## Regioselectivity of methoxydebromination of substituted pentabromobenzenes $C_6Br_5X$ in pyridine

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The kinetics and regioselectivity of methoxydebromination of some substituted pentabromobenzenes  $C_6Br_5X$  (X = NO<sub>2</sub>, CN, NH<sub>2</sub>, MeNH, and MeO) were studied in pyridine at 115 °C. The partial rate factors ( $k_f$ ) were calculated for different positions of the polybrominated ring in these compounds. The effect of substituents X on methoxydebromination at the *meta*- and *para*-positions is satisfactorily described only by the Hammett substituent constants ( $\rho = 2.22$ , r = 0.96). This allows one to conclude that direct polar conjugation of the substituents contributes only slightly to the transition state of the reaction. The *ortho*bromine atoms have a significant steric effect.

Key words: substituted pentabromobenzenes, methoxydebromination, regioselectivity.

Previously<sup>1</sup> we showed that the activating effect of Br atoms on the direction of nucleophilic attack during methoxydebromination of polybromobenzenes decreases in the order: *ortho* > *meta* > *para*, while the regioselectivity of the reaction is low. Methoxydebromination in  $C_6Br_5X$  with  $X = H, ^1$  Me, MeOCH<sub>2</sub>,<sup>2</sup> Cl,<sup>3</sup> and NO<sub>2</sub> <sup>4</sup> occurs nonselectively to give mixtures of *ortho*-, *meta*-, and *para*-substituted products, while only with  $X = OMe^5$  does substitution of bromine on treatment with MeONa occur exclusively at the *meta*-position.

In the present work we studied the direction of methoxydebromination and the reaction rates for a series of pentabromobenzenes  $C_6Br_5X$  (where  $X = NO_2$ , CN, NH<sub>2</sub>, MeNH, and MeO) containing both electron-withdrawing and electron-donating substituents.

The reactions with MeONa were carried out in pyridine in an argon atmosphere at an equimolar ratio of the reagents. The conversion was 60-80 % for X = NO<sub>2</sub>, CN, or Cl and 20-40 % for X = NH<sub>2</sub>, MeNH, and MeO. The analysis of the reaction mixtures and identification of the products were performed by GLC, <sup>1</sup>H NMR, and IR spectroscopy using authentic samples.

When  $C_6Br_5NO_2$  and MeONa are refluxed in pyridine, the reaction occurs very quickly. For example, only ~15 % of the pentabromonitrobenzene remains unreacted 10 s after the reagents are mixed, and the reaction mixture mostly contains products of replacement of bromine and nitro group by methoxy groups (Scheme 1), while the content of the products of disubstitution and reductive debromination is <5 %. The ratio of reaction products remains the same, within the determination error, both during this experiment and when the reaction is carried out at lower temperatures (60 °C, 30 °C).

Scheme 1



(43.8±3 mol. %)



(13.1±0.7 mol. %) (20.4±1 mol. %) (24.6±1.5 mol. %)

The behaviors of different pentahalonitrobenzenes  $C_6Y_5NO_2$  (Y = F, Cl, Br) in this reaction differ considerably (Table 1). One can see from the data in Table 1 that the methoxy group replaces only a F atom in pentafluoronitrobenzene, while in pentachloro- and pentabromonitrobenzene, a halogen atom and the nitro group are substituted; the degree of substitution of the nitro group increasing in the order:  $F \ll Cl \leq Br$ . This

Y	Comp reaction pr	oosition of oducts (mol. %)	Content of $C_6Y_4(OMe)NO_2$ isomers (%)			
	C <sub>6</sub> Y <sub>5</sub> OMe	C <sub>6</sub> Y <sub>4</sub> (OMe)NO <sub>2</sub>	para-	ortho-	meta-	
Fa	0	100	92	8	0	
Clb	40	60	67	33	0	
Br	42	58	42.3	22.6	35.1	

**Table 1.** Orientation of nucleophilic substitution in reactions of pentahalonitrobenzenes  $C_6Y_5NO_2$  with MeONa

<sup>a</sup> MeOH, 25.2 °C.<sup>6</sup> <sup>b</sup> MeOH, 45-55 °C,<sup>7</sup> cf. Ref. 8.

