Nitric Acid Oxidation of Polyalkylbenzenes

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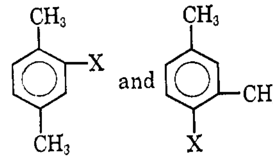
2-Substituted *p*-xylenes on oxidation with nitric acid gave both isomeric toluic acids with the 3-substituted acid predominating. 4-Substituted *m*-xylenes gave only one product, the 4-substituted *m*-toluic acids. Ease of oxidation of a methyl group *meta* to the substituent is in the order Br > Cl > NO_2 > F, that in the *ortho* position is Cl > Br > F > NO_2, while the order at the *para* position is Br > Cl > F > NO_2. The effect appears to be inductive rather than mesomeric.

It has been known for many years that dilute nitric acid will selectively oxidize polyalkylbenzenes to the corresponding benzoic acids.[4] For example, the syntheses of *o*-toluic acid and *p*-toluic acids by oxidation of the corresponding xylenes are reported.[5] However, a search of the literature fails to reveal any studies made on the influence of substituent groups on the course of the reaction. Accordingly, we have studied substituted xylenes of the types



in which X = NO_2, F, Cl, and Br, in order to determine the effect of electron-withdrawing groups as to which methyl group is oxidized.

In the case of the F, Cl, and Br xylenes, the 2-substituted compounds on refluxing for 20 hr with 45% HNO_3 gave two products, the 3-substituted *p*-toluic acid and 2-substituted *p*-toluic acid (Table I). 2-Nitro-*p*-xylene gave only 3-nitro-*p*-toluic acid.

TABLE I

$$\text{2-X—}p\text{-xylene} \xrightarrow[\text{reflux}]{\text{20-hr}} \text{3-X—}p\text{-toluic acid} + \text{2-X—}p\text{-toluic acid}$$

		Yield, %	
X	Temp, °C	3-X—*p*-Toluic acid	2-X—*p*-Toluic acid
Br	117	47	24
Cl	117	44	26
F	117	19	10
NO_2	119	31	0

A 15-hr oxidation of the 4-substituted *m*-xylenes gave, in each case, only one product, the 4-substituted *m*-toluic acids (Table II). Some dibasic acids began to appear after 20 hr (Table III); however, no 2-substituted *m*-toluic acids were isolated from the reactions of any of the 4-substituted *m*-xylenes.

TABLE II

$$\text{4-X—}m\text{-xylene} \xrightarrow{\text{reflux}} \text{4-X—}m\text{-toluic acid}$$

		Yield, %	
X	Temp, °C	10 hr	15 hr
Br	114	41.2	58.5
Cl	114	25.0	33.4
F	114	19.3	26.2
NO_2	117	16.1	22.5

TABLE III

$$\text{4-X—}m\text{-xylene} \xrightarrow[\text{reflux}]{\text{20-hr}} \text{4-X—}m\text{-toluic acid} + \text{4-X—isophthalic acid}$$

	Yield, %	
X	4-X—*m*-Toluic acid	4-X—Isophthalic acid
Br	56	13
Cl	44	1.5
F	36	1.7
NO_2	27	0

Kratochvil, Kupeik, Kudlacek, and Havel[6] have reported the formation of nitrotoluic acids from the nitric acid oxidation of xylenes. In our studies none of the nitrated acids was observed. Some small amounts of nitrated xylenes were obtained along with the unreacted starting materials, but no attempt was made to separate and identify this fraction.

Separation of the isomeric 2- and 3-substituted *p*-toluic acids from the oxidation of the 2-substituted *p*-xylenes was initially carried out making use of their solubility differences in hot water. However, this method was not sufficiently quantitative for our purpose. Consequently the liquid–liquid partition method of Bharaqava and Heidelberger[7] was used with considerable success. In each case the 3-substituted acid was eluted from the column first followed by the 2-substituted acid.

