ACTA CHEMICA SCANDINAVICA 23 (1969) 7–13

Hydrogen Isotope Effects in the Bromination of 2-Methyl-1,3,5-triethylbenzene and 2,4-Dimethyl-1,3,5-triethylbenzene

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The substrates, prepared by direct methods from 1,3,5-triethylbenzene, were brominated by molecular bromine in dimethylformamide. Competitive experiments with partially deuterated compounds gave the isotopic rate ratios $k_D/k_H = 0.95 \pm 0.03$ and $k_D/k_H = 0.86 \pm 0.03$ for the bromination of 2-methyl-1,3,5-triethylbenzene and 2,4-dimethyl-1,3,5-triethylbenzene, respectively, at −20°C.

The results of this investigation are to be compared with previously reported work on the bromination of bromo and methyl substituted 1,3,5-trimethoxybenzenes [1,2] and bromo substituted 1,3,5-triethylbenzenes.[3] In these investigations it was found that both methyl and bromo substituents in 1,3,5-trimethoxybenzene caused rather strong isotope effects, the isotope effects for the bromo derivatives being somewhat stronger than those for the methyl derivatives. Bromo substituted 1,3,5-triethylbenzenes, however, gave comparatively weak isotope effects and therefore it was of interest to see what effect methyl substituents would have on the isotope effect in the case of 1,3,5-triethylbenzene.

EXPERIMENTAL

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

Fischer's certified dimethylformamide had a specified water content of 0.001 %.

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

Preparative gas chromatography was performed on an Autoprep A-700. Conditions: 3 m column "O", internal diameter 9.2 mm, temp. 200°C, carrier gas N_2, flow rate 120 ml/min.

Analyses. All deuterium analyses were carried out with a Varian A 60 NMR spectrometer.

Analytical gas chromatography was performed on a Perkin-Elmer Model 116 E instrument. Conditions: 2 m column "O", internal diameter 4 mm, temp. 190–200°C, carrier gas He, flow rate 60–80 ml/min. The signals were integrated by a Perkin-Elmer

Model D2 electronic integrator. For each type of substrate mixture a calibration curve was made up from mixtures with known compositions.

2-Methyl-1,3,5-triethylbenzene was prepared by chloromethylation of 1,3,5-triethylbenzene [4,5] and subsequent reduction of the product, 2-chloromethyl-1,3,5-triethylbenzene, with lithium aluminium hydride.

1,3,5-Triethylbenzene (50.0 g, 0.309 mole), chloromethyl-methylether (49.7 g, 0.618 mole) and glacial acetic acid (93.0 g, 1.55 moles) were mixed and heated (90°C) for 50 h. The reaction mixture was then poured into 500 ml of water. The organic layer was separated, and the aqueous layer was extracted with petroleum ether (40–60°C). The organic layers were combined and washed with a dilute aqueous solution of sodium carbonate and then with water. The solution of 2-chloromethyl-1,3,5-triethylbenzene in petroleum ether was dried over anhydrous calcium sulphate. The solvent was evaporated and the residue distilled *in vacuo*, b.p.$_{0.5}$: 93°C, n_D^{23} 1.5298. (Reported:[5] b.p.$_4$: 116–118°C, n_D^{20} 1.5301). Yield: 34.4 g (53 %).

To a well-stirred suspension of lithium aluminium hydride (8.3 g, 0.218 mole) in anhydrous ether (150 ml) a solution of 2-chloromethyl-1,3,5-triethylbenzene (34.4 g, 0.164 mole) in anhydrous ether (75 ml) 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 lithium aluminium hydride was destroyed by the addition of ethyl acetate. During this operation various salts precipitated, and dilute sulphuric acid was added to the mixture until the salts were dissolved. The mixture was extracted with ether and the organic solution washed with a dilute aqueous solution of sodium hydrogen carbonate and then with water. The ether solution was dried over anhydrous magnesium sulphate. The solvent was evaporated and the residue distilled *in vacuo*, b.p.$_7$: 98°C, n_D^{25} 1.5065. Yield: 24.9 g (86 %). The product was pure according to gas chromatography. NMR spectroscopy gave the following chemical shifts: 6.75 ppm (2 aromatic H), 2.56 ppm (quartet, 2 CH_2), 2.51 ppm (quartet, 1 CH_2), 2.13 ppm (1 nuclear CH_3), 1.18 ppm (triplet, 1 CH_3) and 1.15 ppm (triplet, 2 CH_3). All shifts were measured relative to TMS.

