OXIDATION OF MESITYLENE BY HYDROGEN PEROXIDE IN AcOH–Ac_2O–H_2SO_4

O. A. Kholdeeva and I. V. Kozhevnikov

UDC 541.124:542.943.7:547.
535.3'033:546.215

By the oxidation of mesitylene by hydrogen peroxide in AcOH–Ac_2O–H_2SO_4 one can obtain mesitol (2,4,6-trimethylphenol) (with a selectivity of 57-69% at a mesitylene conversion of 22-16% and the acetate of mesitol with a selectivity of 72-85% at 25-22% conversion. The peroxide responsible for the oxidation of mesitylene in this system is in the form of peracetic acid, formed in situ. Over the concentration range studied, the reaction is first order in AcOOH, mesitylene, and H_2SO_4. Hydroxylation of mesitylene by AcOOH proceeds by an electrophilic substitution mechanism, the limiting step being the formation of the σ-complex.

The hydroxylation of mesitylene (I) is of considerable interest, and it can be effected with quite high selectivity on account of the stability of mesitol (II) to further oxidation [1-3]. This reaction proceeds under the influence of CF_3COOOH, $H_2O_2 + AlCl_3$, H_2O_2 + HF [1], H_3PO_5 [3], and other oxidants. It has been reported that H_2O_2 in AcOH–H_2SO_4 is an effective hydroxylating system [2] but this system, which is so simple and convenient to prepare, has been very little studied. The hydroxylation of arenes by highly active oxidants in strongly acidic media ($CF_3COOOH + CF_3COOH$, H_2O_2 + 80% H_2SO_4) takes place by an electrophilic substitution mechanism involving the OH^+ cation which is generated by the oxidant system [4, 5]. The present work is concerned with a study of the oxidation of the aromatic nucleus (I) by H_2O_2 in AcOH–Ac_2O–H_2SO_4.

EXPERIMENTAL

Mesitylene (pure grade), acetic acid (chemically pure), and acetic anhydride (pure) were purified by redistillation (AcOH was first treated at bp with CrO_3). The remaining reagents (chemically pure or analytical grade) were used without further purification. Hydrogen peroxide was a 30% aqueous solution. $C_6D_3(CH_3)_3$ was prepared by exchange of (I) with 80% D_2SO_4 at 70°C over 5 days. The extent of exchange was 86% as monitored by mass spectrometry. The results of [6] show that only the ring protons are exchanged but we established that the $C_6D_3(CH_3)_3$ obtained (identified by the molecular ion: m/z = 123) contained 10% deuteromesitylene with m/z = 124.

Oxidation of (I) was carried out in a flask provided with a stirrer, dropping funnel, thermometer and reflux condenser. A mixture of (I), AcOH, and H_2SO_4 was stirred and a solution of H_2O_2 in Ac_2O added dropwise. Concentrations: (I) [ArH] = 1.0 to 2.2, $[H_2O_2]$ = 0.5 to 1.5, $[H_2SO_4]$ = 0.05 to 0.75 mole/liter. The overall volume of the reaction mixture was 50 ml, reaction time 0.5 to 4 h, temperature 20 to 40°C. The method of isolating the products is set out below.

Identification and analysis of the products was carried out by chromatography-mass spectrometry and by GLC as in [7]. The concentrations of H_2O_2, peracetic acid, and diacetyl peroxide were determined by the method of [8].

Method for the Preparation of Mesitol (II). In a flask of 2-liter capacity was placed 28 ml AcOH, 14 ml conc. H_2SO_4, and 280 ml (I). A solution prepared by mixing 140 ml 30% H_2O_2 with 540 ml Ac_2O was added dropwise with stirring over a period of 2 h while cooling to ~40°C. The reaction mixture was stirred for a further 1.5 h at 40°C and then diluted with ~1 liter water, the organic layer separated and the aqueous layer extracted with 2 × 200 ml ether. The extract was washed with solutions of $NaHCO_3$, Na_2SO_3, and water (to give a negative reaction with KI), dried over $CaCl_2$, and the ether distilled off. The organic phases were combined and extracted with 2 × 200 ml 10% NaOH. Unreacted (I) (209 ml) was

---

Institute of Catalysis, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2716-2721, December, 1990. Original article submitted October 10, 1989.

distilled from the residue and used again. The alkaline extract was cooled and neutralized with 10% HCl and the crystals of (II) which separated were filtered off, washed with cold water, and dried. The yield of (II) was 36.4 g (53% calculated on (I) reacted). Redistillation in vacuum yielded white crystals with mp 69-70° (cf. [9]). The IR and PMR spectra of the (II) so obtained were in agreement with those of a standard sample.

