ACTA CHEMICA SCANDINAVICA 19 (1965) 1583–1590

Primary Hydrogen Isotope Effects in the Bromination of 2-Bromo-1,3,5-trimethoxybenzene and 2,4-Dibromo-1,3,5-trimethoxybenzene. Proximity Effects of Bromine

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An investigation of the bromination of partially deuterated substrates with molecular bromine in dimethylformamide has been carried out. There is no primary isotope effect in the bromination of 1,3,5-trimethoxybenzene, but rather large effects in the bromination of its bromo derivatives, $k_D/k_H = 0.28 \pm 0.08$ for 2-bromo-1,3,5-trimethoxybenzene at 25°C and $k_D/k_H = 0.21 \pm 0.04$ for 2,4-dibromo-1,3,5-trimethoxybenzene at 65°C.

It is thought that the primary isotope effects found in the brominations of the bromo derivatives of 1,3,5-trimethoxybenzene are caused mainly by increased steric hindrance to conjugation of the methoxy groups, due to the proximity effect of bromine.

Steric hindrance has been established as the main cause of primary isotope effects in several cases of aromatic substitution.[1a,2a] It has previously been found that there is no primary isotope effect in the bromination of 1,3,5-trimethoxybenzene with N-bromosuccinimide in dimethylformamide, where free bromine is actually the brominating reagent.[3] It was of interest to see if there are any primary isotope effects in the brominations of 2-bromo-1,3,5-trimethoxybenzene and 2,4-dibromo-1,3,5-trimethoxybenzene. In these two compounds steric hindrance should be greater than in 1,3,5-trimethoxybenzene, due to the proximity effect of bromine on the methoxy groups.

The system selected for the brominations was molecular bromine in dimethylformamide.[3] By varying the temperature considerably, it was possible to use this system for competitive investigations of both 1,3,5-trimethoxybenzene and its bromo derivatives, in spite of the great differences in reactivity among these compounds.

In order to measure primary isotope effects with enough accuracy for this type of investigation, it is possible to use a simpler competitive method than

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the one involving tritium analyses used previously.[3,4] It was found possible to use partially deuterated samples of the substrates and to analyze for deuterium content indirectly through proton analyses by NMR spectroscopy.

EXPERIMENTAL

Materials used. The preparations of 1,3,5-trimethoxybenzene and 1,3,5-trimethoxybenzene-2,4,6-d_3 have been described previously.[4] Partially deuterated 1,3,5-trimethoxybenzene (with statistically distributed deuterium) was prepared in the following way: 1,3,5-trimethoxybenzene (16.8 g, 0.100 mole) was equilibrated at 90°C with a mixture of heavy water (25.0 g, 1.24 mole, Norsk Hydro) and acetic acid (122 ml, 2.14 mole, Fisher, redistilled at reduced pressure). After 3 h the solvent was evaporated and the residue was dried *in vacuo* over silica gel. According to NMR spectroscopy the recovered material was deuterated to an extent close to 50 % (for all aromatic hydrogens) and was not contaminated with any measurable amounts of impurities.

Partially deuterated 2-bromo-1,3,5-trimethoxybenzene was prepared by brominating the partially deuterated 1,3,5-trimethoxybenzene with N-bromosuccinimide in dimethylformamide.[3] According to NMR spectroscopy the product was deuterated to the same extent (for the two aromatic hydrogens left) as the starting material. This was expected since there is no isotope effect or hydrogen exchange in this bromination reaction.[3] It can be assumed that deuterium is statistically distributed in this compound, as it was n the starting material.

Partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene was prepared by a direct bromination of equilibrated 1,3,5-trimethoxybenzene in a heavy water-acetic acid mixture. To an equilibrated mixture of 1,3,5-trimethoxybenzene (10.0 g, 0.059 mole), heavy water (25.0 g, 1.24 mole, Norsk Hydro) and acetic acid (30 ml, 0.53 mole, Fisher, redistilled at reduced pressure), liquid bromine was slowly added with vigorous stirring until the theoretical amount had been consumed. The mixture was cooled with ice and the crystals formed were filtered off, washed with water and then recrystallized from 95 % ethanol. The dry product weighed 15.2 g, 78 % of the theoretical yield. The melting point was 132°C (determined on a Kofler Hot Stage apparatus) undepressed by 2,4-dibromo-1,3,5-trimethoxybenzene prepared by a reported method.[5] The identity and the purity of the product was also confirmed by NMR spectroscopy and gas chromatography. The deuterium content was 83 % and in this case deuterium is confined to only one position. By recrystallizing the partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene with some undeuterated compound a suitably deuterated material for the competitive experiments was obtained.

