Primary Hydrogen Isotope Effects in the Nuclear Bromination of 1,3,5-Trimethoxy-2-methylbenzene and 1,3,5-Trimethoxy-2,4-dimethylbenzene

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The substrates, prepared by direct methods from 1,3,5-trimethoxybenzene, were brominated by molecular bromine in dimethylformamide. A competitive method using partially deuterated compounds gave the isotope effects $k_D/k_H = 0.49 \pm 0.04$ and $k_D/k_H = 0.34 \pm 0.04$ for the bromination of 1,3,5-trimethoxy-2-methylbenzene and 1,3,5-trimethoxy-2,4-dimethylbenzene, respectively, at $-20^\circ C$. For the former substance, the influence on the isotope effect of added water, sodium perchlorate, and sodium bromide was also studied to some extent. It was found that the apparent isotope effect became stronger with increasing concentration of bromide ion.

The results are discussed in relation to previous work.

It has previously been found that the presence of substituents in 1,3,5-trimethoxybenzene has a profound influence on the mechanism of its bromination, causing the removal of the aromatic hydrogen to become more or less rate-determining. In those experiments an electron attracting element, bromine, was used as the substituent. It was of interest to see what effect an electron repelling group of similar size, e.g. the methyl group, would have on the same substitution reaction.

In order to be able to compare the results of the present investigation with the results on the bromination of bromo derivatives of 1,3,5-trimethoxybenzene, the system chosen for the reaction was the same as the one used in the earlier work, namely molecular bromine in dimethylformamide. The experimental technique is described in greater detail in the previous paper.

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EXPERIMENTAL

1,3,5-Trimethoxy-2-methylbenzene was prepared by a Wolff-Kishner reduction of 2,4,6-trimethoxybenzaldehyde which was obtained via formylation of 1,3,5-trimethoxybenzene by a reported method. 2

2,4,6-Trimethoxybenzaldehyde (18.0 g, 0.092 mole) was dissolved in 150 ml of ethanol and hydrazine hydrate (9.3 g, 0.18 mole) was added. The reaction mixture was boiled for 2 h and then the solvent was evaporated. The resulting solid residue (hydrazone) was melted with solid potassium hydroxide at 120°C until the evolution of nitrogen had ceased (about 3 min). The reaction mixture was cooled, treated with water and worked up by steam distillation. Extraction of the distillate with carbon tetrachloride, drying the extract over anhydrous sodium sulfate and evaporation of the solvent gave a slightly coloured product. Yield 18.2 g (79%); Purification by distillation at reduced pressure gave a colourless substance; m.p. 25°C, reported * 27–28°C. Analysis by NMR spectroscopy * (1 g/ml of CDCl₃) gave the following chemical shifts: 6.04 ppm (2 aromatic H), 3.67 ppm (1 OCH₃), 3.70 ppm (2 OCH₃), 2.00 ppm (1 CH₃).

Deuterated 1,3,5-trimethoxy-2-methylbenzene containing 97% D (in the aromatic ring, determined by NMR spectroscopy) was prepared by equilibrating the light material twice with a suitable mixture of deuterated acetic acid and deuteriumoxide. The aromatic compound was distilled between and after the equilibrations.

Both the undeuterated and the deuterated 1,3,5-trimethoxy-2-methylbenzene were found to be pure by gas chromatography.1

1,3,5-Trimethoxy-2,4-dimethylobenzene was prepared by chloromethylation of 1,3,5- trimethoxybenzene and subsequent reduction of the product, 2,4-bis(chloromethyl)-1,3,5-trimethoxybenzene, with lithium aluminium hydride.

To a stirred mixture of 1,3,5-trimethoxybenzene (30.0 g, 0.178 mole) in 175 ml of benzene (free from thiophene) and 60 ml of conc. hydrochloric acid kept at 0°C, 60 ml of aqueous formaldehyde (36.6%) was added and hydrogen chloride was introduced until absorption of the gas was inappreciable. The two phases of the reaction mixture were separated and the benzene phase was washed with cold water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue recrystallized from benzene. Yield 41.4 g (88%); m.p. 140°C (a Kofer Hot Stage apparatus was used for all melting point determinations). (Found: ** OCH₃ 34.64; Cl 26.03. Calc. for C₁₁H₈ClO₂: OCH₃ 35.11; Cl 26.74.) NMR analysis (0.3 g/ml of CDCl₃) gave the following chemical shifts: 6.28 ppm (1 aromatic H), 4.01 ppm (1 OCH₃), 3.90 ppm (2 OCH₃), 4.70 ppm (2 CH₂Cl). It can be concluded that the product is 2,4-bis(chloromethyl)-1,3,5-trimethoxybenzene.