The kinetics of the oxidation of (I) by peracetic acid were studied in a thermostatted (±0.1°C) glass reactor with a reflux condenser and magnetic stirrer at 20 to 50°C, [ArH] = 0.1 to 1.0, $[H_2O_2]$ = 0.025 to 0.1, $[H_2SO_4]$ = 0.01 to 0.7 mole/liter. 30% H_2O_2, AcOH, H_2SO_4, and Ac_2O were mixed in advance, the latter being taken in quantity sufficient to react with all the water present in the H_2O_2 and H_2SO_4. Under these conditions, the H_2O_2 is converted to the extent of 98-99% into peracetic acid. The time taken to establish equilibrium depends on the acidity of the medium: from 5 min with $[H_2SO_4] = 0.7$ mole/liter to 2 h with $[H_2SO_4] = 0.01$ mole/liter. After equilibrium was established, (I) was added and the decrease in peracetic acid content followed iodometrically. In the absence of (I), the rate of decomposition of the AcOOH was lower by an order of mangitude. The rate constants were determined from the initial rates using the equation $w_0 = k_2[ArH]_0[AcOOH]_0$.

The isotope effect in the hydroxylation of (I) was determined from the rates and products of the reaction of $C_6D_3(CH_3)_3$ and $C_6H_3(CH_3)_3$ by a kinetic method as the ratio of the rate constants $k_2{}^H/k_2{}^D$ and by mass spectrometry as the ratio of the molecular ions of (II)–D_2 (m = 138) and (II)–D_0 (m = 136).

RESULTS AND DISCUSSION

Preparation of Mesitol and Its Acetate. It was established that in the hydroxylation of (I) by hydrogen peroxide in the system $AcOH–Ac_2O–H_2SO_4$ only the products of oxidation of the nucleus are formed – (II) and its acetate (III) (Table 1) – which is evidence that the reaction proceeds by an electrophilic substitution mechanism [1, 2]. Products of the oxidation of the CH_3 group are found only when $[H_2O_2]/[ArH] > 1$. Tars are formed by secondary reactions, probably by the further oxidation of the primary product.

TABLE 1. Oxidation of Mesitylene by H_2O_2 in $AcOH–Ac_2O–H_2SO_4$ ([ArH] = 1.0 mole/liter, 30°C)

No.	$[H_2O_2]$	$[H_2SO_4]$	$[Ac_2O]/[H_2O_2]$	Time, h	Conversion of mesitylene,	Product	Yield, mole %^{a}
	mole/liter						
1	0,5	0,5	5,5	0,5	16	(II)	69 (11,0)
				1	21	(II)	62 (13,0)
				2	25	(II)	54 (13,5)
2	0,75	0,5	4,8	0,5	23	(II)	56 (12.9)
3	0,5	0,75	5,5	0,5	28	(II)	42 (11,8)
				2	37	(II)	40 (14,8)
4	0,5	0,25	7,2	0,5	21	(III)	85 (17,9)
				2	21	(III)	83 (17,4)
5	0,5	0,05	7,2	0,5	19	(III)	79 (15,0)
				4	19	(III)	80 (15,4)
6	0,5	0,5	7,2^b	36	–	(III)	0
						(II)	0
7	1,1^c	0,25	4,9	4	19	(II)	63 (12.0)
8	1,2^c	0,1	5,0^d	4,5	–^{e}	(II)	Trace
						(III)	Trace
9	0,5	0,5	2,1^f	1	9	(II)	38 (3,4)
10	0,25	0,25	14,4	1	–	(III)	– (4)
11	0,5	0,5	f, g	6	–	(II)	– (4)
12	0,5	0,5	f, h	36	–	(II)	Trace

a) Yield calculated on mesitylene reacted (in brackets, on initial mesitylene).
b) Solution of H_2O_2 in AcOH added to mixture of Ac_2O + AcOH + H_2SO_4 + ArH.
c) [ArH] = 2.2 mole/liter.
d) H_2O_2 added to mixture of Ac_2O + AcOH + H_2SO_4 + ArH.
e) Conversion not determined.
f) System separated into aqueous and organic layers.
g) Reaction in absence of Ac_2O.
h) Dioxane used instead of Ac_2O + AcOH.