May & Baker's bromine (not less than 99.5 % w/w) was used without any further purification.

Fisher's certified dimethylformamide had a specified water content of 0.03 %.

Other chemicals were all commercial products and used without further purification.

Analyses. The gas chromatography was performed on a Perkin-Elmer Model 116 E gas chromatograph. Conditions: 90 cm column "O" (silicon grease on chromosorb), int. diam. 4 mm, temp. 192°C, carrier gas He, flow rate 90 ml/min. In the quantitative analyses the signals from the gas chromatograph were integrated by a Perkin-Elmer Model D2 electronic integrator. By using reference solutions[3] the compositions of the samples obtained from the competitive experiments (to be described later) were measured with relative errors less than ± 3 %.

Quantitative proton analyses were carried out with a Varian A 60 NMR spectrometer. Average values of several integrals for each different proton peak were used and the integrations were performed in the same way for all samples. By varying the amplitude of the radio frequency field it was controlled that the integrations of the different types of peaks were adequate with respect to saturation phenomena.

All samples analyzed were composed of 1,3,5-trimethoxybenzene, its mono-, di- and tribromo derivatives and the corresponding deuterated compounds or mixtures thereof. The spectra of the pure undeuterated compounds are given in Figs. 1—4.* These spectra

* Chemical shifts were measured relative to TMS.

were run at standard conditions (1 mmole/ml deuteriochloroform). In the following the symbols used in Figs. 1—4 also stand for average integral values of the corresponding peaks. The actual analyses performed are described for each competitive experiment.

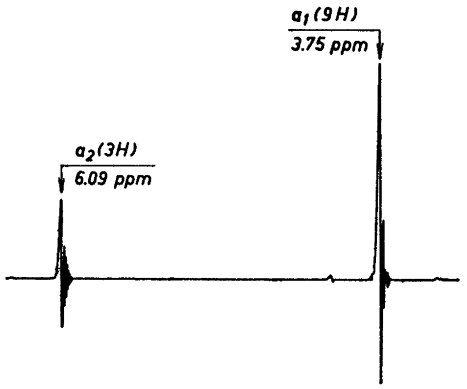

Fig. 1. NMR spectrum of 1,3,5-trimethoxybenzene, 1 mmole/ml deuteriochloroform.

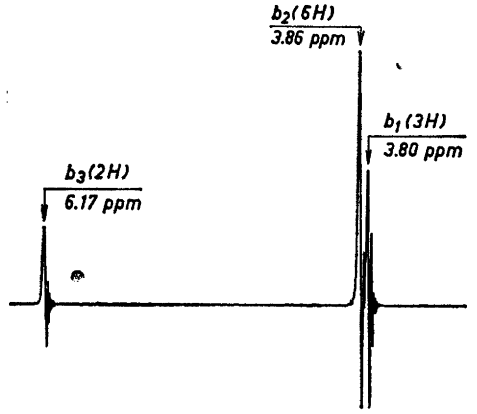

Fig. 2. NMR spectrum of 2-bromo-1,3,5-trimethoxybenzene, 1 mmole/ml deuteriochloroform.

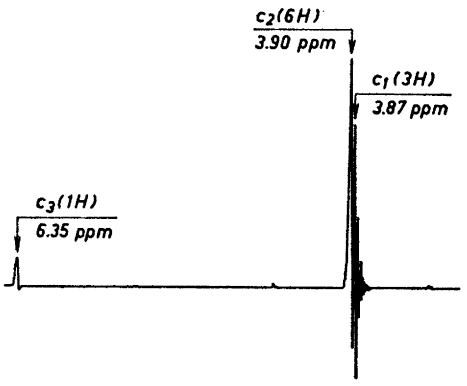

Fig. 3. NMR spectrum of 2,4-dibromo-1,3,5-trimethoxybenzene, 1 mmole/ml deuteriochloroform.