can be explained by a decrease in the positive charge on the C atoms linked to a halogen atom due to a decrease in the -I-effect of halogen atoms in the same order, which increases the probability of attack at the C atom linked to the nitro group. In addition, the nitro group in pentachloro- and pentabromonitrobenzenes is likely to stabilize the transition  $\sigma$ -complex less effectively than that in pentafluoronitrobenzene due to violation of the coplanarity of this group with the aromatic ring by the more bulky Cl and Br atoms (see below), and hence the degree of substitution of heavier halogens decreases.

According to GLC data, the methoxydebromination of pentabromobenzonitrile in pyridine at 25 °C gives two products (the <sup>1</sup>H NMR spectrum of the mixture contains two singlets at  $\delta$  3.87 and 4.01 with an integral intensity ratio of 1.36 : 1). When excess MeONa is present, these products are transformed into the same compound (the <sup>1</sup>H NMR spectrum displays two singlets of equal intensity with the same chemical shifts). The reaction probably results in a mixture of ortho- and para-methoxytetrabromobenzonitriles, which can undergo deeper methoxydebromination to give 2,4-dimethoxy-3,5,6-tribromobenzonitrile. As follows from a comparison of <sup>1</sup>H NMR spectra of pentabromoanisole and isomeric tetrabromonitrobenzenes (see Experimental), the introduction of a strong electronwithdrawing group at the ortho-position relative to the methoxy group results in a greater increase in its chemical shift (in comparison with that for pentabromoanisole) than in the case when the same group is introduced at the meta- or para-position. Based on these data, the signal at  $\delta$  3.87 was assigned to the methoxy group in 4-methoxytetrabromobenzonitrile, while that at  $\delta$  4.01 was assigned to the methoxy group in 2-methoxytetrabromobenzonitrile. The content of the para- and ortho-isomers in the reaction mixture determined from the integral intensity ratio of the above signals (57.7 and 42.3 %, respectively) was confirmed by GLC analysis data.

The reaction of  $C_6Br_5NH_2$  with MeONa in pyridine at 115 °C occurs very slowly. For example, ~50 % of the starting pentabromoaniline is consumed in 2 h, and only one product is formed. The latter was identified as 5-amino-2,3,4,6-tetrabromoanisole (according to <sup>1</sup>H NMR and IR spectroscopic data and GLC analyses). In the case of *N*-methylpentabromoaniline and pentabromoanisole, methoxydebromination by MeONa also occurs at the *meta*-position.

We measured the rates of methoxydebromination of the compounds studied and calculated the partial rate factors  $(k_f)$  for different positions of the polybrominated ring (Table 2). For comparison, Table 2 presents reported data on the rates and orientation of methoxydebromination of some substituted pentabromobenzenes. One can see that the selectivity of the reaction is generally low. Only when a methoxy, amino, or an N-methylamino group is present, exclusively meta-substitution occurs, although the rate of methoxydebromination of pentabromoanisole is higher than that of pentabromotoluene, which gives only 50 % of the metaisomer. Conversely, pentabromonitrobenzene reacts very quickly, and the distribution of isomers almost coincides with that observed for pentabromobenzene and methoxymethylpentabromobenzene. This behavior of polybromoaromatic compounds in methoxydehalogenation reactions differs from that described previously for their polyfluorinated<sup>6,9,10</sup> and polychlorinated<sup>7,11</sup> analogs.