2-Methyl-1,3,5-triethylbenzene-4,6-d_2 was prepared in three steps in the following way. 2-Methyl-1,3,5-triethylbenzene (5 g, 0.028 mole) was equilibrated with efficient stirring with concentrated deuterated sulphuric acid (40 g, 0.388 mole, CIBA, 96–98 %, d= 1.86, > 99 % D) and deuterium oxide (10 g, 0.500 mole, CIBA, 99.75 % D) for four days at room temperature. The mixture was then poured into a mixture of 350 g of water and 150 g of ice. The organic layer was separated and the aqueous layer was extracted with carbon tetrachloride. The organic layers were combined and washed with a dilute aqueous solution of sodium carbonate and then with water. The solution was then dried over anhydrous magnesium sulphate. The solvent was evaporated and the procedure repeated twice. The product was distilled *in vacuo*, b.p.$_{10}$: 109°C. Yield: 3.7 g (74 %). The product was pure according to gas chromatography and no aromatic protons could be detected by NMR spectroscopy, indicating more than 98 % deuterium in the aromatic ring.

4-Bromo-2-methyl-1,3,5-triethylbenzene was prepared for calibration purposes by bromination of 2-methyl-1,3,5-triethylbenzene with molecular bromine in carbon tetrachloride and with iron as catalyst.[6] To a stirred solution of 2-methyl-1,3,5-triethylbenzene (2 g, 0.011 mole) in carbon tetrachloride (1.13 ml) containing iron powder (0.056 g, 1.01 mmoles), kept at 0°C and protected from light, a solution of bromine (2 g, 0.013 mole) in carbon tetrachloride (1.25 ml) was added drop by drop during 1 h. The mixture was allowed to react for another 2 h at 0°C. Then the mixture was diluted with 50 ml of carbon tetrachloride and washed with an aqueous solution of sodium sulphite and sodium carbonate and then with water. The solution was dried over anhydrous calcium chloride and the solvent was evaporated.

In order to remove possible side-chain brominated material the residue was refluxed for half an hour with a solution of sodium (0.114 g, 5.98 mmoles) in 95 % ethanol (2.27 ml). The reaction mixture was allowed to stand at room temperature for another 1½ h and was then diluted with 10 ml of water. The organic layer was separated and the aqueous layer was extracted with carbon tetrachloride. The organic layers were combined and dried over anhydrous calcium chloride. The yellow colour of the solution was removed by adsorption chromatography (aluminium oxide, neutral, activity 1, eluate: carbon tetra-

chloride). The solvent was evaporated and the residue distilled *in vacuo*, $b.p._{10}$: 145°C. Yield: 1.8 g (64 %). The product was pure according to gas chromatography. NMR spectroscopy gave the following chemical shifts: 6.80 ppm (1 aromatic H), 3.10—2.30 ppm a band with incompletely resolved peaks (3 CH_2), 2.20 ppm (1 nuclear CH_3) and 1.37—0.97 ppm a band with incompletely resolved peaks (3 CH_3). All shifts were measured relative to TMS.

2,4-Dimethyl-1,3,5-triethylbenzene was prepared by chloromethylation [7] of 2-chloromethyl-1,3,5-triethylbenzene and subsequent reduction of the product, 2,4-bis(chloromethyl)-1,3,5-triethylbenzene, with lithium aluminium hydride.

To a stirred solution of 2-chloromethyl-1,3,5-triethylbenzene (64.1 g, 0.304 mole) and chloromethyl-methylether (40 g, 0.520 mole) in carbon disulphide (125 ml) kept at 0°C, stannic chloride (25 g, 0.095 mole) was added during a period of 1 h. After the addition the solution was kept at 0°C and stirred for another 1 h. The mixture was then poured onto ice. The organic layer was separated and the water layer was extracted with carbon tetrachloride. The two organic layers were combined, washed with water and then with a dilute aqueous solution of sodium carbonate, and then again with water. The carbon tetrachloride solution was dried over anhydrous sodium sulphate. The solvent was evaporated and the crystalline residue was recrystallized twice from xylene, m.p. 84.5—85.0°C. Yield: 57.0 g (72 %). The product was pure according to gas chromatography. NMR analysis gave the following chemical shifts: 6.87 ppm (1 aromatic H), 4.59 ppm (2 CH_2Cl), 2.86 ppm (quartet, 1 CH_2), 2.73 ppm (quartet, 2 CH_2) and 1.26 ppm (triplet, 3 CH_3). All shifts were measured relative to TMS.

