corresponding *o*- or *p*-**1**.[34] Thus, the meta selectivity and substituent effect of MeO > Me ≫ Cl for the oxygen incorporation could be explained reasonably by the competition mechanism where reactivities are governed by the redox potentials of **1**. The more significant substituent effect for the addition of O_2, in comparison to the H• abstraction by O_2, is comprehensible because the substituents are attached and interacting directly with the dienyl group in **1**. In other words, the addition of O_2 to dienyl radical **1** is not fast enough for the case of **1** (R = Cl) and *m*-**1** (R = Me or MeO), where the H• abstraction is predominant. This explains well the ^{18}O tracer study and the oxygen effect on the NIH shift.

Mechanism of the NIH Shift. Importance of one-electron oxidation in the NIH shift has been stressed in the above discussion. The likely mechanism for the shift is summarized as Scheme II. The NIH shift % is governed by the efficiencies for the one-electron oxidation of **5** (step 5A), the rearrangement from **6** to **7** (step 6A) and the k_H/k_D for deprotonation of **7**. The

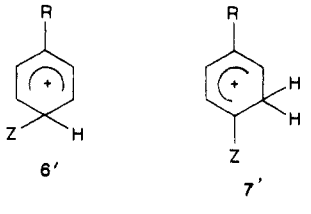
(32) Grätzel, M.; Henglein, A.; Lilie, J.; Scheffler, M. *Ber. Bunsen-Ges. Phys. Chem.* **1972**, *76*, 67.
(33) For the case of Cu^{2+}, it may involve organocopper intermediates.[9] But it is likely that cationic intermediate **2** is ultimately produced since the resultant shift and isomer distribution are the same with Fe^{2+}.
(34) Raghavan, N. V.; Steenken, S. *J. Am. Chem. Soc.* **1980**, *102*, 3495.
(35) Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095.
(36) Hendry, D. G.; Schuetzle, D. *J. Am. Chem. Soc.* **1975**, *97*, 7123.
(37) Narita, N.; Tezuka, T. *J. Am. Chem. Soc.* **1982**, *104*, 7316.
(38) The selective meta introduction of oxygen is also in line with the increased yields of *m*-phenols under O_2 as shown in run 16 or 45 and reported previously.[9b]
(39) Tokumaru, K. *Nippon Kagaku Zasshi* **1971**, *92*, 887.



reduction of the shift by oxygen (step 5B) is discussed in the preceding section.

Arene oxides such as **8** have been often written as a key intermediate in the NIH shift. However, this is not the case since a similarly large NIH shift is observable also in the methoxylation (i.e., Y = Me in Scheme II) where epoxide formation is impossible. Then, reactions 6A and 6B are competitive as a reaction of dienyl cation **6**. Since it is well-known that the deprotonation of carbenium ions is base-catalyzed, reaction 6B is accelerated much more by water than by MeCN as a weaker base. The observed higher shift values in MeCN are well understood, in addition to the increased redox potential of Fe^{3+} accelerating reaction 5A, on the basis of the solvent effect on the deprotonation step 6B.

The conversion of **6** into **7** (step 6A) is the well-known Wagner-Meerwein type rearrangement, the driving force of which is its exothermicity yielding more stable products. For example, rearrangements of carbenium ions usually observed are in the direction of primary → secondary → tertiary and not the reverse one. The present study revealed a substituent effect that the NIH shift for the hydroxylation of anisole (**5**, R = MeO and Y = H) is significantly low in comparison to the cases of R = Me, Cl, and MeCO (cf. Table IIA). A more interesting effect is the very low shift value for the acetoxylation (Y = MeCO), as shown in Table IIB, while the methoxylation (Y = Me) is a large value. These apparently complex substituent effect on the NIH shift is well understood by assuming that the rearrangement 6A becomes faster as the exothermicity increases in going from **6′** and **7′**. Heats



of formation of **6′** and **7′** (Z = OH) were calculated by the MINDO/3 method[40] and listed in Table V. For the cases of Z = OH and R = Me, Cl, and MeCO, the stabilization of cation **7′** by an OH group is important, and the enthalpy difference (ΔH_f) is as large as ca. −20 kcal/mol. In contrast, the enthalpy difference

(40) MINDO/3, RHF method, QCPE Program No. 309.