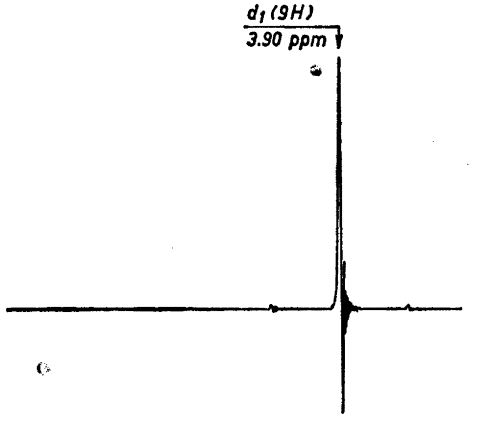

Fig. 4. NMR spectrum of 1,3,5-tribromo-2,4,6-trimethoxybenzene, 1 mmole/ml deuteriochloroform.

Competitive experiments with partially deuterated 1,3,5-trimethoxybenzene. The starting material used was a mixture of 1,3,5-trimethoxybenzene-d_3 (97 % D) and ordinary 1,3,5-trimethoxybenzene.* The material (0.3 g, 1.8 mmole) was dissolved in 2 ml of dimethylformamide and the solution was cooled to −20°C (± 2°C). To this solution about 1 ml of a 1 M solution of bromine in dimethylformamide kept at −20°C was added.

* In some less sensitive experiments partially deuterated 1,3,5-trimethoxybenzene with statistically distributed deuterium was used.

After a few minutes at −20°C the bromine was consumed * and the solution became colourless. 10 ml of a 5 % (by weight) aqueous sodium carbonate solution was then added and the precipitate formed was filtered off, washed with water and dried *in vacuo* over silica gel. The sample thus obtained was analyzed by gas chromatography and NMR spectroscopy. It contained unreacted 1,3,5-trimethoxybenzene, 2-bromo-1,3,5-trimethoxybenzene and minor amounts of 2,4-dibromo-1,3,5-trimethoxybenzene. The total yield of unreacted starting material and products was better than 95 %.

Quantitative gas chromatographic analysis gave the fraction of each compound in the sample and, since the total yield of the reaction was high, the extent of reaction is thus also known.

Concentrated chloroform solutions (0.5 g/ml chloroform) of the starting material and the reacted material were used for the NMR spectroscopy. The fraction of deuterium in the starting material is $1-3a_2/a_1$ (see Fig. 1) and the fraction of deuterium in the unreacted 1,3,5-trimethoxybenzene in the reacted material is $1-3a_2/(a_1 + b_1 + b_2 + c_1 + c_2) \times$ (fraction of 1,3,5-trimethoxybenzene in sample) (see Figs. 1−3).

Competitive experiments with partially deuterated 2-bromo-1,3,5-trimethoxybenzene. Starting material with statistically distributed deuterium was used. The material (0.3 g, 1.2 mmole) was dissolved in 1 ml of dimethylformamide and the solution cooled to −20°C. At this temperature about 1 ml of a 2 M solution of bromine in dimethylformamide, kept at −20°C, was added. The homogeneous solution was then immediately warmed to 25°C (± 2°C) and kept there for 20 min. Then the solution was again cooled to −20°C and 10 ml of a 5 % (by weight) aqueous sodium carbonate solution was added. The precipitate formed was filtered off, washed with water and dried *in vacuo* over silica gel. The product obtained was analyzed by gas chromatography and NMR spectroscopy. It was found that the sample consisted of 2,4-dibromo-1,3,5-trimethoxybenzene and less than 1 % unreacted starting material. The product identity was confirmed by comparisons with 2,4-dibromo-1,3,5-trimethoxybenzene prepared by the reported method.[5] The yield was quantitative within a few percent.

Concentrated chloroform solutions (0.8 g/ml chloroform) of the starting material and the reacted material were used for the NMR spectroscopy. The fraction of deuterium in the starting material is $1-9b_3/2(b_1 + b_2)$ (see Fig. 2) and the fraction of deuterium in 2,4-dibromo-1,3,5-trimethoxybenzene is $1-9c_3/(c_1 + c_2)$ (see Fig. 3).

In a couple of control experiments the reaction mixture was quenched with aqueous sodium sulfite solution at different time intervals. It was found that most of the reaction took place at 25°C.