To a stirred solution of lithium aluminium hydride (20.1 g, 0.53 mole) and lithium hydride (6.7 g, 0.84 mole) in 600 ml of anhydrous ether, a suspension of 2,4-bis(chloromethyl)-1,3,5-trimethoxybenzene (55.0 g, 0.208 mole) in about 250 ml of anhydrous ether was added at such a rate that refluxing could be maintained without the application of heat. When all of the chloromethyl compound had been added, the reaction mixture was refluxed for another 2 h. The mixture was then cooled and the excess of hydrides was destroyed by the addition of cold water.

Steam distillation gave 33.4 g (82%) of the product; m.p. 61°C, reported for 1,3,5- trimethoxy-2,4-dimethylbenzene 61°C. NMR analysis (1 g/ml of CDCl₃) gave the following chemical shifts: 6.27 ppm (1 aromatic H), 3.67 ppm (1 OCH₃), 3.78 ppm (2 OCH₃), 2.12 ppm (2 CH₃).

Partially deuterated 1,3,5-trimethoxy-2,4-dimethylbenzene was prepared by equilibrating the undeuterated compound with a suitable mixture of acetic acid and deuterium oxide. Since there is only one aromatic hydrogen in the substrate, deuterium is confined to one position. The deuterated material was found to be pure by gas chromatography.

4-Bromo-1,3,5-trimethoxy-2-methylbenzene was obtained for calibration purposes by bromination of 1,3,5-trimethoxy-2-methylbenzene with molecular bromine in carbon tetrachloride. 1,3,5-Trimethoxy-2-methylbenzene (1.00 g, 5.52 mmole) in 25 ml of carbon

* All NMR analyses were performed on a Varian A 60 instrument and the chemical shifts were measured relative to TMS (tetramethylsilane).
** All analyses were carried out by Dr. A. Bernhardt, Mülheim/Ruhr.

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tetrachloride was treated with bromine (0.88 g, 5.50 mmole) in 25 ml of carbon tetrachloride at 25°C. When the colour had disappeared the solvent was evaporated and the residue worked up by steam distillation. The solid material in the distillate was filtered off, washed with water and dried in vacuo over silica gel. Yield 1.36 g (95 %); m.p. 93°C. (Found: OCH, 35.82; Br 30.78. Calc. for C₅H₅BrO₂: OCH, 35.65; Br 30.60.) NMR analysis (1 g/ml of CDCl₃) gave the following chemical shifts: 6.30 ppm (1 aromatic H), 3.85 ppm (1 OCH₃), 3.81 ppm (1 OCH₃), 3.78 ppm (1 OCH₃), 2.11 ppm (1 CH₃). The material was pure according to gas chromatography.

6-Bromo-1,3,5-trimethoxy-2,4-dimethylbenzene was prepared by bromination of 1,3,5-trimethoxy-2,4-dimethylbenzene with molecular bromine in dimethylformamide. To a stirred solution of 1,3,5-trimethoxy-2,4-dimethylbenzene (2.00 g, 10.2 mmole) in 5 ml of dimethylformamide kept at 0°C, bromine (4.8 g, 30 mmole) was added and the solution was allowed to react for 1.5 h at 0°C. The excess of bromine was then destroyed by addition of an aqueous solution of sodium sulfite. The product was completely precipitated by addition of water and the precipitate was filtered off, washed with water and dried over silica gel. Yield 2.75 g (98 %). The material was recrystallized from methanol and sublimed in vacuo. The product, which was pure according to gas chromatography, existed in two different crystalline forms; m.p. 57°C and 67°C. (Found: OCH₃ 33.90 Br 29.25. Calc. for C₅H₅BrO₂: OCH₃ 33.84; Br 29.04.) NMR analysis (1 g/ml of CDCl₃) gave the following chemical shifts: 3.70 ppm (1 OCH₃), 3.78 ppm (2 OCH₃), 2.23 ppm (2 CH₃).