Scheme II. Mechanism of the NIH Shift

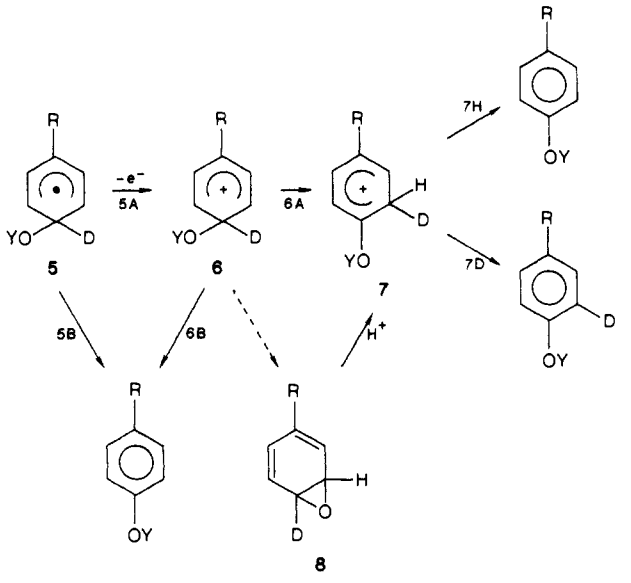


Table V. Substituent Effect for the Heat of Formation of **6** and **7′**

	substituent[a]		NIH shift	heat of formation[c]		
run	R	Z	obsd[b]	H_f(6′)	H_f(7′)	ΔH_f[d]
51	MeO	OH	small	113.48	107.80	−5.68
52	Me	OH	large	154.70	134.74	−19.96
53	Cl	OH	large	155.77	138.20	−17.57
54	MeC=O	OH	large	134.44	109.56	−24.88

[a] Substituent in dienyl cations **6′** and **7′**. [b] Approximate magnitude of observed NIH shift in the Fenton oxidation. [c] Heats of formation (kcal/mol) of cations **6′** and **7′** calculatedc by MINDO/3. The geometries of **6′** and **7′** were optimized by starting from the related values in ref 8. [d] The difference (kcal/mol) corresponds to the heat of reaction for the rearrangement of **6** to **7**.

for the anisole case (R = MeO) is very small (i.e., only −5.7 kcal/mol). This is because the stabilization of **6′** (R = MeO, Z = OH) by the MeO group is significant, and hence the effect of the second stabilizing OH group in **7′** is not so large. Thus, the rearrangement of **6′** is slowed down when R = MeO, the deprotonation (i.e., path 6B) becoming predominant.

The shift value was low for the case of acyloxylation (Z = OCOMe). This might be explained by a smaller enthalpy difference between **6′** and **7′** because of the reduced stabilizing ability of the acyloxy group in comparison to that of the hydroxyl group. An alternative explanation is an enhanced deprotonation of **6′**, owing to the electron-attracting acyloxyl group. At present, we have no definite evidence to differenciate them.

The final step for the NIH shift accompanies the kinetic isotope effect on the deprotonation of cation **7**. In a recent detailed study on microsomal hydroxylation, a k_H/k_D value of 4.0 has been reported.[6] As for the related nonenzymatic reactions, k_H/k_D values of ca. 2 are estimated indirectly from relative yields of olefins in the deprotonation of carbenium ions.[41] In fact, the value of 1.72 for the deprotonation was obtained directly in the acid-catalyzed dehydration of $PhCH(OH)CH_2D$.[42] A related deprotonation of toluene cation radical to form benzyl radical afforded the k_H/k_D value of around 3.0.[43] These results for nonenzymatic reactions indicate the k_H/k_D values of 1.7–3.0 for the deprotonation of **7**. Then, the observed NIH shift of 50.8% for toluene suggests the

(41) Shiner, V. J., Jr. In *Isotope Effects in Chemical Reactions*; Collins, C. J., Bowman, N. S., Eds.; Reinhold: New York, 1970; p 130.