Competitive experiments with partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene. To a solution of partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene (0.3−0.4 g, 0.9−1.2 mmole) in 3−4 ml of dimethylformamide kept at 65°C (± 2°C), liquid bromine (0.1−0.3 g, 0.6−1.9 mmole) was added slowly. The solution was allowed to stand for 30−45 min at 65°C (± 2°C) and was then rapidly diluted with cold water and cooled to −10°C. The precipitate formed was filtered off, washed with water and air-dried at 90°C. The isolated material was analyzed by NMR spectroscopy. The sample consisted of unreacted starting material and 1,3,5-tribromo-2,4,6-trimethoxybenzene, the latter compound being identified by comparison with a sample prepared by a reported method.[6] The total yield of unreacted starting material and product was better than 95 %.

Concentrated benzene-d_6 solutions (0.8 g/ml benzene-d_6) of the starting material and the reacted material were used for the NMR spectroscopy. The fractions of deuterium in the starting material and in the unreacted 2,4-dibromo-1,3,5-trimethoxybenzene of the reacted material are both given by $1-9c_3/(c_1 + c_2)$ (see Fig. 3). The fraction of product in the reacted material is $d_1/(d_1 + c_1 + c_2)$ and, since the total yield of the reaction was high, this fraction is also very close to the extent of reaction. The separate analyses of peaks c_1, c_2, and d_1 obtained from the reacted material seem to be difficult according to the spectra in Figs. 3 and 4, but in the solvent benzene-d_6 these peaks are well separated.**

* The time for "complete" reaction is much greater than the time for mixing of the reagents and therefore there should be fair competition between the isotopic species. For the other competitive reactions to be described later the reaction time was still greater.

** Benzene solvent gave the largest separation of these peaks. Rather large solvent effects were found for this type of sample.

In a control experiment quenching with cold water and quenching with aqueous sodium sulfite solution were compared. It was found that aqueous sodium sulfite solution was only slightly more effective as a quenching agent. Only an insignificant part of the reaction could therefore have taken place in an aqueous solvent or at a lower temperature than 65°C.

Control experiments on the absence of hydrogen exchange during the competitive experiments. The control experiments for 1,3,5-trimethoxybenzene and 2-bromo-1,3,5-trimethoxybenzene were carried out in the same way as the corresponding competitive experiments but with 1,3,5-trimethoxybenzene-d_3 (97 % D) as the starting material. (More than one equivalent of bromine was used in the case of 2-bromo-1,3,5-trimethoxybenzene). For such a nearly completely deuterated compound only very small changes in deuterium content due to isotope effects are possible. Since there was no difference in the isotopic composition of the starting material and the isolated products from the control experiments, it can be concluded that there is no measurable hydrogen exchange under these conditions.

The control experiment for 2,4-dibromo-1,3,5-trimethoxybenzene was carried out by treating partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene (83 % D), with some 1,3,5-tribromo-2,4,6-trimethoxybenzene added,* with an equivalent amount of hydrobromic acid (63 % by weight) in the same solvent, at the same concentration and temperature and during the same time as used in the competitive experiments. The recovered 2,4-dibromo-1,3,5-trimethoxybenzene had the same isotopic composition (83 %) as before the treatment with hydrobromic acid. Hydrogen exchange is obviously negligible under these conditions.

Control experiments on the absolute accuracy of the experimental method. The competitive experiments were repeated, but now ordinary light material was used. The reacted material was worked up and analyzed as described before. All protons pertinent to the deuterium analyses in the main experiments were accounted for quantitatively within the limits of the estimated random errors.

CALCULATIONS AND RESULTS

In order to calculate the isotope effect, k_D/k_H, the following equation [7a] can be used in cases where the fraction of deuterium in the recovered unreacted starting material is compared to the same fraction in the starting material:

$$k_D/k_H = [\log(1-x_D)]/[\log(1-x_H)]$$

x_D and x_H denote the fractions of starting material containing deuterium and protium, respectively, which have reacted. Using the symbol y_D' for the fraction of deuterium in the starting material, y_D for the fraction of deuterium in the recovered unreacted starting material, y_H' and y_H for the corresponding fractions of protons, and x for the extent of reaction, it can be shown that $1-x_D = y_D(1-x)/y_D'$ and $1-x_H = y_H(1-x)/y_H'$, and thus

$$k_D/k_H = \{\log[y_D(1-x)/y_D']\}/\{\log[y_H(1-x)/y_H']\}$$

This expression is valid for the isotope effect in the competitive experiments with a mixture of 1,3,5-trimethoxybenzene and 1,3,5-trimethoxybenzene-d_3**

* The product obtained in the corresponding competitive experiment was included in order to control that there was no indirect hydrogen exchange *via* an eventual protio-debromination of the product.