The effects of temperature and reaction time were studied to determine the effect of changes of reaction conditions on the isomer distribution in the case of 2-halo-*p*-xylenes (Table IV). In addition to the decrease

TABLE IV

$$\text{2-X—}p\text{-xylene} \xrightarrow[\text{reflux}]{\text{8 hr}} \text{3-X—}p\text{-toluic acid} + \text{2-X—}p\text{-toluic acid}$$

	Yield, %	
X	3-X—*p*-Toluic acid	2-X—*p*-Toluic acid
Br	41.6	12
Cl	22.7	7.3
F	9	0

$$\text{2-X—}p\text{-xylene} \xrightarrow[\text{48 hr}]{\text{80}} \text{3-X—}p\text{-toluic acid} + \text{2-X—}p\text{-toluic acid}$$

	Yield, %	
X	3-X—*p*-Toluic acid	2-X—*p*-Toluic acid
Br	23	0
Cl	20.7	6.4

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(1) In part from the M.S. thesis of R. Beasley.

(2) In part from the M.S. thesis of L. Lambing.

(3) In part from the M.S. thesis of R. Moriconi.

(4) (a) R. Fittig and W. Bieber, *Ann.*, **156**, 242 (1870); (b) Y. de Schepper and A. Beilstein, *Ann.*, **137**, 302 (1866). (c) O. Reuter, *Ber.*, **17**, 2028 (1884).

(5) "Organic Syntheses" Coll. Vol III, John Wiley and Sons, Inc., New York, N. Y., 1955: (a) H. E. Zaugg and R. T. Rapala, p 820; (b) W. F. Tuley and C. S. Marvel, p 822.

(6) P. Kratochvil, F. Kupeik, V. Kudlacek, and S. Havel, *Chem. Prumsyl*, **8**, 499 (1958).

(7) P. M. Bharaqava and C. Heidelberger, *J. Am. Chem. Soc.*, **77**, 166 (1955).

TABLE V

ULTRAVIOLET ABSORPTION DATA OF TOLUIC ACIDS

[solvent, dioxane; λ_{max} mμ (log ϵ)]

	2-X—*p*-Toluic acid		3-X—*p*-Toluic acid		4-X—*m*-Toluic acid	
X	^1L_a	^1L_b	^1L_a	^1L_b	^1L_a	^1L_b
H	237 (4.17)	270 (S) 281 (2.80)			233 (4.17)	280 (2.80) 287 (2.60)
F	233 (4.33)	275 (3.43) 282 (s)	235 (4.46)	275 (3.53) 283 (3.50)	233 (4.23)	270 (3.06)
Cl	235 (4.24)	280 (3.12)	236 (4.29)	280 (3.13) 289 (3.13)	241 (4.32)	278 (3.22)
Br	214 (4.26)[a] 236 (s)	280 (2.91)	213 (4.35)[a] 235 (4.26)	280 (3.02) 289 (3.02)	244 (4.02)	278 (3.12) 287 (3.12)
NO_2			227 (4.20)	255 (s)	221 (s)[a] 255 (3.25)	299 (s)

4-Bromo-3,5-dimethylbenzoic acid		2-Bromo-3,5-dimethylbenzoic acid	
^1L_a	^1L_b	^1L_a	^1L_b
242 (4.36)	287 (3.46)	210 (4.28)	

[a] Methanol.

in total yield, an oxidation time of 8 hr compared with 20 hr shows a decrease in the amount of 2-substituted acid compared with the 3-substituted acid. In fact, 2-fluoro-*p*-xylene after an 8-hr reflux period gave only 3-fluoro-*p*-toluic acid; no 2-fluoro-*p*-toluic acid formed. The effect of using temperatures below reflux temperatures showed a similar effect for the 2-bromo- and 2-chloro-*p*-xylenes. 2-Bromo-*p*-xylene after oxidation for 48 hr at 80° gave only one product, 3-bromo-*p*-toluic acid. 2-Chloro-*p*-xylene gave both isomeric acids, but 2-chloro-*p*-toluic acid formed in much lower yield. These data indicate that the methyl group *meta* to the substituent group is oxidized more readily than the methyl group *ortho* to the substituent.

