The Acid-Catalyzed Oxidation of Methoxybenzenes to *p*-Benzoquinones by Dimethyldioxirane

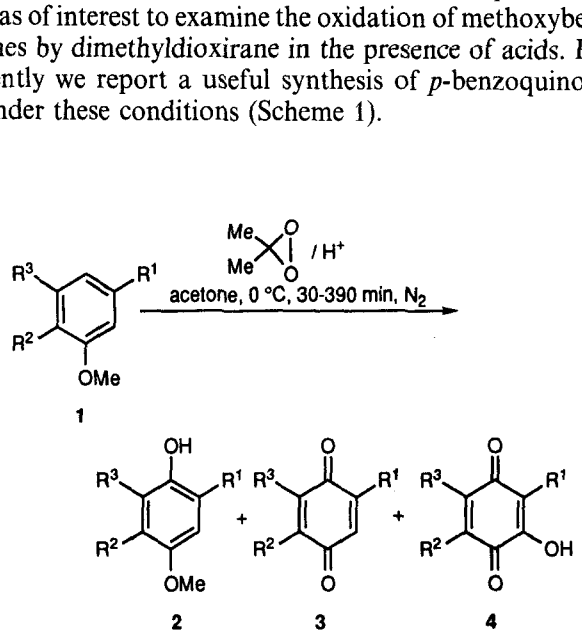
Waldemar Adam,* Masao Shimizu#
Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany
Received 7 October 1993; revised 14 November 1993

Methoxybenzenes **1** were oxidized to phenols and/or *p*-benzoquinones by dimethyldioxirane; in the presence of strong acids, the intermediate phenols were effectively converted to the *p*-benzoquinones **3**.

Numerous quinones show pronounced bioactivity[1] and, consequently, serve as important compounds in medicine.[2] For example, trimethyl-*p*-benzoquinone and 2,3-dimethoxy-5-methyl-*p*-benzoquinone are especially important as starting materials for the synthesis of vitamin E and coenzyme Q, while 2-methyl-1,4-naphthoquinone constitutes vitamin K_3, a wide spread food additive in animal feed. Therefore, efficient synthetic methods for quinones have been sought for, especially the direct oxidation of arenes.[3]

Dimethyldioxirane is a well-known selective oxidant;[4] however, its oxidation power can sometimes be controlled only with difficulty. For example, Crandall stated that the complex product mixtures, which result in the oxidation of simple phenols and anisoles, do not warrant detailed study.[5] Therefore, only the oxidation of hindered phenols[5,6] or hydroquinones[7] by dioxiranes has afforded preparatively useful results.

Most oxidations of arenes to quinones have been carried out under acidic conditions, for example, in acetic acid as solvent. Since acid catalysis appears to play an important role in the conversion of arenes to quinones, it was of interest to examine the oxidation of methoxybenzenes by dimethyldioxirane in the presence of acids. Presently we report a useful synthesis of *p*-benzoquinones under these conditions (Scheme 1).



1-4	R^1	R^2	R^3
a	Me	MeO	H
b	Me	H	MeO
c	MeO	Me	MeO
d	Me	MeO	MeO

Scheme 1

The product distributions of the oxidation of methoxybenzenes **1** by dimethyldioxirane are shown in Table 1, the spectral characterization in Table 2. When 1,3,5-trimethoxy-2-methylbenzene (**1c**), the arene derivative investigated in greater detail, was treated with two equivalents of dimethyldioxirane in the presence of sulfuric acid, the 2,6-dimethoxy-3-methyl-*p*-benzoquinone (**3c**) was isolated in 50% yield (run 8). Other strong acids were also effective for the formation of the benzoquinone **3c** (runs 10 and 11), but a weak acid such as acetic acid (run 12) and 12-molybdophosphoric acid (run 9) gave only low yields of the benzoquinone **1c**. However, in the absence of acid, the formation of the benzoquinone was not oberved and 2,4,6-trimethoxy-3-methylphenol (**2c**) was obtained in 27% yield (run 6).

In the case of the other methoxybenzenes **1a,b,d**, addition of acid was also essential for the synthesis of the benzoquinones **3a,b,d**. When acid was not added, in the case of arene **1d**, a complex, intractable mixture of oxidation products was obtained (run 13). For arene **1a**, the benzoquinone **3a** was isolated in low yield (run 1) with substantial amounts (23%) of 2-hydroxy-5-methoxy-3-methyl-*p*-benzoquinone (**4b**), while for arene **1b** only a low yield (13% at 95% conversion) of the hydroxyquinone **4a** was obtained (run 3). The structure of the hydroxyquinone **4b** was determined by ^{1}H NMR analysis, which revealed the disappearance of the 5-H signal for the quinone **3b**.

