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Hydrogen Isotope Effects in the Bromination of 1,3,5-Triethylbenzene, 2-Bromo-1,3,5-triethylbenzene, and 2,4-Dibromo-1,3,5-triethylbenzene

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Competitive experiments with partially deuterated material gave the isotope effects $k_D/k_H = 0.99 \pm 0.02$, $k_D/k_H = 0.80 \pm 0.04$ and $k_D/k_H = 0.60 \pm 0.03$ for the bromination of 1,3,5-triethylbenzene at −20°C, 2-bromo-1,3,5-triethylbenzene at 25°C and 2,4-dibromo-1,3,5-triethylbenzene at 65°C, respectively, with molecular bromine in dimethylformamide.

In a previously reported investigation of the bromination of mono- and dibromosubstituted 1,3,5-trimethoxybenzene it was suggested that the isotope effects found were primarily due to steric hindrance to conjugation between the methoxy groups and the ring because of the proximity effect of bromine.[1] In order to see if this was the case it was of interest to investigate a compound with steric effects similar to those of trimethoxybenzene but without the same possibilities of conjugation. 1,3,5-Triethylbenzene was supposed to be the best model. The same system, molecular bromine in dimethylformamide, was chosen in order to make a comparison possible between the results of this investigation and the results obtained in the bromination of the bromo derivatives of 1,3,5-trimethoxybenzene.[1]

EXPERIMENTAL

Chemicals used. 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 % and was distilled before use.

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

1,3,5-Triethylbenzene was prepared from benzene and ethyl bromide with aluminium chloride as catalyst according to a reported method.[3] The crude product was a mixture of isomers. In order to obtain pure 1,3,5-triethylbenzene, the isomeric mixture was sulfonated with concentrated sulfuric acid and subsequently hydrolyzed with hydrochloric

acid as described by Norris and Ingraham.[4] This procedure was repeated once. B.p. 215°C, n_D^{19} 1.4955 (Reported:[4] B.p. 214.8°C, $n_D^{18.1}$ 1.4956). No isomers or other impurities could be detected by NMR spectroscopy or gas chromatography.

1,3,5-Triethylbenzene-2,4,6-d_3 containing more than 98 % D in the aromatic ring (determined by NMR spectroscopy) was prepared in three steps in the following way.

Triethylbenzene (6 g, 3.7 × 10^{-2} mole) was equilibrated under efficient stirring with 15 g (0.75 mole) of deuterium oxide (Norsk Hydro, 99.7 % D_2O) and 60 g (0.61 mole) of concentrated sulfuric acid (95–97 %, d = 1.84) for four days at room temperature. The mixture was then poured drop by drop into a mixture of 50 g of ice and 100 g of water. The triethylbenzene layer was separated and the aqueous layer extracted with carbon tetrachloride. The two organic layers were combined and washed with an aqueous solution of sodium carbonate and then with water until the water became neutral. The remaining solution of triethylbenzene in carbon tetrachloride was first dried over anhydrous sodium sulfate and then over anhydrous magnesium sulfate. After the solvent had been evaporated the remaining triethylbenzene was distilled at reduced pressure. According to NMR spectroscopy 51.5 % of the aromatic protons had been exchanged for deuterium.

In the next step 5.5 g (3.4 × 10^{-2} mole) of triethylbenzene (51.5 % D in the aromatic ring) was equilibrated in the same way as described above with 16 g (0.155 mole) of deuterated sulfuric acid (CIBA, 96–98 %, d = 1.86, > 99 % D) and 4 g (0.2 mole) of deuterium oxide. It was worked up in the same way as described above. NMR spectroscopy indicated the presence of 90 % D in the aromatic ring.

In the third equilibration 5.1 g (3.1 × 10^{-2} mole) of triethylbenzene from the preceding step, 20 g (0.195 mole) of deuterated sulfuric acid and 5.3 g (0.265 mole) of deuterium oxide was used. The work up process was the same as before. Yield 4.7 g (2.8 × 10^{-2} mole). Overall yield 77 %. The deuterium content in the aromatic ring was estimated to be more than 98 % by NMR spectroscopy.

2-Bromo-1,3,5-triethylbenzene was prepared by bromination of 1,3,5-triethylbenzene with molecular bromine[5] in dimethylformamide. Triethylbenzene (1.50 g, 9.25 mmole) was dissolved in 3.75 ml of dimethylformamide and kept at −20°C. A solution of 2.94 g (18.4 mmole) of Br_2 in 3.75 ml of dimethylformamide kept at −20°C was added. The solution was allowed to react for 1.5 h at −20°C protected from light.