** No corrections have been made for the small amounts of 1,3,5-trimethoxybenzene-d_2 and 1,3,5-trimethoxybenzene-d in the sample of 1,3,5-trimethoxybenzene-d_3, together about 3 %.

and in the competitive experiments with partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene. The isotope effects in these experiments are clearly intermolecular.

For the partially deuterated 2-bromo-1,3,5-trimethoxybenzene, with statistically distributed deuterium, the following reactions are possible:

$$ArD_2 + Br_2 \longrightarrow ArBrD + DBr$$
$$ArH_2 + Br_2 \longrightarrow ArBrH + HBr$$

$$ArHD + Br_2 \begin{cases} \xrightarrow{k_H} ArBrD + HBr \\ \xrightarrow{k_D} ArBrH + DBr \end{cases}$$

Ar is used to denote an aromatic nucleus without aromatic hydrogens. The isotope effect k_D/k_H is here intramolecular. If the deuterium is statistically distributed in the starting material,[8] then ArD_2 is a fraction $y_D'^2$, ArHD is a fraction $2y_D'(1-y_D')$ and ArH_2 is a fraction $(1-y_D')^2$ of the starting material, where y_D' denotes the average fraction of deuterium for the two aromatic hydrogens in the starting material. The assumption that the deuterium is statistically distributed seems to be well justified in the present case. Since the reaction of the partially deuterated 2-bromo-1,3,5-trimethoxybenzene was run to completion (less than 1 % starting material had not reacted), the intramolecular isotope effect is relatively easy to calculate. Using the symbol y_D for the fraction of deuterium in the product one obtains

$$k_D/k_H = [2y_D'(1-y_D')/(y_D-y_D'^2)]-1$$

The results of the various calculations of the isotope effects have been summarized in Table 1. The errors given are maximum deviations from the mean values.

Table 1. Summary of isotope effects found in the brominations of different substrates. A = mixture of 1,3,5-trimethoxybenzene and 1,3,5-trimethoxybenzene-d_3, B = partially deuterated 2-bromo-1,3,5-trimethoxybenzene with statistically distributed deuterium, and C = partially deuterated 2,4-dibromo-1,3,5-trimethoxybenzene.

Substrate	Temp. °C	x	y_D/y_D'	k_D/k_H	k_D/k_H mean value
A	−20	0.45	0.98	1.07	1.02 ± 0.05
A	−20	0.57	1.01	0.97	
B	25	1.00	1.31	0.23	
B	25	1.00	1.25	0.34	
B	25	1.00	1.30	0.25	0.28 ± 0.08
B	25	1.00	1.24	0.36	
B	25	1.00	1.32	0.23	
C	65	0.35	1.33	0.18	
C	65	0.42	1.42	0.19	
C	65	0.45	1.47	0.19	0.21 ± 0.04
C	65	0.52	1.55	0.20	
C	65	0.57	1.59	0.23	
C	65	0.58	1.57	0.25	

The result of the two experiments with a mixture of 1,3,5-trimethoxybenzene-d_3 and 1,3,5-trimethoxybenzene was confirmed by a couple of less sensitive experiments with 1,3,5-trimethoxybenzene containing statistically distributed deuterium.

If the isotope effects given in Table 1 are due solely to differences in zero-point energies, they can be normalized to the same temperature,[7b] 25°C and one obtains $k_D/k_H = 1.02 \pm 0.05$ for 1,3,5-trimethoxybenzene, $k_D/k_H = 0.28 \pm 0.08$ for 2-bromo-1,3,5-trimethoxybenzene and $k_D/k_H = 0.17 \pm 0.03$ for 2,4-dibromo-1,3,5-trimethoxybenzene. The latter two isotope effects are clearly primary effects and the effect obtained in the bromination of 2,4-dibromo-1,3,5-trimethoxybenzene seems to be near the maximum value obtainable for this kind of reactions.[2b]

DISCUSSION

The observed values of k_D/k_H show that the structural differences between the substrates have been accompanied by a change in the mechanism of the bromination reaction. In the substitutions of 2-bromo-1,3,5-trimethoxybenzene and 2,4-dibromo-1,3,5-trimethoxybenzene the removal of the aromatic hydrogens must be at least partly rate-determining, while in the substitution of 1,3,5-trimethoxybenzene the bond between the aromatic hydrogen and the aromatic carbon is not much changed in the rate-determining transition state.