The results obtained by us can be explained taking the overall effect of the substituents into account. Correlation analysis showed that the effect of an X group on the methoxydebromination at the meta- and para-positions is satisfactorily described only by the Hammett substituent constants (Fig. 1). Hence, in the case of nucleophilic substitution in polybromoaromatic compounds, the contribution of direct polar conjugation to the transition state, which is evidently very similar to the Meisenheimer complex, is very small. This explains the relatively high content of the meta-isomer in the products of the reaction of pentabromonitrobenzene with MeONa, which can suggest that partial violation of conjugation of the nitro group with the ring occurs due to steric hindrance introduced by the ortho Br atoms. This is confirmed by the fact that, although the CN group has a lower electron-withdrawing effect than the  $NO_2$  group,<sup>12</sup> it directs the substitution exclusively to the ortho- and para-positions, and so pentabromobenzonitrile reacts much more rapidly than pentabromonitrobenzene (see Table 2). Partial violation of conjugation due to steric hindrance is also observed for the N-methylamino group, since the rate of methoxydebromination of N-methylpentabromoaniline is higher than that of pentabromoaniline, although the MeNH group is a stronger electron donor than the NH<sub>2</sub> group  $(\sigma_m(NH_2) = -0.16, \sigma_m(MeNH) = -0.3)^{12}$ 

It should be noted that the reactions studied are insensitive to the presence of  $O_2$  and irradiation. For example, the rate constant of methoxydebromination of  $C_6Br_5X$  (X = MeO, Cl, and sBr) remains almost the same under irradiation by a quartz halogen lamp and in the dark, as well as in the presence or absence of air oxygen (Table 3).

x	Content of isomers (%)			$k_{obs} \cdot 10^2$ /L mol <sup>-1</sup> s <sup>-1</sup>	Direction of	$k_{\rm f}^a \cdot 10^2$ /L mol <sup>-1</sup> s <sup>-1</sup>
	ortho-	meta-	para-		attack	
NH <sub>2</sub>	0	100	0	0.39±0.15	3	0.195±0.075
MeNH	0	100	0	$1.6 \pm 0.5$	3	$0.8 \pm 0.25$
MeO	0	100	0	12.7±2	3	6.35±1
Me <sup>b</sup>	28.6±1.4	50.7±1.6	520.6±1.4	5.5±1	2 3 4	$0.79 \pm 0.2$ 1.4 $\pm 0.3$ 1.1 $\pm 0.3$
Η¢	20.9±2.0	36.9±3.0	42.2±2.5	27±4	2 3 4	$2.9\pm0.7$ 5.0±1.1 11.5±2.3
MeOCH <sub>2</sub> <sup>l</sup>	<sup>9</sup> 25.0±0.7	30.9±0.7	43.9±2.0	25±5	2 3 4	$3.1\pm0.7$ $3.9\pm0.9$ $11.4\pm2.7$
Cl <sup>d</sup>	43.0±4.0	38.0±4.0	19.0±3.0	106±20	2 3 4	23.2±6.4 20.6±4 20.7±7
Br				134±27		22.3±4.5
NO <sub>2</sub>	22.6±1.5	35.1±2	42.3±2.5	2860±900	1 2 3 4	1200±460 174±87 296±106 716±265
NO <sub>2</sub> <sup>e</sup>				27.1±4	1 2 3 4	11.4±2.5 1.87±0.4 2.86±0.5 6.7±1.4
CN	42.4±2.0	0	57.6±2.0	128±13	2 4	27.3±4 74±10

**Table 2.** Orientation and rates of methoxydebromination of pentabromobenzenes  $C_6Br_5X$  (pyridine, 115 °C)

<sup>*a*</sup> Taking account of the statistical factor. <sup>*b*</sup> Reported data.<sup>2</sup> <sup>*c*</sup> Reported data.<sup>1</sup> <sup>*d*</sup> The ratio of isomers is taken from the literature data.<sup>3</sup> <sup>*e*</sup> The reaction was carried out at 30 °C. <sup>*f*</sup> The reaction was carried out at 25 °C.

## Experimental

IR spectra were recorded on a UR-20 spectrophotometer in Vaseline oil suspensions. <sup>1</sup>H NMR spectra were recorded on a Tesla BS-467 spectrometer (60 MHz) in  $CCl_4$  using HMDS as the internal standard.

The purity of the starting compounds and final products and the compositions of the reaction mixtures were monitored by GLC on a Chrom-42 chromatograph ( $3000 \times 3.5$  mm glass columns with Chromaton N-Super (0.16-0.20 mm) + 5 % OV-17 packing; temperature of the columns: 180-240 °C; thermoionic detector; nitrogen as the carrier gas).