The reaction was then quenched by the addition of an aqueous solution of sodium sulfite. The resulting mixture was extracted with carbon tetrachloride. The extract was washed with an aqueous solution of sodium carbonate and sodium sulfite and then with water. The extract was dried over anhydrous sodium sulfate.

After the solvent had been evaporated the crude product (slightly coloured) was analyzed by gas chromatography. According to this less than 0.5 % of the starting material was left. There was no sign of dibromination or side chain bromination.

Vacuum distillation gave 1.8 g of 2-bromo-1,3,5-triethylbenzene. Yield 80 %, b.p.$_3$ 98.4–99°C, n_D^{20} 1.5365 (Reported:[5] B.p.$_{2-3}$ 98.5–99°C, n_D^{20} 1.5366). The product was identified by NMR spectroscopy. No appreciable amounts of impurities could be detected by NMR spectroscopy or gas chromatography.

2-Bromo-1,3,5-triethylbenzene-4,6-d_2 was prepared from 1,3,5-triethylbenzene-2,4,6-d_3 in the same way as the light bromo derivative. The deuterium content in the 4 and 6 positions of the aromatic ring was the same in the product as in the starting material according to NMR spectroscopy.

2,4-Dibromo-1,3,5-triethylbenzene was prepared by bromination of 2-bromo-1,3,5-triethylbenzene with molecular bromine in dimethylformamide. 2-Bromo-1,3,5-triethylbenzene (4.17 g, 1.73 × 10^{-2} mole) was dissolved in 10 ml of dimethylformamide and 11.1 g (6.95 × 10^{-2} mole) of bromine was dissolved in another 10 ml of dimethylformamide. Both solutions were cooled to −20°C and then the bromine solution was added to the 2-bromo-1,3,5-triethylbenzene solution. The reaction mixture was protected from light and kept at 25°C for 2 h. The excess of bromine was destroyed by the addition of an aqueous solution of sodium sulfite. The product was isolated in the same way as in the preparation of 2-bromo-1,3,5-triethylbenzene. Gas chromatography on the crude product indicated more than 99 % bromination.

After distillation *in vacuo* (b.p.$_{4-5}$ 144–145°C) 4.90 g (88 %) was obtained, n_D^{20} 1.5730. NMR spectroscopy gave the following chemical shifts: 6.90 ppm (1 aromatic H), 3.12 ppm a quartet (1 CH_2), 2.79 ppm a quartet (2 CH_2), 1.18 ppm a triplet (3 CH_3).

All shifts were measured relative to TMS. No impurities were detected by NMR spectroscopy and gas chromatography.

A mixture of deuterated and undeuterated 2,4-dibromo-1,3,5-triethylbenzene was prepared in two steps in the following way. First, partially deuterated 2-bromo-1,3,5-triethylbenzene was prepared by equilibrating light material with sulfuric acid and deuterium oxide at 75°C. The reaction mixture was prepared with the relative composition of 1 g (4.15 mmole) of 2-bromo-1,3,5-triethylbenzene, 10 g of sulfuric acid (95—97 %), 2.52 g (0.126 mole) of deuterium oxide (Norsk Hydro) and was heated at 75°C with efficient stirring for one week. The product was isolated in the same way as in the preparation of 1,3,5-triethylbenzene-2,4,6-d_3. Yield 84 %.

According to NMR spectroscopy the deuterium content was 46 % in the aromatic ring.

In the next step the partially deuterated 2-bromo-1,3,5-triethylbenzene was brominated in the same way as the light material. The product was then distilled with some undeuterated compound to obtain a suitable deuterated material for the competitive experiments.

2,4,6-Tribromo-1,3,5-triethylbenzene was prepared for calibration purposes by bromination of 2,4-dibromo-1,3,5-triethylbenzene with molecular bromine in dimethylformamide. To a solution of 0.8 g (2.5 mmole) of 2,4-dibromo-1,3,5-triethylbenzene in 2 ml of dimethylformamide kept at 65°C, 2 g (12.5 mmole) of bromine was added and the solution was allowed to react for 3.5 h in darkness. It was then cooled to 0°C and the excess of bromine destroyed by the addition of an aqueous solution of sodium sulfite. Product and unreacted material were isolated in the same way as described for the other bromo derivatives. Gas chromatography on the isolated material dissolved in carbon tetrachloride indicated the extent of bromination to be 65 %. There was some sign of side chain bromination at this extent of bromination.