It is known from dipole moment [9] and spectral studies [10] that an aromatic methoxy group, which is flanked by more than one *ortho* substituent, is forced out of the plane of the aromatic nucleus. This causes a considerable loss of π-electron conjugation and thus an increase in the potential energy.

The two-step model for electrophilic aromatic substitution in this case may be outlined as follows:

$$ArH + Br_2 \underset{-1}{\overset{1}{\rightleftharpoons}} [ArBrH]^+ + Br^- \xrightarrow{2} ArBr + H^+ + Br^-$$

This model will be employed in the discussion of the bromination of all substrates investigated here.* A primary isotope effect results only if the rate of step 2 is comparable to or slower than that of step -1.[1b,2a] In step 2 the bulky bromine atom moves into the plane of the aromatic nucleus, while in step -1 the much smaller hydrogen atom becomes coplanar with the aromatic nucleus. It is thus not surprising that a primary isotope effect can be caused by steric hindrance.

The increase of the kinetic importance of step 2 in going from the bromination of 1,3,5-trimethoxybenzene to the bromination of 2,4-dibromo-1,3,5-trimethoxybenzene may be ascribed to a general increase in steric hindrance. The large primary isotope effect observed by Myhre [11] in the bromination of 1,3,5-tri-*t*-butylbenzene was explained in similar terms.

Another possible cause of a primary isotope effect may become very important in the bromination of the mono- and dibromo derivatives of 1,3,5-trimethoxybenzene, namely steric hindrance to conjugation. In step 2 in the

* Since there were primary isotope effects for the reactions of 2-bromo-1,3,5-trimethoxybenzene and 2,4-dibromo-1,3,5-trimethoxybenzene a one-step model is in principle also acceptable for these reactions.

bromination of 1,3,5-trimethoxybenzene only one bromine atom can be situated in or near the plane of the aromatic nucleus and all methoxy groups are able to obtain the most favourable conformation. Therefore there does not seem to be any reason for a primary isotope effect caused by steric hindrance to conjugation in this case. In the bromination of 2-bromo-1,3,5-trimethoxybenzene the situation is different since in step 2, two bromine atoms will become situated in or near the plane of the aromatic nucleus and at least one methoxy group is not able to obtain its most favourable conformation. In this case the situation is more favourable for a primary isotope effect. The situation in the bromination of 2,4-dibromo-1,3,5-trimethoxybenzene will be still more favourable for a primary isotope effect since in step 2, all three methoxy groups will be prevented from obtaining their most favourable conformations. This steric difference between the reactions of 2-bromo-1,3,5-trimethoxybenzene and 2,4-dibromo-1,3,5-trimethoxybenzene may explain the observed difference in the magnitudes of the isotope effects for these substrates. Here it has been assumed that the second transition state is only partly rate-determining in the bromination of 2-bromo-1,3,5-trimethoxybenzene, but the weaker isotope effect found in this case may also be due to a more asymmetric transition state with regard to the extent of proton transfer in a completely rate-determining step. Only a kinetic investigation, including the dependence of rate on the concentration of bromide ions and base can solve this ambiguity.

It seems reasonable that the isotope effect found by Farell and Mason[12] in the bromination of N,N-dimethylaniline *ortho* to the dimethylamino group has primarily the same cause as the one discussed here, namely steric hindrance to conjugation. In the case of the very bulky dimethylamino group one substituent alone *ortho* to this group will have an influence.

Since the structural changes in the substrates are made *meta* to the reaction site, the direct electronic effects are more or less purely inductive and the influence on the mechanism of the bromination reaction due to these effects are probably small in comparison to steric influences *via* the methoxy groups.

Acknowledgements. The author wishes to thank Professor Lars Melander for his kind interest and for valuable discussions. This investigation was supported by the *Swedish Natural Science Research Council*. Dr. Robert Carter has kindly revised the English.

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Received June 4, 1965.