Pentabromonitrobenzene,<sup>13</sup> pentabromobenzonitrile,<sup>13</sup> pentabromoaniline,<sup>14</sup> pentabromochlorobenzene,<sup>3</sup> isomeric tetrabromoanisoles,<sup>15</sup> and 5-amino-2,3-dibromoanisole<sup>15</sup> were synthesized according to the procedures reported previously.

To perform reactions under irradiation, the reaction mixtures were irradiated by a KG 220/550 lamp. The techniques for kinetic measurements were reported previously.<sup>2</sup>

**Pentabromoanisole** was obtained by methylation of pentabromophenol with dimethyl sulfate,<sup>3</sup> yield 84 %, m.p. 172– 173 °C.<sup>16</sup> The IR spectrum agrees with that reported in the literature.<sup>16</sup> <sup>1</sup>H NMR,  $\delta$ : 3.80 (s, MeO).

*N*-Methylpentabromoaniline. A mixture of pentabromoaniline (5 g) and dimethyl sulfate (20 mL) was heated for 3 h at

130 °C with vigorous stirring and then poured into water. The mixture was adjusted to an alkaline pH by adding NaOH and then refluxed for 0.5 h. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization of the raw product from glacial acetic acid gave 2.75 g (53.4 %) of

**Table 3.** Rates of reactions of certain polybromobenzenes  $C_6Br_5X$  with MeONa in pyridine (115 °C)

X	Reaction conditions	$k_{obs}$ /L mol <sup>-1</sup> s <sup>-1</sup>
MeO	In the absence of $O_2$ In the absence of $O_2$ , in the dark In the presence of $O_2$ , under irradiation In the presence of $O_2$ in air	$\begin{array}{c} 0.13 \pm 0.02 \\ 0.10 \pm 0.02 \\ 0.08 \pm 0.03 \\ 0.12 \pm 0.04 \end{array}$
Cl	In the absence of $O_2$ In the absence of $O_2$ , under irradiation In the presence of $O_2$ in air	1.06±0.17 1.10±0.45 1.13±0.25
Br	In the absence of $O_2$ In the absence of $O_2$ , under irradiation In the presence of $O_2$ in air	1.34±0.27 1.12±0.31 0.80±0.49





**Fig. 1.** Correlation between the logarithms of rate constants of  $C_6Br_5X$  methoxydebromination (pyridine, 115 °C) and Hammett  $\sigma$ -constants;  $\rho = 2.22$ , r = 0.96. For *para*-substitution:  $\Sigma \sigma = \sigma_p(X) + \sigma_m(Br)$ , for *meta*-substitution:  $\Sigma \sigma = \sigma_m(X) + \sigma_p(Br)$ .

*N*-methylpentabromoaniline as colorless crystals, m.p. 152– 153 °C. IR,  $v/cm^{-1}$ : 3380 w, 1550 m, 1535 m, 1320 m, 1230 w, 1130–1140 m.br, 1040 m. <sup>1</sup>H NMR,  $\delta$ : 2.28 (s, 3 H, MeN); 4.10 (br.s, 1 H, NH). Found (%): C, 16.94; H, 0.91; Br, 79.41. C<sub>7</sub>H<sub>4</sub>Br<sub>5</sub>N. Calculated (%): C, 16.76; H, 0.80; Br, 79.64.

5-Amino-2,3,4,6-tetrabromoanisole. A solution of  $Br_2$  in AcOH (5 mL; 1.56 mmol mL<sup>-1</sup>  $Br_2$ ) was added at 20 °C to a solution of 5-amino-2,3-dibromoanisole (1 g) in AcOH (20 mL). The reaction mixture was kept for 0.75 h at 50 °C and then poured into water. The resulting precipitate was filtered off, washed with 5 % Na<sub>2</sub>SO<sub>3</sub> and water, dried, and recrystallized from petroleum ether (b.p. 70–100 °C). Yield 1.3 g (86 %), colorless crystals, m.p. 128–129 °C. IR, v/cm<sup>-1</sup>: 1610 s, 1430 m, 1310 w, 1270 w, 1120 m, 1087 w, 965 s, 860 w, 750 m, 715 m. <sup>1</sup>H NMR,  $\delta$ : 3.75 (s, 3 H, MeO); 4.77 (br.s, 2 H, NH<sub>2</sub>). Found (%): C, 19.36; H, 1.08; Br, 73.02. C<sub>7</sub>H<sub>5</sub>Br<sub>4</sub>NO. Calculated (%): C, 19.13; H, 1.13; Br, 72.89.