To a stirred mixture of lithium aluminium hydride (17 g, 0.44 mole) in anhydrous ether (280 ml), kept at 40°C, a solution of 2,4-bis(chloromethyl)-1,3,5-triethylbenzene (28 g, 0.11 mole) in anhydrous ether (260 ml) was added at such a rate that gentle reflux was obtained. After the addition the reaction mixture was refluxed for another 5 h. The mixture was then cooled and the excess of lithium aluminium hydride was destroyed by addition of ethyl acetate. Water was then added and the aluminium hydroxide formed was dissolved by addition of dilute sulphuric acid. The organic layer was separated and the water layer extracted twice with ether. The combined organic layers were washed with a dilute aqueous solution of sodium hydrogen carbonate, then with water and dried over anhydrous sodium sulphate. After the solvent had been evaporated the residue, slightly coloured, was distilled at reduced pressure, $b.p._{2-3}$: 79—80°C, n_D^{22} 1.5162, Yield: 17 g (83 %).

According to gas chromatography there was an impurity of less than 0.5 %, with a boiling point close to that of the main product. The material used for the isotope effect investigation was therefore purified by preparative gas chromatography.

NMR analysis gave the following chemical shifts: 6.71 ppm (1 aromatic H), 2.67 ppm (quartet, 1 CH_2), 2.54 ppm (quartet, 2 CH_2), 2.18 ppm (2 nuclear CH_3), 1.15 ppm (triplet, 2 CH_3) and 1.08 ppm (triplet, 1 CH_3). All shifts were measured relative to TMS.

Partially deuterated 2,4-dimethyl-1,3,5-triethylbenzene was prepared by equilibrating the undeuterated compound with a suitable mixture of sulphuric acid and deuterium oxide. Since there is only one aromatic hydrogen in the substrate, deuterium is confined to one position. The deuterated material was purified by preparative gas chromatography.

6-Bromo-2,4-dimethyl-1,3,5-triethylbenzene was obtained for calibration purpose by bromination of 2,4-dimethyl-1,3,5-triethylbenzene in carbon tetrachloride.

To a stirred solution of 2,4-dimethyl-1,3,5-triethylbenzene (2 g, 10.5 mmoles) in carbon tetrachloride (2 ml), containing 0.03 g (0.54 mmole) of iron powder, a solution of bromine (1.85 g, 11.6 mmoles) in carbon tetrachloride (1.5 ml) was added at 0°C during a period of half an hour. The mixture was then stirred for another 1 h at 0°C. The reaction mixture was diluted with 15 ml of carbon tetrachloride, washed with an aqueous solution of sodium carbonate and sodium sulphite and dried over sodium sulphate. The solvent was evaporated and the crude material analysed by gas chromatography. According to this less than 1 % of the starting material was unreacted. The product was recrystallized twice from ethanol, m.p. 61.0—61.5°C. Yield: 1.3 g (46 %). The material was pure according to gas chromatography.

NMR analysis gave the following chemical shifts: 2.86 ppm (quartet, 2 CH_2), 2.60 ppm (quartet, 1 CH_2), 2.26 ppm (2 nuclear CH_3), 1.13 ppm (triplet, 2 CH_3) and 1.06 ppm (triplet, 1 CH_3). All shifts were measured relative to TMS.

Competitive experiments with a mixture of 2-methyl-1,3,5-triethylbenzene-4,6-d_2 and 2-methyl-1,3,5-triethylbenzene, containing 38.8 % deuterated material. To a stirred solution of 0.7 g (3.97 mmoles) of the starting mixture in 95 ml of dimethylformamide kept at -20.0 ± 0.2°C a solution of 1.02 g (6.39 mmoles) of bromine in 10.5 ml of dimethylformamide kept at the same temperature was rapidly injected with a pipette fitted to a piston. The solution (protected from light) was allowed to react at -20.0 ± 0.2°C for a time which varied between ½ h and 1 h in the different experiments. The reaction was quenched by an aqueous solution of sodium sulphite and sodium carbonate. The mixture was extracted with carbon tetrachloride and the organic layer was washed with water. The carbon tetrachloride solution was dried over anhydrous magnesium sulphate. The solvent was evaporated and the extent of reaction was determined by gas chromatography. No dibrominated product could be detected. Unreacted starting material and product were separated by preparative gas chromatography. The fraction of deuterated material in the recovered unreacted starting material was determined by NMR spectroscopy by comparing the sum of the intensities of the aromatic protons with the sum of the intensities of all protons in the ethyl and nuclear methyl groups. The fraction of deuterated material in the product was determined in the same way.