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

Competitive experiments with a mixture of 1,3,5-trimethoxy-2-methylbenzene-d₄ (97 % D) and 1,3,5-trimethoxy-2-methylbenzene (typical experiment). The mixture (0.30 g, 1.64 mmole) with a total deuterium content of 49 % was dissolved in 1 ml of dimethylformamide and cooled to −20°C (±2°C). To this solution, 1 ml of a 0.82 M solution of bromine in dimethylformamide kept at −20°C was added and the solution was allowed to stand for 35 min at −20°C (±2°C). It was then quenched by the addition of an aqueous solution of sodium sulfite and sodium carbonate and the resulting mixture was extracted with carbon tetrachloride. The extract was dried over anhydrous sodium sulfate, the solvent evaporated and the residue dissolved in deuteriochloroform (1.2 g/ml) and analyzed by NMR spectroscopy. The sample was composed of unreacted 1,3,5-trimethoxy-2-methylbenzene and the product, 4-bromo-1,3,5-trimethoxy-2-methylbenzene, which was identified by comparison with an authentic sample of 4-bromo-1,3,5-trimethoxy-2-methylbenzene. The total yield of unreacted starting material and product was very high. The extent of reaction is then given accurately by comparison of the intensities of the NMR signals from the protons of the nuclear methyl groups in the unreacted starting material and the product. The deuterium content of the starting material and the unreacted starting material in the reacted sample was indirectly determined by comparison between the intensities of the NMR signals from the protons of the aromatic nucleus and the protons of the nuclear methyl groups, the latter intensity being directly correlated with the total content of hydrogens in the aromatic nucleus.

In the same way, some competitive experiments were carried out in which the solvent was dimethylformamide containing 10 % (by volume) of water. The influence of added sodium perchlorate (1 M solution) and sodium bromide (1 M solution) was also studied.

Control experiments on the absence of hydrogen exchange during the competitive experiments were carried out in the same way as the ordinary competitive experiments but with totally (97 %) deuterated substrate. 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 material from the control experiments, it can be concluded that there is no measurable hydrogen exchange under these conditions.

It was also shown that there was no hydrogen exchange between partially deuterated substrate and an equivalent amount of hydrobromic acid (63 % by weight) in dimethylformamide, when the conditions were otherwise the same as in the main experiments.

Competitive experiments with partially deuterated 1,3,5-trimethoxy-2,4-dimethylbenzene. To a solution of partially deuterated (50 % D) substrate (0.40 g, 2.0 mmole) in 2 ml of

dimethylformamide kept at -20°C (±2°C), about 1.5 ml of a 2 M solution of bromine in dimethylformamide kept at -20°C was added. After 30 min at -20°C (±2°C), the reaction solution was quenched by aqueous solutions of sodium sulfite and sodium carbonate. The precipitate was filtered off, washed with water and dried over silica gel. The material obtained was dissolved in carbon tetrachloride (1.2 g/ml) and analyzed by NMR spectroscopy. The sample was composed of unreacted 1,3,5-trimethoxy-2,4-dimethylbenzene and the product, 6-bromo-1,3,5-trimethoxy-2,4-dimethylbenzene, which was identified by comparison with an authentic sample. The total yield of unreacted starting material and product was high (95%). The extent of reaction and the deuterium content of the starting material and the unreacted starting material in the reacted sample were determined by NMR analyses in exactly the same way as described above for the competitive experiments with 1,3,5-trimethoxy-2-methylbenzene.

There was no hydrogen exchange in the competitive experiments according to a control experiments involving treatment of the partially deuterated starting material with an equivalent amount of hydrobromic acid (63 % by weight) under the same conditions as those used in the main experiments. Control experiments on the absolute accuracy of the experimental method. The competitive experiments were repeated, but now ordinary light materials were used. The reacted material was worked up and analyzed as described before. All protons pertinent to analyses in the main experiments were accounted for quantitatively within the limits of the estimated random errors.

According to gas chromatographic analyses, no impurities were present in the samples analysed by NMR spectroscopy.

CALCULATIONS AND RESULTS

In all competitive experiments the fraction of deuterium in the recovered unreacted starting material is compared to the same fraction in the starting material. It can be shown\(^1\) that the intermolecular isotope effect in this case is given by the expression

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

where \(y_D'\) and \(y_H'\) are the fractions of deuterium and protium in the starting material, \(y_D\) and \(y_H\) are the corresponding fractions in the recovered unreacted starting material in the reacted sample, and \(x\) is the extent of reaction. The results obtained from the various competitive experiments are summarized in Table 1.* The errors given are the maximum deviations from the mean values.