The order of ease of oxidation of a methyl group both *meta* and *para* to a halogen is in the order Br > Cl > F. This is in the order of the inductive contribution of the halogen, but the reverse of the mesomeric order as indicated by various σ values and rate studies.[8a] The respective σ_I values for Br, Cl, and F are +0.45, +0.47, and + 0.52[8b] as opposed to the reverse order for σ_p and σ_m of +0.23, +0.227, and +0.062 and +0.39, +0.37, and +0.34, respectively.[9]

These results are similar to those obtained by Cullis and Ladbury[10] for the permanganate oxidation of toluenes. They observed that +I substituents facilitate oxidation while −I substituents inhibited oxidation of the CH_3 group. For NO_2 and Cl the effect of position with respect to the CH_3 was *para* > *meta* > *ortho*.

Attempts were made to oxidize substituted mesitylenes. In the case of chloro-, fluoro-, and nitromesitylenes, nitration was the preferred reaction even at nitric acid concentrations as low as 10%. Bromomesitylene with 23% HNO_3 gave a mixture of mono- and dibasic acids and nitration products that could not be separated. With 10% nitric acid after 24 hr, the two isomeric bromomesitylenic acids were obtained. 4-Bromo-3,5-dimethylbenzoic acid was isolated in 28% yield and 2-bromo-3,5-dimethylbenzoic acid was obtained in 21% yield. No dibasic acids were isolated.

All of the isomeric toluic acids isolated are known except 2-fluoro-*p*-toluic acid which was obtained along with the isomeric 3-fluoro-*p*-toluic acid upon oxidation of 2-fluoro-*p*-xylene. We have assigned the 2-fluoro structure on the basis of its ultraviolet spectra, the order of elution in the chromatographic separation, and the fact that analysis indicates it is isomeric with 3-fluoro-*p*-toluic acid.

The ultraviolet absorption spectra (Table V) of the halotoluic acids show the characteristic ^1L_a and ^1L_b regions of benzenoid systems.[11] The 3-halo-*p*-toluic and 4-halo-*m*-toluic acids show two low intensity bands in the ^1L_b region, while for the 2-halo-*p*-toluic acids the longest wavelength band of this pair is missing, or, in the case of fluoro, has become a shoulder.

Experimental Section

Solvent Preparation.—Ligroin (bp 60°–90°, 500 ml) was shaken in a separatory funnel with 50 ml of 9:1 aqueous methanol (90%) 0.5 *N* sulfuric acid. The upper layer was used as the mobile phase and the lower layer was used as the stationary phase.

Column Preparation.—Mallinckrodt analytic reagent grade 100-mesh silicic acid was washed free of fine particles by repeated (five to six times) suspensions in distilled water and decantation after 1 hr. The hydrated acid was filtered under suction and dried overnight at 120° and stored in a desiccator.

Seventy-five grams of this acid was mixed with 50 ml of the stationary phase, added in 5–10-ml portions. To this was added 150 ml of the mobile phase and the mixture was poured into a 3.5 × 15 cm chromatographic column fitted with a stopcock. A weighed sample (0.1–0.3 g) of the toluic acid mixture dissolved in 5 ml of ethyl acetate and 10 ml of the equilibrated ligroin was added to the top of the column and the solvent was allowed to drain through the column under vacuum from a water aspirator. Fifty-milliliter cuts were made and the solvent was evaporated. The solid material was recrystallized from hot water or water–ethanol mixtures.

2-Fluoro-*p*-xylene.—The following procedure for the preparation of *p*-fluorotoluene was used.[12] *p*-Xylidene (26 g, 0.21 mole) was dissolved in a mixture of 63 ml of concentrated hydrochloric acid and 63 ml of water. The mixture was warmed and then cooled to −5° in a salt–ice bath with vigorous stirring. *p*-Xylidine hydrochloride separated as a finely divided, crystalline precipitate. To this mixture was added a solution of 18 g of sodium nitrite in 35 ml of water in small portions over a period of 15 min until KI–starch paper indicated an excess of nitrous acid. Thirty-eight grams of ammonium fluoroborate dissolved in 75 ml of water was chilled and added to the nitrous acid solution with good stirring.