Competitive experiments with a mixture of 2,4-dimethyl-1,3,5-triethylbenzene-6-d and 2,4-dimethyl-1,3,5-triethylbenzene, containing 40.0 % deuterated material (typical experiment). To a stirred solution of the starting mixture (0.709 g, 3.73 mmoles) in 40 ml of dimethylformamide kept at -20.0 ± 0.2°C a solution of bromine (0.63 g, 4.85 mmoles) in 24 ml of dimethylformamide kept at the same temperature was rapidly added with a pipette fitted to a piston. The solution (protected from light) was allowed to react at -20.0 ± 0.2°C for 1 h. The product and the unreacted starting material were isolated as in the preceding competitive experiment. The residue was dissolved in 1 ml of carbon tetrachloride and analysed by gas chromatography. The extent of reaction was found to be 60.9 %. The unreacted starting material was separated from the product by preparative gas chromatography. NMR spectroscopy gave the fraction of protium in the unreacted starting material by comparison of the intensity of the aromatic proton with the sum of the intensities of the nuclear groups.

Control experiments on the absence of hydrogen exchange during the competitive experiments. The control experiments were carried out by treating each type of the starting mixtures of isotopic organic molecules with 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 analysed as described before. All protons pertinent to analysis in the main experiments were accounted for quantitatively within the limits of the estimated random errors.

Control of the reaction rates. In order to check that the reactions were not too rapid as compared to the time for mixing the reagents, a necessary condition for having fair competition between the different isotopic species of organic molecules in the competitive experiments, the reaction rates were studied with ordinary light materials at the same conditions as in the latter experiments. The reactions were followed by taking aliquots of the reaction solutions at suitable time intervals, quenching in an aqueous solution of sodium sulphite and sodium carbonate and extracting with carbon tetrachloride. The extent of reaction was determined by gas chromatography. The following results were obtained for the monomethyl derivative: Time/% bromination = 1 − 2 sec/3 %, 10 sec/15.2 %, 30 sec/22.1 %, 60 sec/35.6 %, 1.5 min/44.8 %, 2 min/45.2 %, 4 min/52.2 %, 13 min/59.9 %, 30 min/63.2 %. For the dimethyl derivative was found: Time/% bromination = 1 − 2 sec/1.9 %, 7 sec/8.4 %, 30 sec/25.9 %, 60 sec/35.8 %, 2 min/41.4 %, 7 min/50.7 %, 15 min/52.2 %, 20 min/56.7 %, 60 min/60.7 %. The initial rates were considered to be just at the upper limit to allow measurements of the isotope effect with the present technique.

CALCULATIONS AND RESULTS

In all competitive experiments there has been purely intermolecular competition. No corrections have been made for the small amount of 2-methyl-1,3,5-triethylbenzene molecules containing both deuterium and protium (<4 %). 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 isotopic rate ratio k_D/k_H: [1,8a]

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

where y_D and y_D' denote the fraction of deuterium in the recovered unreacted starting material and the initial starting material, respectively, and y_H and y_H' the corresponding fractions of protium, and x denotes the overall extent of reaction.

In the case of the bromination of the monomethyl derivative the isotope effect has also been calculated by comparing the fraction of deuterium in the product with the same fraction in the starting material. In this case the following equation can be used:

$$k_D/k_H = \{\log (1-x\cdot y_D''/y_D')\}/\{\log (1-x\cdot y_H''/y_H')\} \quad (2)$$

where y_D'' and y_H'' denote the fraction of deuterium and protium, respectively, in the product; x, y_D', and y_H' are the same symbols as used above.

The results from the various calculations of the isotopic rate ratios are summarized in Table 1.

DISCUSSION

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-triethylbenzene.[3] The isotope effect found for the bromination of the dimethyl derivative is even weaker than that found for the mono-

Table 1. Summary of the isotopic rate ratios found in the bromination of 2-methyl-1,3,5-triethylbenzene=A and 2,4-dimethyl-1,3,5-triethylbenzene=B. The errors given are the maximum deviations from the mean values. For symbols, see the text.