As is shown in the table, bromination of both substrates gives rise to primary isotope effects, although the values are far from the strongest ones obtainable for this kind of reaction.\(^{3a}\) As can also be seen from the table, added water, salt, and bromide ions have a pronounced influence on the isotope effect found in the bromination of 1,3,5-trimethoxy-2-methylbenzene.

DISCUSSION

Although the primary isotope effects found in this investigation are weaker than the corresponding isotope effects found in the bromination of the bromo derivatives of 1,3,5-trimethoxybenzene,\(^1\) the presence of methyl groups in

* No corrections have been made for the small amount of monodeuterated substrate in the competitive experiments with 1,3,5-trimethoxy-2-methylbenzene, since such corrections are smaller than the experimental error of the isotope effect.
Table 1. Summary of isotope effects in the bromination of 1,3,5-trimethoxy-2-methylbenzene = A and 1,3,5-trimethoxy-2,4-dimethylbenzene = B, at -20°C. DMFA = dimethylformamide.

<table>
<thead>
<tr>
<th>Exptl. Substrate</th>
<th>Solvent</th>
<th>$x$</th>
<th>$y_D/y_D'$</th>
<th>$k_D/k_H$ mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>DMFA</td>
<td>0.42</td>
<td>1.18</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.46</td>
<td>1.22</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.52</td>
<td>1.27</td>
<td>0.48 ± 0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.55</td>
<td>1.32</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.61</td>
<td>1.33</td>
<td>0.50</td>
</tr>
<tr>
<td>1</td>
<td>DMFA + 10 % H$_2$O</td>
<td>0.42</td>
<td>1.23</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.47</td>
<td>1.28</td>
<td>0.41 ± 0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.55</td>
<td>1.36</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>DMFA + 10 % H$_2$O, 1 M NaClO$_4$</td>
<td>0.47</td>
<td>1.19</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>1.19</td>
<td>0.57 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>DMFA + 10 % H$_2$O, 1 M NaBr</td>
<td>0.48</td>
<td>1.34</td>
<td>0.34 ± 0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.55</td>
<td>1.45</td>
<td>0.31</td>
</tr>
<tr>
<td>4</td>
<td>DMFA</td>
<td>0.41</td>
<td>1.28</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.45</td>
<td>1.34</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>1.36</td>
<td>0.30 ± 0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.55</td>
<td>1.39</td>
<td>0.35</td>
</tr>
</tbody>
</table>

1,3,5-trimethoxybenzene apparently also makes proton removal at least partly rate-determining. The reason for these isotope effects seems to be the same, namely steric hindrance to conjugation of the methoxy groups, which is most pronounced in the proton removal step.$^1$

The two-step model for the bromination of all substrates investigated in this and the previous work$^1$ may be outlined as follows:

$$
\text{ArH} + \text{Br}_2 \xrightarrow{\text{1}} \frac{1}{2} \text{ArBrH}^+ + \text{Br}^- \xrightarrow{\text{2 base}} \text{ArBr} + \text{H}^+ + \text{Br}^- 
$$

This model will be employed in the following discussion.

The observed variation in the isotope effect among the substrates may be explained in two different ways. Firstly, the variation may depend on a balance between step -1 and step 2$^6$,$^7$ and secondly the variation may depend on differences in the geometry of the activated complex in step 2.$^8$,$^9$ In the latter case it is of course not necessary to assume a two-step model for the reaction.

The bromination of the disubstituted 1,3,5-trimethoxybenzene should be highly influenced by steric hindrance to conjugation of the methoxy groups since all three methoxy groups will be more or less prevented from conjugation in step 2. It is thus natural that step 2 will dominate more over step -1, i.e. a stronger isotope effect will be observed, in the bromination of the disubstituted 1,3,5-trimethoxybenzene than in the bromination of the mono-

substituted substrate, where only one methoxy group is completely prevented from conjugation in step 2.