The solvent was evaporated and the residue was dissolved in 1.5 ml of dimethylformamide by heating on a steam bath. After the solution had cooled to room temp. it was cooled to −20°C. At this temperature most of the 2,4,6-tribromo-1,3,5-triethylbenzene precipitated. The precipitate was filtered off. The crystals were sucked dry and then recrystallized from methanol. Yield 0.4 g (41.2 % of the theoretical), m.p. 103,5—104°C. (Reported:[4] 104.6—104.8°C). The product was pure according to gas chromatography and NMR spectroscopy.

Analyses. All deuterium analyses were carried out with a Varian A60 NMR spectrometer.[1]

The gas chromatography was performed on a Perkin-Elmer Model 116 E instrument. Conditions: 2 m column "O", int. diam. 4 mm, temp. 190—200°C, carrier gas He, flow rate 60—80 ml/min. The signals were integrated by a Perkin-Elmer Model D_2 electronic integrator. For each type of substrate mixture a calibration curve was made up from mixtures with known compositions.

Competitive experiments with a mixture of 1,3,5-triethylbenzene-2,4,6-d_3 (> 98 % D) and 1,3,5-triethylbenzene. To a solution of the starting mixture (0.4 g, 2.47 mmole; for proportions of isotopic species see Table 1) in 3 ml of dimethylformamide kept at −20°C (± 0.2°C) a solution of bromine (0.75 g, 4.7 mmole) in 3 ml of dimethylformamide kept at the same temperature was added. The solution (protected from light) was allowed to react at −20°C (± 0.2°C) for 1 h. It was then quenched by an aqueous solution of sodium sulfite and sodium carbonate. In order to isolate the product and the unreacted starting material the mixture was treated in the same way as in the preparative experiment. The mixture of 2-bromo-1,3,5-triethylbenzene and 1,3,5-triethylbenzene obtained was analyzed by gas chromatography in order to determine the extent of reaction. According to the chromatogram 85—95 % of the starting material had been brominated (determined from the calibration curve). By NMR spectroscopy the total fraction of aromatic protons per molecule in the mixture could be measured, by comparing the sum of the intensities of the aromatic protons with the sum of the intensities of the methylene groups divided by six. From this, the result of gas chromatography and the initial ratio of light to heavy material, the fraction of deuterium in the unreacted recovered starting material could be calculated according to the following scheme and equations. (Ar denotes the substrate without aromatic hydrogen)

$$ArH_3 \text{ (starting material)} \longrightarrow ArH_2Br + ArH_3 \text{ (products)}$$
$$ArD_3 \text{ (starting material)} \longrightarrow ArD_2Br + ArD_3 \text{ (products)}$$

In the following the chemical symbols denote molar amounts.
GLC gives the ratio $(ArH_3 + ArD_3)/(ArH_2Br + ArD_2Br)$.
NMR gives the ratio $(3\ ArH_3 + 2\ ArH_2Br)/(ArH_3 + ArD_3 + ArH_2Br + ArD_2Br)$.
It is evident that $(ArH_3 + ArH_2Br)/(ArD_3 + ArD_2Br) = (ArH_3)_{t=0}/(ArD_3)_{t=0}$. $(ArH_3)_{t=0}/(ArD_3)_{t=0}$ is given by NMR spectroscopy on the starting mixture.

From these three ratios it is possible to calculate the fraction of deuterium in the recovered unreacted starting material.

The total yield of 2-bromo-1,3,5-triethylbenzene and unreacted starting material was better than 97 %. As the reaction was not instantaneous it was possible to control the extent of reaction by varying the time.

Competitive experiments with a mixture of 2-bromo-1,3,5-triethylbenzene-4,6-d_2 (> 98 % D) and 2-bromo-1,3,5-triethylbenzene containing 50.5 % deuterium. The starting material (0.41 g, 1.7 mmole) was dissolved in 1 ml of dimethylformamide and the solution was cooled to −20°C. At this temperature a solution of 0.56 g (3.5 mmole) of bromine in 1 ml of dimethylformamide cooled to −20°C was added. The reaction mixture was protected from light and warmed to 25°C (± 1°C). The solution was allowed to react at this temperature for 45 min. It was then cooled to −20°C and an aqueous solution of sodium sulfite and sodium carbonate was added to quench the reaction. Product and unreacted starting material were isolated from the resulting mixture by extraction with carbon tetrachloride. The extract was washed with water and dried over anhydrous sodium sulfate. After the solvent had been evaporated the residue was analyzed by gas chromatography. The extent of reaction was found to be 71−81 %. In order to get the total amount of protium the NMR spectrum of the mixture was obtained. The evaluation of the deuterium content in the unreacted starting material was carried out in a way similar to that in the competitive experiments with triethylbenzene.