Substrate	Temp °C	x	y_D'	y_D	y_D''	k_D/k_H from eqn. 1	k_D/k_H from eqn. 2	k_D/k_H mean value
A	−20	0.622	0.388	0.399	0.384	0.95	0.97	
A	−20	0.689	0.388	0.401	0.384	0.95	0.97	0.95 ± 0.03
A	−20	0.721	0.388	0.412	0.380	0.92	0.93	
A	−20	0.755	0.388	0.415	0.386	0.92	0.98	
B	−20	0.478	0.400	0.429		0.83		
B	−20	0.511	0.400	0.421		0.89		0.86 ± 0.03
B	−20	0.609	0.400	0.431		0.87		

bromo derivative. However, even in this investigation there is a small change in the isotope effect with the degree of substitution. The reason for the isotope effects found in this investigation seems to be the same as in the bromination of the bromo derivatives, namely steric hindrance for the bromine to enter the plane of the ring in the proton removal step. The general agreement with previous results indicates that the present effects are primary rather than secondary ones.

The two-step mechanism for the bromination of both substrates may be outlined as follows:

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

This model will be used in the discussion of the bromination of both the substrates. As a primary isotope effect results only if the rate of step 2 is less than, or, at most, comparable to the rate of step -1 [9,10] the results seem to indicate that the proton removal step is more and more rate determining with increasing steric hindrance. The same was also found for the bromo derivatives. For the methyl derivatives it might be assumed that the basicity of the products is increasing with the degree of methyl substitution and this could possibly make step 2 relatively slower for the dimethyl derivative than for the monomethyl derivative and thus cause the change in isotope effect. In the case of the bromo derivatives, however, the basicity of the products is decreased with the degree of substitution. Moreover, such effects could be compensated by corresponding differences in nucleophilicity towards the bromine.

In the bromination of the monobromo and dibromo derivatives there were found the isotopic rate ratios 0.80 ± 0.04 at 25°C and 0.60 ± 0.03 at 65°C, respectively.[3] In this investigation the rate ratio 0.86 ± 0.03 at -20°C was found for the most substituted material. The fact that the van der Waals volume of a methyl group is smaller than that of a bromine [11] and thus the steric effect of a methyl group is smaller than that of a bromine might explain the difference in isotope effects between the methyl and the bromo derivatives. In a paper on bromination of polyalkylbenzenes by Baciocchi *et al.*[12] there is reported a small change in isotope effect in going from mesitylene to pentamethylbenzene.

In previously reported isotope effect investigations [1-3] attempts were made to explain the isotope effects found by approximating the activated complex in a rate-determining proton removal step by a linear three-centre model [8b,13] S---H---B, where S denotes the brominated substrate, H is hydrogen and B is a base (solvent). It was thought that the change in basicity of S could be the cause of the change in isotope effect. From the present investigation and from the results of previous work on the bromo derivatives of 1,3,5-triethylbenzene [3] it is evident that the three-centre model is not applicable to the triethylbenzene derivatives. In the present investigation it has been found that the isotope effect increases as the basicity of the substrate increases but in the case of the bromo derivatives the isotope effect increased as the basicity of the substrate decreased. As the isotope effects are going in the same direction with the degree of substitution for both kinds of derivatives but the

electronic effects of the two kinds of substituents should work in opposite directions, the three-centre model cannot explain the results obtained.

The isotope effects found in this investigation for the methyl derivatives of 1,3,5-triethylbenzene and the isotope effects previously found for the bromo derivatives [3] support the suggestion which was made in the case of methyl- and bromo-substituted 1,3,5-trimethoxybenzenes [1,2] that the appreciable isotope effects found in those cases were due mainly to steric hindrance to conjugation between the methoxy groups and the aromatic ring in the proton removal step. The size of an ethyl group should be about the same as that of a methoxy group. In fact, a methoxy group may be a little smaller than an ethyl group,[14] and therefore the stronger isotope effects found for the trimethoxybenzene derivatives cannot be due only to general steric effects.

Acknowledgements. We wish to thank Professor Lars Melander and Docent Arne Brändström for their kind interest and for valuable discussions. Dr. Robert E. Carter is thanked for helpful linguistic criticism. Thanks are hereby rendered to Mr. Reine Torberntsson for technical aid in the determination of the NMR spectra.

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Received May 31, 1968.