The weaker isotope effects found in the bromination of the methyl derivatives of 1,3,5-trimethoxybenzene in comparison with the corresponding bromo derivatives\(^1\) may possibly be explained in the following way. The difference in inductive effect between a methyl group and a bromine atom tends to make the conjugation of the methoxy groups with the aromatic nucleus less important for the methyl compounds than for the bromo compounds. There is therefore less conjugation energy to be lost in step 2 relative to step \(-1\) in the bromination of the methyl compounds than in the bromination of the bromo compounds. Step 2 is then less dominating over step \(-1\), \emph{i.e.} a weaker isotope effect is observed, in the bromination of the methyl compounds than in the bromination of the bromo compounds. It seems less probable that the small difference (if any) in size between a methyl group and a bromine atom could have such a relatively large influence on the relative rates of step 2 and step \(-1\).

It has recently been shown\(^{10}\) that the presence of two \emph{ortho} substituents in anisole causes a considerable change in both the ultra violet absorption and the stretching frequency of the bond between the aromatic carbon and the oxygen of the methoxy group, while substitution of only one \emph{ortho} group has no influence. These effects are independent of the size of the \emph{ortho} substituents, \emph{e.g.} a methyl and a \emph{t}-butyl group have the same influence.

As pointed out above, the variation of the isotope effects could also be explained by differences in the geometry of the activated complex in the proton removal step. If this activated complex is approximated by a linear three-center model $S$---$H$---$B$, where $S$ comes from the substrate, $H$ is protium (or deuterium) and $B$ is a base (solvent), the observed isotope effect should vary with the relative bond strengths of $S$---$H$ and $H$---$B$ in such a way as to make the isotope effect weaker as the difference between the bond strengths becomes greater.\(^{5,9}\) Since a rather strong primary isotope effect was observed in the bromination of 2,4-dibromo-1,3,5-trimethoxybenzene,\(^1\) it may be assumed that $S$---$H$---$B$ is nearly symmetrical in this case. In going through the series of substrates, dibromo-, bromo-, dimethyl-, and methyltrimethoxybenzene, the basicity of $S$ might be assumed to increase partly for steric reasons and therefore $S$---$H$---$B$ should become more and more unsymmetrical, which would lead to a corresponding decrease in the isotope effect.

In order to see if there was a balance between step \(-1\) and step 2 at least in the bromination of 1,3,5-trimethoxy-2-methylbenzene (weakest isotope effect observed), the experiments with added water, sodium perchlorate, and sodium bromide were carried out. The variation of the apparent over all isotope effect with the concentration of bromide ions at constant ionic strength (Table 1, exptl. set 3 and 4) clearly points to such a balance. An increase in the concentration of bromide ions should specifically increase the rate of step \(-1\) and as observed give rise to a stronger isotope effect. If the bromide ion is an effective base in step 2, it should have influenced the rate of step \(-1\) and step 2 in the same way and the observed isotope effect should have been independent of the concentration of bromide ions. It seems therefore probable that the solvent is the base in step 2.

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A similar influence of added bromide ions on an isotope effect has been demonstrated by Bournes in the bromination of anisole-4-sulphonic-2,6-d$_2$ acid, although in his case the over all isotope effect (rate ratio) was absent in the absence of added bromide ions. The mechanism of bromination in this case is also closely related to the mechanism found by Grovenstein for the iodination of 4-nitrophenol-2,6-d$_2$. In these cases it was possible to calculate the specific isotope effect on the proton removal step from the variation of the over all isotope effect (rate ratio) with the concentration of halide ions.

In our case such a calculation is impossible due to the complexity of the reaction system. It is probable that the large amount of bromide ions in experimental set 4 converts much of the molecular bromine into tribromide ions. Even if the tribromide ion is much less effective than molecular bromine as a brominating agent, it can not be excluded that some part of the brominations in experimental set 4 takes place via the tribromide ion. This will probably only have an influence on the rate of step 1, because the free bromide ion must still be more effective in decomposing the intermediate ArBrH$_2$ (in step -1 and even step 2) than the tribromide ion. In any case, since the over all isotope effect becomes stronger at higher concentrations of bromide ions, the qualitative conclusions drawn above about a balance between step -1 and step 2 is still valid.

The influence of the ionic strength on the observed isotope effect (Table 1, exptl. set 2 and 3) is also in accordance with a balance between step -1 and step 2. If the ionic strength is increased, step -1 should be slowed down relative to step 2, because step -1 consists of a reaction between a negatively charged bromide ion and a positively charged intermediate, while in step 2 (with uncharged base) no complete formation or destruction of charge take place.

The influence of added water is not so clear, because both the solvating ability and the basicity of the solvent are changed and this may influence both the balance between step -1 and step 2, and the geometry of the activated complex in step 2.

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