The total yield of product and unreacted starting material was better than 96%. It was found that the reaction was not instantaneous. By varying the time it was possible to control the extent of bromination.

Competitive experiments with a mixture of 40 % 2,4-dibromo-1,3,5-triethylbenzene-6-d and 60 % 2,4-dibromo-1,3,5-triethylbenzene. To a solution of the starting material (0.71 g, 2.2 mmole) in 2 ml of dimethylformamide kept at 65°C (± 1°C), 1.40 g (8.8 mmole) of bromine was added. The solution was allowed to react for 3 h while protected from light. It was then cooled to 0°C and the reaction was quenched by the addition of an aqueous solution of sodium sulfite and sodium carbonate. The product and the unreacted starting material were isolated as in the preceding competitive experiments. The residue was dissolved in 0.5 ml of carbon tetrachloride and analyzed for the extent of reaction by gas chromatography. According to this 40−50 % of the starting material had been brominated. The solvent was evaporated and 1.2 ml of dimethylformamide was added to the residue. The mixture was brought into solution by heating on a steam bath. While cooling to room temperature, tribromo-1,3,5-triethylbenzene began to precipitate. In order to precipitate most of the tribromo derivative, the mixture was cooled to −25°C. The precipitate was filtered off and washed with 0.5 ml of dimethylformamide. The dimethylformamide solution containing the unreacted starting material was diluted with water and extracted with carbon tetrachloride. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue analyzed by gas chromatography in order to determine the remaining content of tribromo derivative, which amounted to 3 %. NMR spectroscopy gave the fraction of aromatic protium in the unreacted starting material as usual. The intensities of the signals from the methylene groups had been corrected for the signals from the small amount of methylene groups arising from the remaining tribromo derivative. As the reaction was not instantaneous it was possible to control the reaction by varying the time.

Control experiments on the absence of hydrogen exchange during the competitive experiments. The control experiments were carried out by treating each of the starting mixtures of isotopic organic molecules with an equivalent amount of anhydrous hydrogen bromide in the same solvent, at the same concentration and temperature and during the same time as used in the competitive experiments. No change in isotopic composition was observed.

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.

CALCULATIONS AND RESULTS

In all competitive experiments there has been purely intermolecular competition. The fraction of deuterium in the recovered unreacted starting material is compared to the same fraction in the starting material. In such a case the following equation can be used to calculate the isotope effect k_D/k_H: [1,6a]

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

where y_D and y_D' denotes the fraction of deuterium in the unreacted recovered starting material and the initial starting material respectively, y_H and y_H' the corresponding fractions of protium, and x denotes the extent of reaction. The results from the various calculations of the isotope effects are summarized in Table 1.

DISCUSSION

As is seen from Table 1 the isotope effects observed are far from the maximum strength obtainable for this kind of reaction.[7a] In going from unsubstituted to mono- and dibromo substituted 1,3,5-triethylbenzene there is, however, a clean change in the isotope effect with the degree of substitution.

If we assume a two step model for the reaction

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

Table 1. Summary of isotope effects found in the bromination of 1,3,5-triethylbenzene = A,* 2-bromo-1,3,5-triethylbenzene = B * and 2,4-dibromo-1,3,5-triethylbenzene = C.

Substrate	Temp. °C	x	y_D'	y_D	k_D/k_H	k_D/k_H mean value
A	−20	0.856	0.472	0.486	0.97	
A	−20	0.883	0.495	0.505	0.98	0.99 ± 0.02
A	−20	0.888	0.495	0.499	0.99	
A	−20	0.942	0.495	0.485	1.01	
B	25	0.715	0.505	0.575	0.80	
B	25	0.745	0.505	0.602	0.76	0.80 ± 0.04
B	25	0.758	0.505	0.586	0.80	
B	25	0.807	0.505	0.589	0.83	
C	65	0.400	0.400	0.460	0.60	
C	65	0.433	0.400	0.470	0.59	0.60 ± 0.03
C	65	0.457	0.400	0.468	0.63	
C	65	0.500	0.400	0.485	0.58	

* No corrections have been made for the small amount of molecules containing both deuterium and protium.

the isotope effects obtained in the experiments with the monobromo and dibromo substrates show that the rate of step 2 is smaller than or at most comparable to the rate of step -1.[7b,8] The results show that step 2 will be more and more rate-determining with increasing steric effects. This is also what has recently been reported for the bromination of some polyalkylbenzenes in acetic acid and nitromethane.[9] A small isotope effect for the bromination of mesitylene in acetic acid has also been reported.[9] In the present work, however, no isotope effect has been found for the bromination of 1,3,5-triethylbenzene. Similarly no isotope effect has been found for the bromination of 1,3,5-trimethoxybenzene in dimethylformamide.[1] The steric effects, however, of the ethyl and the methoxy groups are greater than the effects of the methyl groups in mesitylene. The difference in isotope effects is probably due to solvent effects. Dimethylformamide is a stronger base than acetic acid and will thus make the proton removal less rate-determining.