5-Nitro-2,3,4,6-tetrabromoanisole. Furning nitric acid (15 mL; d = 1.5 g cm<sup>-3</sup>) was added with stirring and cooling

to a solution of 2,3,4,6-tetrabromoanisole (2 g) in acetanhydride (35 mL) at such a rate that the temperature of the reaction mixture did not exceed 30 °C. The mixture was kept for 1 h at this temperature, then conc.  $H_2SO_4$  (15 mL) was added, and stirring was continued for an additional 2 h. The reaction mixture was poured into cold water (200 mL), and the precipitate was filtered off, washed with water, and dried. Recrystallization of the raw product from ethanol gave 0.91 g (41 %) of 5-nitro-2,3,4,6-tetrabromoanisole as light-yellow crystals, m.p. 103–104 °C. IR, v/cm<sup>-1</sup>: 1550 m, 1340 m, 1260 w, 1180 w, 1080 w, 1030 s, 920 w, 890 w, 795 w, 735 w. <sup>1</sup>H NMR,  $\delta$ : 3.87 (s, 3 H, MeO). Found (%): C, 18.05; H, 0.72; Br, 68.31. C<sub>7</sub>H<sub>3</sub>Br<sub>4</sub>NO<sub>3</sub>. Calculated (%): C, 17.93; H, 0.65; Br, 68.19.

**4-Nitro-2,3,5,6-tetrabromoanisole.** 2,3,5,6-Tetrabromoanisole (1 g) was added with vigorous stirring to fuming nitric acid (20 mL; d = 1.5 g cm<sup>-3</sup>). After 4–5 min, the reaction mixture was poured onto ice. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization from petroleum ether (b.p. 70–100 °C) gave 4-nitro-2,3,5,6tetrabromoanisole as yellow crystals, m.p. 146–147 °C (Ref. 17: m.p. 159 °C). IR, v/cm<sup>-1</sup>: 1550 s, 1350 s, 1310 w, 1110 w, 1070 w, 1015 m, 925 w, 843 w, 750 w, 728 w, 655 w, 627 w. <sup>1</sup>H NMR,  $\delta$ : 3.80 (s, 3 H, MeO). Found (%): C, 18.12; H, 0.81; Br, 68.05. C<sub>7</sub>H<sub>3</sub>Br<sub>4</sub>NO<sub>3</sub>. Calculated (%): C, 17.93; H, 0.65; Br, 68.19.

**2-Nitro-3,4,5,6-tetrabromoanisole.** Fuming nitric acid (20 mL; d = 1.5 g cm<sup>-3</sup>) was added over 20 min at 35–40 °C to a solution of 3,4,5,6-tetrabromoanisole (1 g) in acetanhydride (50 mL). The reaction mixture was kept for an additional 1.3 h at the same temperature, cooled, and poured onto ice. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization from petroleum ether (b.p. 70–90 °C) gave 0.85 g (76 %) of 2-nitro-3,4,5,6-tetrabromoanisole as yellow crystals, m.p. 107–108 °C (Ref. 17: m.p. 116 °C). IR, v/cm<sup>-1</sup>: 1560 s, 1540 m, 1335 m, 1235 w, 1130 w, 1002 s, 904 w, 883 w, 762 w, 728 w, 674 m, 578 m. <sup>1</sup>H NMR,  $\delta$ : 3.90 (s, 3 H, MeO). Found (%): C, 17.98; H, 0.83; Br, 68.30. C<sub>7</sub>H<sub>3</sub>Br<sub>4</sub>NO<sub>3</sub>. Calculated (%): C, 17.93; H, 0.65; Br, 68.19.

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