The rate of oxidation was significantly influenced by the position of the methoxy groups in the arene. Since the ortho and para positions of methoxybenzenes are reactive toward electrophiles, the hydroxylation of the methoxybenzenes **1** by dimethyldioxirane is expected to occur at these positions in view of the activating character exercised by methoxy groups. When the reactivities of the trimethoxybenzenes **1c** and **1d** are compared (runs 8 and 14), the 1,3,5-regioisomer **1c**, in which the two identical unsubstituted positions are activated by two ortho and one para interactions with the three methoxy groups, was more reactive than the 3,4,5-regioisomer **1d**, for which each one ortho, meta, and para interaction apply.

The phenols **2** (hydroquinone monomethyl ethers) presumably intervene as reaction intermediates in the oxidation of the methoxybenzenes **1** to the benzoquinones **3**. When a decreased amount of dimethyldioxirane to the methoxybenzene **1c** was employed, at low conversion (17%) the phenol **2c** was obtained in high yield (73%) even in the absence of acid (run 7). As a control experiment, the phenol **2c** was treated with dimethyldioxirane in the presence of acid and, indeed, the benzoquinone **3c** was isolated in high yield (77% at 100% conversion), but in the absence of acid its yield was drastically lower (23% yield at 74% conversion). Further control experiments established that the benzoquinones **3** did not react with dimethyldioxirane with or without acid (sulfuric

Table 1. Dimethyldioxirane Oxidation of Methoxybenzenes **1** in the Presence of Acids[a]

Entry	Arene	Acid	Reaction Time (min)	Conv. (%)	Mass Balance (%)	Product Distribution,[b] Yield (%)[c]		
						2	**3**	**4**
1[d]	**1a**	–	360	47	66	0	21(6)	79(23)
2[d]	**1a**	H_2SO_4	60	48	62	0	76(16)	24(5)
3	**1b**	–	300	95	17	0	0	100(13)
4	**1b**	H_2SO_4	45	77	64	2(1)	85(45)	13(7)
5	**1b**	HMP[e]	300	75	65	2(1)	93(50)	5(3)
6	**1c**	–	30	96	30	100(27)	0	0
7[f]	**1c**	–	30	17	95	100(73)	0	0
8	**1c**	H_2SO_4	60	100	50	0	100(50)	0
9	**1c**	HMP[e]	30	100	23	0	100(23)	0
10	**1c**	H_3PO_4	30	100	51	0	100(51)	0
11	**1c**	CF_3CO_2H	30	100	46	0	100(46)	0
12	**1c**	AcOH	30	100	22	27(6)	73(16)	0
13	**1d**	–	390	90	10	complex mixture		
14	***1d***	H_2SO_4	240	92	32	44(12)	56(15)	0
15[g]	**1d**	H_2SO_4	120	84	49	54(21)	46(18)	0

[a] Reaction conditions: Arene (1 mmol), dimethyldioxirane (2 mmol), acid (50 mg), acetone (40 mL), 0 °C, N_2.
[b] Normalized to 100 %.
[c] Yield of isolated product based on converted starting materials is given in parenthesis.
[d] Dimethyldioxirane (3 mmol).
[e] HMP = $H_3PMo_{12}O_{40} \cdot nH_2O$.
[f] Arene (2 mmol), dimethyldioxirane (0.47 mmol), −15 °C.
[g] At room temperature (ca. 20 °C).

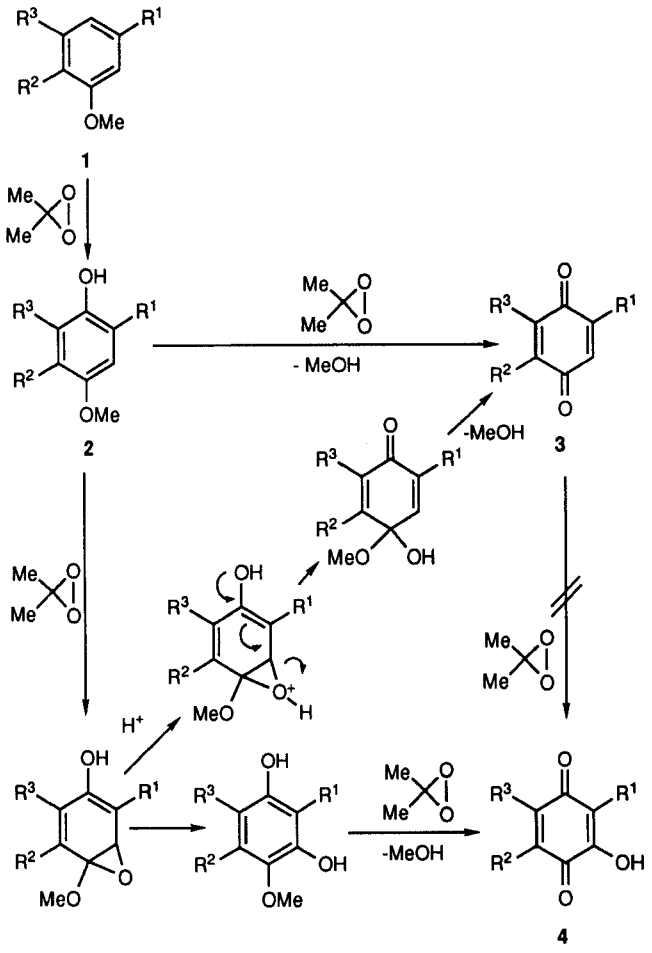
Table 2. Physical and Spectral Data of the Arene Oxidation Products **2**, **3**, and **4**