TABLE 2. Distribution of Peroxide Forms in the System H_2O_2–$AcOH$–Ac_2O–H_2SO_4 with Variation in Process Conditions (30°C, $[H_2SO_4]$ = 0.25 mole/liter)

No.	$[H_2O_2]$, mole/liter	$[Ac_2O]/[H_2O_2]^a$	Time, h^b	Distribution of peroxide forms, %		
				H_2O_2	AcOOH	AcOOAc
1	0,5	7,2	$0,25^c$	4	80	16
			0,5	–	12	88
			2,0	–	5	95
2	0,5	$7,2^d$	$0,25^c$	–	2	98
3	0,5	5,5	0,5	2	96	2
			1,0	1	97	2
4	0,25	5,5	0,5	2	96	2
5	$1,5^e$	3,9	0,5	12	88	–
			1,0	7	92	1
6	$1,2^e$	$5,0^f$	1,0	–	26	74

a) Previously homogenized mixture of H_2O_2 and Ac_2O added dropwise over 0.5 h to solution of $AcOH + H_2SO_4$.
b) From beginning of H_2O_2 addition.
c) Half of $Ac_2O + H_2O_2$ mixture added.
d) Mixture of $H_2O_2 + AcOH$ added to solution of $Ac_2O + AcOH + H_2SO_4$.
e) $[H_2SO_4]$ = 0.1 mole/liter.
f) H_2O_2 added to solution of $Ac_2O + AcOH + H_2SO_4$.

The yield of (II) and (III) was dependent on the ratio $[Ac_2O]/[H_2O_2]$. The Ac_2O combines with the water present in the 30% H_2O_2 and formed in the reaction of H_2O_2 with AcOH

$$H_2O_2 + AcOH \rightleftarrows AcOOH + H_2O$$
$$Ac_2O + H_2O \rightarrow 2AcOH$$

At a molar ratio $[Ac_2O]/H_2O_2]$ = 3.9 to 5.5, the main product of the reaction is (II). Here, all the Ac_2O is consumed in combining with H_2O. With $[Ac_2O]/[H_2O_2]$ = 7.2 to 7.6 (an excess of Ac_2O relative to H_2O) the main product becomes (III). With $[Ac_2O]/[H_2O_2]$ between 5.5 and 7.2, a mixture of (II) and (III) is formed while with $[Ac_2O]/[H_2O_2] < 3.9$ the reaction mixture separates into two layers and the yield of (II) is greatly reduced. The selectivity of the process for (III) reaches 85% and for (II), 69% at conversions of (I) between 16 and 25% (Table 1).

We employed an iodometric method [8] to study the distribution of the forms of oxidant as the process conditions varied (Table 2). With $[Ac_2O/[H_2O_2]$ = 3.9 to 5.5 the H_2O_2 in the presence of H_2SO_4 is rapidly and practically completely converted to AcOOH, which is in agreement with the results of [10, 11]. Small amounts of H_2O_2 and AcOOAc are also present. One can assume that under these conditions, the active form of peroxide in the reaction for the preparation of (II) is AcOOH. In fact, when (I) is added to previously prepared AcOOH, mesitol (II) is formed in good yield. H_2O_2 is considerably less active, since on replacing $AcOH + Ac_2O$ with dioxane, in which the formation of AcOOH is not possible, the yield of (II) falls by an order of magnitude (Table 1, No. 12). For effective hydroxylation by H_2O_2, considerably greater acidity is necessary, for example, a medium of HF [1], or 80% H_2O_2 [5].

With $[Ac_2O]/[H_2O_2] > 7.2$, the main peroxide form becomes diacetyl peroxide (Table 2). The formation of AcOOAc can be expressed by the equation [11]

$$Ac_2O + AcOOH \rightleftarrows AcOOAc + AcOH$$

However, equilibrium is not attained under the conditions of our experiments, the ratio of AcOOH/AcOOAc depending on the conditions of mixing of the reagents. One might suppose that AcOOAc would participate in the formation of (III) but we have established that diacetyl peroxide does not react with (I). Hence one should not add H_2O_2 to a mixture of Ac_2O with the other reagents because under these conditions the inactive AcOOAc is preferentially formed (Table 1, Nos. 6 and 8; Table 2, Nos. 2 and 6). On gradual addition of a mixture of H_2O_2 and Ac_2O to a solution of (I) in AcOH and H_2SO_4, the hydroxylation process proceeds more rapidly than the conversion of AcOOH to AcOOAc. Under these conditions one can expect