In the bromination of 2-bromo-1,3,5-trimethoxybenzene at 25°C and 2,4-dibromo-1,3,5-trimethoxybenzene at 65°C there are reported[1] the isotope effects $k_D/k_H = 0.28 \pm 0.08$ and $k_D/k_H = 0.21 \pm 0.04$, respectively. It was supposed that these strong effects were due mainly to steric hindrance to conjugation between the methoxy groups and the ring in the proton removal step. The isotope effects found in the present investigation for the corresponding triethylbenzene derivatives $k_D/k_H = 0.80 \pm 0.04$ and $k_D/k_H = 0.60 \pm 0\ 03$, respectively, are much weaker but still appreciable. Since the latter type of substrate does not offer the same possibilities for conjugation as the former and the steric effects should be about identical in both series, at least part of the isotope effects found in the bromination of bromo- and dibromo-trimethoxybenzene could be considered to be due to general steric hindrance when the bromine is to enter the plane of the ring in the proton removal step.

The effect of steric hindrance to conjugation cannot be quite excluded, however. In recently reported work[10] on the "size" of a lone pair of electrons it has been shown that the electron pair of oxygen in *cis*-2-alkyl-5-t-butyl-1,3-dioxanes is smaller than the corresponding hydrogen in cyclohexane. If this is applied to the trimethoxybenzene derivatives, it would imply that the steric effects of the methoxy groups should be smaller than those of the ethyl groups in triethylbenzene, and thus the trimethoxybenzene derivatives should be less sterically hindered than the corresponding triethylbenzene derivatives. This would again tend to make the steric hindrance to conjugation more important than the general steric effects alone.

Also it is not possible to explain the differences in isotope effects between the trimethoxy- and triethylbenzene derivatives by loss in rotational freedom in the proton removal step for the methoxy groups or the ethyl groups. Such a loss would probably have a stronger influence on the triethylbenzene derivatives than on the trimethoxybenzene derivatives in the latter of which conjugation could be expected to cause preference for the coplanar conformation.

Another explanation of the variation of the isotope effects in this investigation is given if it is assumed that the isotope effects depend on the geometry of the activated complex in a rate-determining proton removal step.[6b,11] If the activated complex is approximated by a linear three-center model

S---H---B, where B is a base, in this case the solvent,[2] H is hydrogen and S denotes the substrate, the isotope effects should vary with the relative bond strengths of S---H and H---B. If the difference between the bond strengths increases the isotope effects will be weaker.[6b,11] In this investigation it is obvious that the basicity of S will decrease with the degree of substitution, as bromine is an electron-demanding substituent. If it is assumed that the triethylbenzene substrate is a stronger base than the solvent (which, however, is somewhat uncertain) it might be assumed, as a result of the observed isotope effects, that the difference in basicity between S and B will decrease with the degree of substitution.

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REFERENCES

1. Helgstrand, E. *Acta Chem. Scand.* **19** (1965) 1583.
2. Helgstrand, E. and Nilsson, Å. *Acta Chem. Scand.* **20** (1966) 1463.
3. Norris, J. F. and Rubinstein, D. *J. Am. Chem. Soc.* **61** (1939) 1163.
4. Norris, J. F. and Ingraham, J. N. *J. Am. Chem. Soc.* **60** (1938) 1421.
5. Fuson, R. C. and Corse, J. *J. Am. Chem. Soc.* **60** (1938) 2063.
6. Melander, L. *Isotope Effects on Reaction Rates*, Ronald Press, New York 1960, (a) p. 48; (b) p. 24.
7. Berliner, E. *Progr. Phys. Org. Chem.* **2** (1964), (a) p. 288; (b) p. 281.
8. Zollinger, H. *Advan. Phys. Org. Chem.* **2** (1964) 167.
9. Baciocchi, E., Illuminati, G., Sleiter, G. and Stegel, F. *J. Am. Chem. Soc.* **89** (1967) 125.
10. Eliel, E. L. and Knoeber, Sr., M. C. *J. Am. Chem. Soc.* **88** (1966) 5347.
11. Westheimer, F. H. *Chem. Rev.* **61** (1961) 265.

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