Product	mp (°C) (solvent)[a]	Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
2b	105–106 (Et_2O/PE)	107[14]	3400	2.19 (s, 3H), 3.70 (s, 3H), 3.83 (s, 3H), 5.21 (s, 1H), 6.25 (d, 1H, J = 0.4), 6.30 (d, 1H, J = 0.4)
2c	oil	oil[15]	3520[b]	2.04 (s, 3H), 3.73 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 5.22 (s, 1H), 6.29 (s, 1H)
2d	oil	–[16]	3490[b]	2.22 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 5.47 (br s, 1H), 6.45 (s, 1H)
3a	176–177 ($CHCl_3$/MeOH)	175–176[17]	1660, 1640	2.08 (s, 3H), 3.81 (s, 3H), 5.94 (s, 1H), 6.56 (s, 1H)
3b	152–153 ($CHCl_3$/MeOH)	153[18]	1650, 1625	2.00 (s, 3H), 3.74 (s, 3H), 5.81 (s, 1H), 6.47 (br s, 1H)
3c	124–125 (PE)	125–126[19]	1685, 1650	1.93 (s, 3H), 3.76 (s, 3H), 3.93 (s, 3H), 5.83 (s, 1H)
3d	59 (PE)	59[16]	1645, 1630	1.96 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 6.33 (s, 1H)
4a	198–199 (PE)	204[20]	3240, 1650, 1610	1.90 (s, 3H), 3.77 (s, 3H), 5.77 (s, 1H), 6.67 (s, 1H)
4b	154–155 (Et_2O/PE)	155–156[21]	3260, 1635, 1630	1.90 (s, 3H), 3.83 (s, 3H), 5.81 (s, 1H), 7.3 (br s, 1H)

[a] PE = Petroleum ether (bp 50–70 °C).
[b] Measured in CCl_4.

acid) and these resistant substrates could be recovered almost quantitatively. Therefore, the overoxidized products, such as the well-defined hydroxyquinones **4**, were not formed from the reaction of benzoquinones with dimethyldioxirane. Nonetheless, treatment of the phenol **2b** with one equivalent of dimethyldioxirane in the presence of sulfuric acid afforded after 85% conversion, besides 47% benzoquinone **3b**, also 16% hydroxyquinone **4b**.

To rationalize these results, the oxidation mechanism shown in Scheme 2 is proposed. First the methoxybenzenes **1** are oxidized by dimethyldioxirane to the phenols **2**, which are subsequently converted to the *p*-benzoquinones **3**. Since the *p*-benzoquinones **3**, once formed, are difficult to be further oxidized by the dimethyldioxirane,[6,8] we suggest that the hydroxyquinones **4** derive from competitive epoxidation of the phenol **2** to the arene oxides,[6] NIH shift,[9] and subsequent oxidation. The favorable role of the acid is to promote ring opening of the intermediary arene oxides to the *p*-benzoquinones **3**.[10]



Scheme 2

In summary, the novel utilization of acid-catalyzed dimethyldioxirane oxidation of methoxybenzenes **1** affords the corresponding *p*-benzoquinones **3** in good yields. Since dimethyldioxirane directly hydroxylates methoxybenzenes **1** to the corresponding phenols **2** with significant overoxidation to the respective hydroxyquinones **4**, the advantage of the acid lies mainly in the controlled and selective oxidation of the intermediary phenols **2** to the *p*-benzoquinones **3**.

All reagents were of commercial quality. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and ^{1}H NMR spectra were measured on Bruker AW80 or Bruker AC 250 spectrometers. Melting points were determined on a Büchi SMP 20 melting point apparatus.