TABLE 3. Kinetics of the Oxidation of Mesitylene by AcOOH

[ArH]	[AcOOH]	[H_2SO_4]	T, °C	$k_2 \cdot 10^5$, liter/mole·sec
mole/liter				
0,5	0,025	0,1	30	2,00±0,20
0,5	0,055	0,1	30	1,86±0,14
0,5	0,050	0,1	30	1,94±0,09 [a]
0,5	0,106	0,1	30	1,92±0,08
0,5	0,054	0,1	30	1,02±0,08 [b]
0,35	0,065	0,1	30	1,83±0,14
0,25	0,053	0,1	30	2,1±0,2
0,1	0,055	0,1	30	2,2±0,2
1,0	0,059	0,1	30	1,40±0,08
0,5	0,053	0,01	30	1,04±0,12
0,5	0,046	0,05	30	1,34±0,10
0,5	0,055	0,2	30	2,8±0,2
0,5	0,050	0,4	30	4,4±0,3
0,5	0,051	0,7	30	7,2±0,3
0,5	0,053	0,1	40	4,5±0,3
0,5	0,057	0,1	50	11,1±1,2
0,5	0,057	0,1	20	0,48±0,08
0,5	0,054	0,1	30	1,56±0,12 [c]

a) Reaction with $C_6D_3(CH_3)_3$.
b) Without addition of Ac_2O; system contained 0.5 vol. % H_2O.
c) CH_3COOD used instead of CH_3COOH.

conversions of (I) of the order of 23-25% and this does not increase further. An excess of Ac_2O over the specified limits is to be avoided since AcOOAc is then formed almost instantaneously and the reaction does not occur. Consequently, with $[Ac_2O]/[H_2O_2] = 7.2$ to 7.6 the AcOOH which is formed in situ is also an active form and (III) is formed by esterification of (II).

Kinetics of Mesitylene Hydroxylation. Detailed studies have been carried out on the kinetics of the hydroxylation of alkylbenzenes by such oxidants as H_2O_2 + 80% H_2SO_4 [5], CF_3COOOH [4], and H_3PO_5 [3]. There are few kinetic data for the system AcOOH + AcOH: only the kinetics of the oxidation of naphthalene and anisole by peracetic acid in CH_2ClCH_2Cl–AcOH (2:1) with [AcOOH] ≫ [ArH] [12] have been studied. We have investigated the kinetics of the hydroxylation of (I) by AcOOH in AcOH in the presence of H_2SO_4 (Table 3).

With [ArH] = 0.1 to 0.5, [AcOOH] = 0.025 to 0.1, [H_2SO_4] = 0.01 to 0.7 mole/liter, the reaction obeys the equation

$$w = k_2 [\mathrm{ArH}][\mathrm{AcOOH}],$$

where $k_2 = k_0 + k_1[H_2SO_4]$ (Fig. 1). At 30°C, [ArH] = 0.5, [AcOOH] = 0.05 mole/liter, $k_0 = 1 \cdot 10^{-5}$, $k_1 = 8.8 \cdot 10^{-5}$ liter/(mole·sec). The same kinetic equation is obtained for the systems H_2O_2 + 80% H_2SO_4 [5] and CF_3COOOH [4, 13]. In the case of the oxidation of (I) by H_3PO_5 in MeCN a linear dependence of log k_2 on the Hammett acidity function H_0 was found [3]. With [ArH] > 0.5 mole/liter the order of reaction in (I) is reduced, apparently on account of a reduction in the polarity of the medium. The reaction is greatly retarded by the presence