(42) The dehydration of $PhCH(OH)CH_2D$ (D %, 93.2%) was undertaken in 18 N H_2SO_4 at 25 °C, and the resulting styrene contained 72.2% D. Then, k_H/k_D is (72.2/2)/(93.2 − 72.2) = 1.72 ± 0.05.

(43) The deuterium isotope effect for the deprotonation of toluene-α-d_1 cation radical in aqueous MeCN: Katoh, M.; Sawaki, Y., unpublished results.

formation of **7** in 67–80% selectivity[44] and the predominant pathway as **5** → **6** → **7**.

Finally, it is interesting to compare the present hydroxylation with enzymatic or model P-450 ones. The present nonenzymatic study demonstrates that a high NIH shift would result if the one-electron oxidation of dienyl radical **5** (i.e., step 5A) is much faster than the hydrogen atom abstraction by oxygen (i.e., step 5B). The reported low values only for nitrobenzene and benzonitrile in the microbial hydroxylation[6] are comprehensible since the one-electron oxidation is slowed down by the electron-attracting group. The high NIH shift, as usually observed, for microbial and model P-450 hydroxylations under aerated conditions reflects an efficient one-electron oxidation, in preference to the H• abstraction by oxygen, immediately after the formation of cyclohexadienyl radical **5**.

Experimental Section

^{1}H NMR spectra were recorded with a Hitachi R24B NMR spectrometer and GC/MS spectra with a JEOL D300 mass spectrometer. Redox potentials were determined on a Yanagimoto P1100 polarographic analyzer. GLC analyses were performed with a Yanagimoto G180 gas chromatograph with 1–2-m columns: PEG 20M, 20% on Chromosorb WAW; KG02 on Uniport HP.

Materials. Toluene-*4-d* was prepared by dropping D_2O into the ethereal solution of the Grignard reagent from *p*-bromotoluene; its yield was 53%, and deuterium content was 92.8% by GC/MS analysis. Anisole-*4-d* and chlorobenzene-*4-d* were prepared similarly from the corresponding bromides in over 65% yield, their deuterium contents being 91.7 and 95.7%, respectively. Acetophenone-*4-d* was prepared in 31% yield via the low-temperature acylation of the Grignard reagent from bromobenzene-*4-d*.[45] Its deuterium content was 95.5%. Metal salts and quinones were of commercial sources and of guaranteed grade.

Fenton Oxidation. A solution containing 1 mmol of toluene-*4-d*, 0.1 mmol of $Fe(ClO_4)_2$, and an appropriate oxidant in 2 mL of 90% MeCN was placed in a 20-mL test tube with a septum cap and flushed with argon, and 0.1 mmol H_2O_2 in 1 mL of 90% MeCN was added slowly through a needle for 10–15 min at 25 °C. After it was stirred for 30 min, the reaction mixture was diluted with saturated NaCl aqueous solution and extracted with ether. The products were analyzed by GLC and/or GC/MS.

The reaction in 100% MeCN was carried out similarly and the oxidation in water in saturated aqueous solution of aromatics. The reaction under oxygen was done with bubbling oxygen gas.

Peroxydisulfate Oxidation. A solution of 1 mmol of toluene-*4-d*, 0.05 mmol of $S_2O_8^{2-}$, and 0.1 mmol of oxidant in 10 mL of 90% MeCN was placed in a 20-mL test tube with a septum cap. During flushing with argon, 0.1 mL of solution of 0.05 M $Fe(ClO_4)_2$ was added dropwise for 5 min. After it was stirred for 30 min, the reaction products were analyzed as described above.

The methoxylation was performed similarly under argon but in MeOH/MeCN/H_2O (5:4:1). The reaction under oxygen was carried out with bubbling oxygen gas.

Acyloxylations. An acetonitrile solution (1 mL) containing 2 mmol of toluene-*4-d* and 0.1 mmol each of $Cu(ClO_4)_2$ and benzoyl peroxide was placed in a 20-mL test tube with a septum cap, flushed with an argon stream for 30 min, and heated at 80–83 °C for 3 h.[17] The product distribution was determined by GLC. The cresyl benzoates were hydrolyzed by refluxing in the presence of excess KOH for 3 h, neutralized, and extracted with ether. The deuterium contents of resulting cresols were determined with GC/MS analyses.