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[8] (a) H. C. Brown and G. Coleman, *J. Am. Chem. Soc.*, **84**, 1650 (1962); (b) R. W.Taft and I. C. Lewis, *ibid.*, **80**, 2436 (1958).

[9] J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 87.

[10] C. F. Cullis and J. W. Ladbury, *J. Chem. Soc.*, 1407 (1955).

[11] J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

[12] A. I. Vogel, "Practical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 611.

The *p*-xylyldiazonium fluoroborate was removed by filtration, washed with 30 ml of ice water, 15 ml of methanol, and 40 ml of diethyl ether, and dried overnight in a desiccator. The yield of dry *p*-xylyldiazonium fluoroborate was 32 g. The diazonium fluoroborate was decomposed by distillation to give 11 g (0.09 mole, 43%) of 2-fluoro-*p*-xylene which boiled at 136–137°.

Anal. Calcd for C_8H_9F: C, 77.40; H, 7.49. Found: C, 77.14; H, 7.49.

4-Fluoro-*m*-xylene.—*m*-Xylidene (26 g, 0.21 mole) was treated in the same manner as for *p*-xylidene. Decomposition of the diazonium fluoroborate gave 12 g (0.097 mole, 46%) of 4-fluoro-*m*-xylene which boiled at 142–143°.[13]

4-Chloro-*m*-xylene.—4-Chloro-*m*-xylene was prepared from *m*-xylidene by the method described by Vogel[8a] for *p*-chlorotoluene. *m*-Xylidene (41 g, 0.34 mole) was diazotized with 24 g of sodium nitrite in 50 ml of water at −5°. This solution was poured into a solution of 65 g of cuprous chloride and 175 ml of concentrated hydrochloric acid. The mixture was warmed to 60° and steam distilled. The chloro-*m*-xylene layer was separated and distilled to give 25 g (0.18 mole, 52%) of 4-chloro-*m*-xylene which boiled at 186–187°.[13]

Oxidation of 2-Fluoro-*p*-xylene.—The following procedure is typical of the method used to oxidize the substituted *m*- and *p*-xylenes. 2-Fluoro-*p*-xylene (5.86 g, 0.047 mole) was refluxed (117°) under a hood with 100 ml (0.9 mole) of 45% nitric acid for 20 hr. The reaction mixture was cooled, diluted with water, and filtered. The crystals collected on the filter were dissolved in 10% sodium bicarbonate solution. This solution was extracted with three 30-ml portions of ether. The aqueous solution was taken to boiling and carefully acidified with 20% hydrochloric acid solution to pH 3.0. The resulting white crystals were filtered, dried, and weighed (2.447 g).

The column was prepared as described and 0.1114 g of the crude oxidation product was added to the column. Fifty-milliliter cuts were made. Fractions 6 to 14 contained 3-fluoro-*p*-toluic acid (0.0649 g, 19%), mp 159–160° (lit.[13] mp 160–161°).

Anal. Calcd for $C_8H_7FO_2$: C, 62.35; H, 4.54. Found: C, 62.01; H, 4.55.

Fractions 16–20 contained 0.0336 g of 2-fluoro-*p*-toluic acid (10%) which melted at 181–182°.

Anal. Calcd for $C_8H_7FO_2$: C, 62.35; H, 4.54. Found: C, 62.08; H, 4.70.

2-Fluoro-*p*-xylene (2.34 g) was refluxed with 50 ml of 45% nitric acid for 8 hr. Isolation of the oxidation product gave 0.26 g of 3-fluoro-*p*-toluic acid, mp 159–160° (9%). No 2-fluoro-*p*-toluic acid was found.