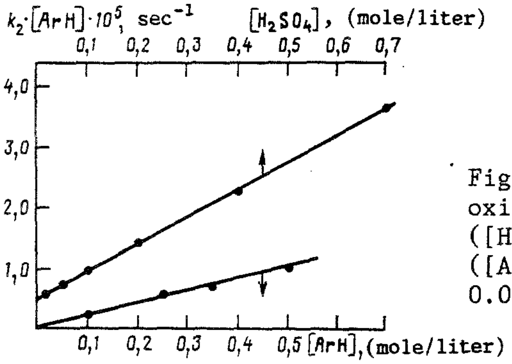


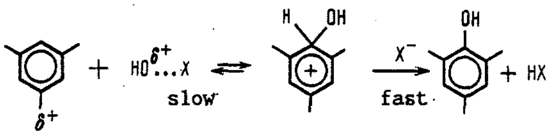
Fig. 1. Variation of rate constants for the oxidation of mesitylene by AcOOH with [ArH] ([H_2SO_4] = 0.1 mole/liter) and with [H_2SO_4] ([ArH] = 0.5 mole/liter) at 30°C and [AcOOH] = 0.05 mole/liter.

of water. The activation energy over the temperature range 20-50°C amounts to 81 ± 7 kJ/mole which is close to the value obtained for other arenes [12].

We have established the absence of any isotope effect on the rates and products of the reaction. For the hydroxylation of (I)–D_3 and (I)–D_0 we found $k_2^H/k_2^D = 1$ (Table 3). In a concurrent oxidation of an equimolar mixture of (I) and (I)–D_3 the ratio of the yields of (II)–D_0 and (II)–D_2 was equal to 1. Apart from this, there is a weak solvent isotope effect: $k_2^{AcOH}/k_2^{AcOD} = 1.2$ (Table 3). It has been shown previously that there is no kinetic isotope effect for the hydroxylation of toluene by H_2O_2 + 80% H_2SO_4 [5] nor by CF_3COOOH [4].

The results obtained are in agreement with a hydroxylation of (I) in the system AcOOH–AcOH–H_2SO_4 by an electrophilic substitution mechanism involving an H atom of the aromatic nucleus and an OH^+ cation generated from a molecule of peracid [4, 5, 14].

$$\mathrm{AcOOH} + \mathrm{H}^+ \underset{\text{fast}}{\rightleftharpoons} \mathrm{AcOOH_2^+}$$



HO...X—$AcOOH_2^+$ or AcOOH.

The absence of any isotope effect shows that the limiting stage is the formation of the σ complex. Thus, one can conclude that hydroxylation of (I) by AcOOH takes place in a similar manner to the reactions of alkylbenzenes with such highly active oxidants as H_2O_2 + 80% H_2SO_4 [5] and CF_3COOOH [4, 14].

The authors express their thanks to L. V. Efremova, G. M. Maksimov, and V. D. Chinakov for their assistance in this work.

LITERATURE CITED

1. A. H. Haines, Methods for the Oxidation of Organic Compounds: Alkanes, Alkenes, Alkynes and Arenes, Academic Press, London (1985).
2. D. H. Derbyshire and W. A. Waters, Nature, 165, 401 (1950).
3. Y. Ogata, Y. Sawaki, K. Tomizawa, and T. Ohno, Tetrahedron, 37, 1485 (1981).
4. E. S. Rudakov and V. L. Lobachev, Kinet. Katal., 28, No. 6, 1335 (1987).
5. E. S. Rudakov and V. L. Lobachev, Ukr. Khim. Zh., 51, No. 10, 1061 (1985).
6. G. P. Miklukhin, Isotopes in Organic Chemistry [in Russian], Izd-vo Akad. Nauk UkrSSR, Kiev (1961), p. 262.
7. O. A. Kholdeeva, I. V. Kozhevnikov, V. N. Sidel'nikov, and V. A. Utkin, Izv. Akad. Nauk SSSR, Ser. Khim., 2069 (1989).
8. F. P. Greenspan and D. G. MacKellar, Anal. Chem., 20, 1061 (1948).
9. Handbook of Chemistry, Khimiya, Moscow–Leningrad, Vol. 2 (1964), p. 775.
10. T. W. Findly, D. Swern, and I. T. Scanlan, J. Am. Chem. Soc., 67, 412 (1945).
11. D. Swern (ed.), Organic Peroxides, Wiley-Interscience, New York–London, Vol. 1 (1970), Vol. 2 (1971).
12. A. A. Akhrem, P. A. Kiselev, and D. E. Metelitza, React. Kinet. Catal. Lett., 2, 177 (1975).
13. A. K. Yatsimirskii and I. V. Berezin, Doklad. Akad. Nauk SSSR, 233, No. 2, 414 (1975).
14. H. Hart, Acc. Chem. Res., 4, 337 (1971).