Dimethyldioxirane (as acetone solution) was prepared as described.[11] 1,2-Dimethoxy-4-methylbenzene[12] **(1a)** and 1,3-dimethoxy-5-methylbenzene **(1b)**[13] were prepared analogous to the reported methods.

Oxidation of Methoxybenzenes 1 to *p*-Benzoquinones 3; General Procedure.

The required amount of the solution of dimethyldioxirane in acetone (0.062–0.085 M), which was dried over molecular sieves (4 Å) at −20 °C, was added rapidly under N_2 atmosphere to a solution of the appropriate methoxybenzene **1a–d** (1 mmol) and an acid (50 mg) in acetone (40 mL). The mixture was stirred at ca. 0 °C (ice-water bath) for 30–390 min and diluted with H_2O. The products were extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers dried ($MgSO_4$), and the solvent was evaporated (ca. 20 °C/20 Torr). The oxidation products were separated by silica gel chromatography with CH_2Cl_2, CH_2Cl_2/acetone/MeOH (100:5:1), or CH_2Cl_2/EtOAc (20:1) as eluents (Tables 1 and 2).

The generous gift of potassium monoperoxy sulfate (Curox®) from Peroxid-Chemie GmbH (München, Germany), and the financial support by the Deutsche Forschungsgemeinschaft (SFB 347 „Selektive Reaktionen Metall-aktivierter Moleküle") and the Fonds der Chemischen Industrie are gratefully appreciated. M.S. thanks the Alexander von Humboldt Foundation for a postdoctoral fellowship.

On leave of absence from the National Institute of Materials and Chemical Research, Tsukuba (Japan).

(1) Otsuka, H.; Komiya, T.; Fujioka, S.; Goto, M.; Hiramatsu, Y.; Fujimura, H. *Yakugaku Zasshi* **1981**, *101*, 1108; *Chem. Abstr.* **1982**, *96*, 91533.
(2) Yamada, S.; Takeshita, T.; Tanaka, J. *Yuki Gosei Kagaku Kyokai Shi* **1982**, *40*, 268; *Chem. Abstr.* **1982**, *97*, 39148.
(3) Orita, H.; Shimizu, M.; Hayakawa, T.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1652.
Orita, H.; Shimizu, H.; Hayakawa, T.; Takehira, K. *React. Kinet. Catal. Lett.* **1991**, *44*, 209.
Adam, W.; Ganeshpure, P.A. *Synthesis* **1993**, 280.
(4) Adam, W.; Hadjiarapoglou, L.P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: Chichester, 1992, p 195.
(5) Crandall, J.K.; Zucco, M.; Kirsch, R.S.; Coppert, D.M. *Tetrahedron Lett.* **1991**, *32*, 5441.
(6) Altamura, A.; Fusco, C.; D'Accolti, L.; Mello, R.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1991**, *32*, 5445.
(7) Adam, W.; Schönberger, A. *Tetrahedron Lett.* **1992**, *33*, 53.
(8) Shimizu, M.; Orita, H.; Hayakawa, T.; Takehira, K. *Tetrahedron Lett.* **1989**, *30*, 471.
(9) Daly, J.W.; Jerina, D.M.; Witkop, B. *Experientia*, **1972**, *28*, 1129.
(10) Similar ring-opening reaction in the presence of acid was reported: Olah, G.A.; Ohnishi, R. *J. Org. Chem.* **1978**, *43*, 865.
(11) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
(12) Ono, K.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 127.
(13) Adams, R.; Wolff, H.; Cain, C.K.; Clark, J.H. *J. Am. Chem. Soc.* **1940**, *62*, 1770.
(14) Späth, E.; Palier, M.; Gergely, G. *Ber.* **1940**, *73*, 795.
(15) Sargent, M.V. *J. Chem. Soc. Perkin Trans. 1* **1982**, 403.
(16) Sugihara, H.; Watanabe, M.; Kawamatsu, Y.; Morimoto, H. *Justus Liebigs Ann. Chem.* **1972**, *763*, 109.
(17) Davidge, H.; Davies, A.G.; Kenyon, J.; Mason, R.F. *J. Chem. Soc.* **1958**, 4569.
(18) Teuber, H.-J.; Hasselbach, M. *Chem. Ber.* **1959**, *92*, 674.
(19) Oxford, A.E. *J. Chem. Soc.* **1942**, 577.
(20) Anslow, W.K.; Ashley, J.N.; Raistric, H. *J. Chem. Soc.* **1938**, 439.
(21) Anslow, W.K.; Raistrick, H. *J. Chem. Soc.* **1939**, 1446.