Oxidation of 2-Chloro-*p*-xylene.—Ten grams (0.07 mole) of 2-chloro-*p*-xylene was refluxed (117°) with 100 ml of 45% nitric acid for 20 hr. The product was worked up as described for 2-fluoro-*p*-xylene. The crude oxidation product weighed 8.633 g. Chromatographic separation of 0.1684 g of this material gave 0.1054 g (44%) of 3-chloro-*p*-toluic acid in fractions 1–6. This compound melted at 199–201° (lit.[13] mp 200–201°).

Anal. Calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.60; H, 3.90.

3-Chloro-*p*-toluamide was prepared and melted at 157–158° (lit.[13] mp 157–158°). Fractions 7–12 contained 0.0606 g of 2-chloro-*p*-toluic acid (26%) which melted at 150–152° (lit.[13] mp 155–156°).

Anal. Calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.44; H, 4.50.

2-Chloro-*p*-toluamide was prepared and melted at 179–180° (lit.[13] mp 182°).

The reaction of 4.63 g of 2-chloro-*p*-xylene with 50 ml of 45% nitric acid for 8 hr gave 2.22 g of crude product. Chromatographic separation of 0.1022 g of this material gave 0.0774 g (22.7%) of 3-chloro-*p*-toluic acid and 0.0248 g (7.3%) of 2-chloro-*p*-toluic acid.

Reacting 2.47 g of 2-chloro-*p*-xylene at 80° with 50 ml of 45% nitric acid with stirring gave 0.9 g of crude material. Separation of 0.1736 g of this material gave 0.1315 g (20.7%) of 3-chloro-*p*-toluic acid and 0.0421 g (6.4%) of 2-chloro-*p*-toluic acid.

Oxidation of 2-Bromo-*p*-xylene.—Ten grams (0.055 mole) of 2-bromo-*p*-xylene refluxed (117°) for 20 hr with 100 ml of 45% nitric acid gave 8.8 g of crude product. Separation of 0.2711 g of this material gave 0.1700 g (47%) of 3-bromo-*p*-toluic acid in fractions 1–5. This acid melted at 204–205° (lit.[13] mp 204°). 3-Bromo-*p*-toluamide was prepared and melted at 164–166°.

Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 45.00; H, 3.61.

Fractions 7–12 contained 0.0869 g (24%) of 2-bromo-*p*-toluic acid, mp 138–139° (lit.[13] mp 140°). 2-Bromo-*p*-toluamide was prepared and melted at 135–136° (lit.[13] mp 137°).

Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 44.84; H, 3.34.

When 4.50 g of 2-bromo-*p*-xylene was refluxed with 50 ml of 45% nitric acid for 8 hr, 3.77 g of crude oxidation product was obtained. A portion of this material (0.1020 g) was chromatographed to give 0.0794 g (41.6%) of 3-bromo-*p*-toluic acid and 0.0226 g (12%) of 2-bromo-*p*-toluic acid. Stirring 2.25 g of 2-bromo-*p*-xylene with 50 ml of 45% nitric acid for 48 hr at 80° gave 0.61 g (23%) of 3-bromo-*p*-toluic acid.

Oxidation of 2-Nitro-*p*-xylene.—Three grams (0.02 mole) of 2-nitro-*p*-xylene when refluxed for 20 hr with 30 ml of 45% nitric acid gave 1.8 g (27%) of 3-nitro-*p*-toluic acid, mp 189–190° (lit.[13] mp 190°).

Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.34. Found: C, 52.73; H, 3.98.

Oxidation of 4-Bromo-*m*-xylene.—4-Bromo-*m*-xylene (4.45 g, 0.024 mole) was refluxed (114°) for 15 hr with 50 ml of 45% nitric acid. The crude oxidation product was taken up in aqueous sodium bicarbonate, extracted with ether, and heated to boiling. Acidification of the boiling bicarbonate solution gave 3.05 g (58.5%) of 4-bromo-*m*-toluic acid, mp 209–210° (lit.[13] mp 209°).