The anodic acetoxylation was carried out in a divided electrode cell. A solution of 0.05 mmol of toluene-*4-d* in 10 mL of AcOH containing 0.1 M AcONa[18] was electrolyzed at 2.0 V vs Ag/AgCl with platinum electrodes. After 5% of electricity was passed, the reaction mixture was treated as described above.

Determination of the NIH Shift Values. The NIH shift values were determined by the GC/MS analyses of cresols. The separation of *o*-, *m*-, and *p*-cresols was adequate with a KG02 column (1 or 2 m) and helium as a carrier gas. The percent D of cresols may be roughly estimated from the peak ratios at 107 and 110, but more accurate values were determined as described below.

Mass spectra of unlabeled cresol (M_H, 108) exhibit a significant amount of M − 1 peak. The peaks at 107 (A), 108 (B), and 109 (C) correspond to M − 1, M, and percent ^{13}C, respectively. The ^{13}C content (x), originated from A, in peak B was calculated as eq 6 from eq 5 where B = 100. Then, the fractions of total ^{13}C (D) and M − H (E) are given in eq 7 and 8.

$$A : x = (100 - x) : C \tag{5}$$

$$x = 50 - (2500 - AC)^{1/2} \tag{6}$$

$$D = (C + x)/(A + 100 - x) \tag{7}$$

$$E = A/(100 - x) \tag{8}$$

GC/MS of cresols from the Fenton oxidation of toluene-*4-d* affords mass spectral peaks at 107, 108, 109, and 110, the base one being 108 or 109. The peak X at 108 involves M_H, a; M_D − H, b; and ^{13}C of (M_H − H), c. The peak Y at 109 contains M_D, d; ^{13}C of M_H, e; and ^{13}C of (M_D − 1), f. Here, $M_H = C_6H_4(CH_3)(OH)$ and $M_D = C_6H_3D(CH_3)(OH)$; ^{13}C and −H means M + 1 and M − 1 peaks, respectively. Then,

$$X = a + aDE + eE = (1 + DE)a + Ee \tag{9}$$

$$Y = e + aD + eDE = Da + (1 + DE)e \tag{10}$$

This leads to eq 11 and 12. Thus, deuterium content in cresol may be calculated from eq 13.

$$a = [DX - (1 + DE)Y]/[DE - (1 + DE)^2] \tag{11}$$

$$d = (X - Ea)/(1 + DE) \tag{12}$$

$$D\ \% = 100a/(a + d) \tag{13}$$

The results are listed in the tables. Deuterium contents for other phenols were determined similarly. Although the calculations were somewhat complicated, the above method gave more reliable data. This is because the GC separation of ortho, meta, and para isomers was adequate for phenols but rather poor for their derivatives, e.g., acetates.

^{18}O-Tracer Study. The oxygen incorporation from O_2 was examined by means of an ^{18}O tracer in the Fenton oxidation. The reaction conditions were the same as described above but under 1 atm of oxygen gas containing 8.4% $^{18}O_2$. H_2O_2(aq) was added slowly with magnetic stirring. Product phenols were analyzed with a GC/MS method. Their ^{18}O contents were conveniently determined at the M + 2 peak in comparison to the peak height at M + 1. Averaged values by three to five determinations were divided by 0.084 and are listed in Table IV.

Table IV also contains the results for benzene oxidation in water. Since the direct determination of 1,4-benzoquinone was impossible because of the appearance of varying and considerable amounts of the M + 2 peak (e.g., the formation of hydroquinone during the GC/MS), its ^{18}O content was determined after converting into 1,4-dimethoxybenzene to afford a reproducible mass spectra. That is, the quinone was reduced to hydroquinone with sodium dithionite and methylated with dimethyl sulfate in alkaline solution. The results, as listed in run 50, indicated no incorporation of oxygen from oxygen gas.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

(44) Formation of **7** is estimated to be 50.8% × (1.00 + 1.72)/1.72 = 80.3% and 50.8% × (1.0 + 3.0)/3.0 = 67.7% for k_H/k_D = 1.72 and 3.0, respectively.

(45) Newman, M. S.; Smith, A. S. *J. Org. Chem.* **1948**, *13*, 592.