Anal. Calcd for $C_8H_7BrO_2$: C, 44.63; H, 3.25. Found: C, 45.20; H, 3.43.

Oxidation of 5.70 g of 4-bromo-*m*-xylene for 20 hr gave 4.71 g of oxidation product which did not have a sharp melting point. Sublimation of 0.5013 g of this material gave 0.3290 g of sublimate which was shown to be 4-bromo-*m*-toluic acid, mp 209–210° (56%). The residue weighed 0.1723 g and melted at 291–292°. The reported[13] melting point of 4-bromoisophthalic acid is 287°.

Oxidation of 4-Chloro-*m*-xylene.—4-Chloro-*m*-xylene (4.02 g, 0.029 mole) was refluxed (114°) with 45 ml of 45% nitric acid. A reflux period of 15 hr gave 1.66 g of 4-chloro-*m*-toluic acid (33.4%) mp 210° (lit.[13] mp 209–210°).

Anal. Calcd for $C_8H_7ClO_2$: C, 56.20; H, 4.10. Found: C, 56.61; H, 4.06.

Refluxing 4.88 g of 4-chloro-*m*-xylene for 20 hr gave 2.74 g of crude material. Sublimation of 0.3100 g of this material gave 0.2150 g (44%) of 4-chloro-*m*-toluic acid as sublimate and 0.0950 g (1.5%) of 4-chloroisophthalic acid, mp 290–292° (lit.[13] mp 294–295°).

Oxidation of 4-Nitro-*m*-xylene.—The oxidation of 4.20 g (0.028 mole) of 4-nitro-*m*-xylene for 15 hr in 45 ml of 45% nitric acid (117°) gave 1.14 g (22.5%) of 4-nitro-*m*-toluic acid, mp 217–218° (lit.[13] mp 218°).

Anal. Calcd for $C_8H_7NO_4$: C, 53.10; H, 3.87. Found: C, 53.41; H, 4.18.

A reflux period of 20 hr gave 1.77 g (27%) of pure 4-nitro-*m*-toluic acid from 5.44 g of starting material.

Oxidation of 4-Fluoro-*m*-xylene.—4-Fluoro-*m*-xylene (2.72 g, 0.022 mole) and 30 ml of 45% nitric acid gave, after a reflux period of 15 hr (114°), 0.89 g (26.2%) of 4-fluoro-*m*-toluic acid, mp 164–165° (lit.[13] mp 165°).

Anal. Calcd for $C_8H_7FO_2$: C, 62.40; H, 4.55. Found: C, 62.60; H, 4.97.

A reflux period of 20 hr gave 2.03 g of oxidation product from 4.29 g of starting material. Sublimation of 0.1535 g of this material gave 0.1450 g (36%) of 4-fluoro-*m*-toluic acid. The residue weighed 0.0085 g (1.7%) and melted at 280–281°, and is assumed to be 4-fluoroisophthalic acid.

Oxidation of Bromomesitylene.—Bromomesitylene (2.53 g) was refluxed (104°) with 50 ml of 10% nitric acid for 20 hr. The crude oxidation product weighed 1.44 g. Chromatographic separation of 0.1676 g of this material gave 0.0768 g (22%) of 4-bromo-3,5-dimethylbenzoic acid, mp 209–210° (lit.[13] mp 214–215°), from aqueous methanol, in fractions 1–4.

Anal. Calcd for $C_9H_9BrO_2$: C, 47.15; H, 3.93. Found: C, 47.12; H, 4.17.

Fractions 5–7 contained 0.0576 g (16%) of 2-bromo-3,5-dimethylbenzoic acid, mp 140–141° from hot water (lit.[13] mp 146–147°).

Anal. Calcd for $C_9H_9BrO_2$: C, 47.15; H, 3.93. Found: C, 47.00; H, 4.06.

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(13) I. Heilbron, "Dictionary of Organic Compounds," Vol. 2, Oxford University Press, London, 1953, p 559.