

1,3,5-Trineopentylbenzene

V.* Hydrogen Isotope Effects in the Chlorination, Bromination, and Positive Iodination of 1,3,5-Trineopentylbenzene

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1,3,5-Trineopentylbenzene was chlorinated and brominated by molecular species in dimethylformamide and iodinated by positive iodine derived from silver perchlorate and molecular iodine in an acetic acid-dioxane (10:1 v/v) solvent. Competitive experiments with the ordinary hydrocarbon and its d_3 nuclear derivative gave the isotopic rate ratios $k_D/k_H = 0.99 \pm 0.03$, 0.91 ± 0.02 , and 0.38 ± 0.02 for chlorination, bromination, and positive iodination, respectively. The results are discussed in terms of probable differences in the energy profile for chlorination, bromination, and iodination of aromatic compounds and of steric repulsion imposed around the reaction site.

The results of the present investigation are to be compared with the isotope effects found for the positive bromination of 2-X-1,3,5-trineopentylbenzenes¹ (X=Cl, Br, I) and with other isotope effect data found for chlorination, bromination, and iodination of aromatics.^{2,3} In general, no primary kinetic isotope effects have been reported for chlorination, but carbon-hydrogen bond breaking may be involved in the rate determining transition state of brominations of highly crowded aromatics, and iodination proceeds almost invariably with a rate-limiting proton transfer. Since in the positive bromination of 2-X-1,3,5-trineopentylbenzenes the strength of the isotope effect increased slightly with increasing spatial requirements of the 2-halogen substituent it was considered to be of interest to see how the strength of the isotope effect would change if the same halogens were the attacking electrophiles.

* Part IV: see Ref. 1.

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EXPERIMENTAL

Chemicals used. 1,3,5-Trineopentylbenzene,⁴ 1,3,5-trineopentylbenzene-2,4,6-*d*₃,¹ 2-chloro-,⁵ 2-bromo-,⁵ and 2-iodo-1,3,5-trineopentylbenzene⁵ were prepared by methods which have been described previously. Fischer's certified dimethylformamide and dioxane had a specified water content of 0.001 % and 0.006 %, respectively, and were used without further purification. Commercial chlorine gas was purified by bubbling through concentrated sulphuric acid. May and Baker's bromine (not less than 99.5 % w/w) and the same manufacturer's iodine (not less than 99.7 % w/w) were used without further purification. Acetic acid was distilled before use. Other chemicals were all commercial products and were used without further purification.

Analyses. The determinations of the extent of the halogenation reactions and of the deuterium contents were carried out with a Varian A-60 NMR spectrometer equipped with a V 6040 variable temperature controller. The extent of the reactions was determined by comparing the integrals of the protons in one of the methylene groups (*ortho* to the halogen substituents) of the products with the sum of the integrals of the protons in the same methylene group in the product and one methylene group in the unconsumed starting material. The fraction of deuterated material in the initial and in the unconsumed reactant was determined by comparing the intensity of the aromatic protons with the intensity of the methylene protons in the same compound. Isotope effect data were calculated from the average result of at least three independent scanings of each sample. Only the aromatic and methylene peaks were recorded by expanding the spectra (sweep width 100 cps, sweep time 250 sec for scanning the spectrum, and 50 sec when integrating). Integrals were recorded ten times for each of the peaks in all cases.

The accuracy of the analyses was checked in all cases with mixtures of known composition of light starting material and reaction product. The results were found to be reliable within ± 1 % for the extent of the reaction as well as the deuterium content. When the same kind of measurements were carried out on the mixture obtained from the halogenation of light material, the intensity obtained from the nuclear protons of the unconsumed hydrocarbon and that from the methylene protons in the same compound had the ratio 1:2 within the above accuracy.

GLC analyses were carried out with a Perkin-Elmer F11 analytical gas chromatograph equipped with a flame ionisation detector. For the analyses a 6 ft \times 0.125 in. 15 % SE-30 silicon gum rubber on 80-100 Chromosorb column was used. Percentage composition refers to the relative areas (planimeter integration) observed for different compounds.

*Chlorination. Competitive experiments with a mixture of 1,3,5-trineopentylbenzene-2,4,6-*d*₃ and 1,3,5-trineopentylbenzene containing 38.2 % of the deuterated material.* To a solution of 290 mg (1.0 mmole) of the starting hydrocarbon mixture in 9 ml of dimethylformamide a solution of about 60 mg (0.9 mmole) of chlorine in 1 ml of dimethylformamide was rapidly added with vigorous shaking. The reaction mixture was protected from light and allowed to react at room temperature for a time which was varied from 4 to 10 min in different experiments. The reaction was quenched by dilution with a large volume of water (250-300 ml) and the mixture extracted with 4 \times 20 ml portions of carbon tetrachloride. The combined carbon tetrachloride layer was washed, first with dilute sodium hydroxide solution, then with water until neutral. The organic solution was dried over anhydrous calcium sulphate and evaporated to dryness. The residue (250-300 mg) was quantitatively transferred to an NMR tube and analyzed as described above.

GLC analysis showed only unreacted 1,3,5-trineopentylbenzene and 2-chloro-1,3,5-trineopentylbenzene. No higher and/or side-chain chlorinated products could be detected.

*Bromination. Competitive experiments with a mixture of 1,3,5-trineopentylbenzene-2,4,6-*d*₃ and 1,3,5-trineopentylbenzene containing 41.0 % of the deuterated material.* To a solution of 290 mg (1.0 mmole) of the starting hydrocarbon mixture in 5 ml of dimethylformamide maintained at $+45 \pm 0.2^\circ\text{C}$ a solution of 320 mg (2.0 mmoles) of bromine in 1 ml of dimethylformamide maintained at the same temperature was rapidly added with a pipet fitted to a piston. During the bromine addition the solution of the aromatic hydrocarbon was vigorously shaken. The reaction mixture was protected from light and allowed to react at 45°C for a time which varied from 1 to 10 min in different experiments. The reaction mixture was quenched, worked up and analyzed as described for the competitive chlorination above. On evaporation of the solvent 250-300 mg residue was recovered in the different experiments.

GLC analysis showed only unreacted 1,3,5-trineopentylbenzene and 2-bromo-1,3,5-trineopentylbenzene. No higher and/or side-chain-brominated products could be detected.

Positive iodination. Competitive experiments with a mixture of 1,3,5-trineopentylbenzene-2,4,6-d₃ and 1,3,5-trineopentylbenzene containing 39.0 % of the deuterated material. To a vigorously stirred solution of various amounts of anhydrous silver perchlorate (previously dried over phosphorus pentoxide for one week) in 4 ml of acetic acid first a solution of 290 mg (1.0 mmole) of the starting hydrocarbon mixture in 1 ml of dioxane and after 1 min a solution of various amounts of iodine in 6 ml of acetic acid were added. The solution (protected from light) was allowed to react at room temperature for 10 to 15 min. In different experiments the quantities of the anhydrous silver perchlorate and iodine were increased as follows:

	AgClO ₄		I ₂	
	mg	mmole	mg	mmole
1.	104	0.50	150	0.59
2.	114	0.55	165	0.65
3.	120	0.59	175	0.69
4.	140	0.69	200	0.79

The reaction mixture was quenched by the addition of a large volume of a dilute aqueous solution of sodium sulphite. The mixture was extracted with 5 × 20 ml portions of carbon tetrachloride, the combined carbon tetrachloride solution was filtered, washed with dilute sodium hydroxide solution, then with water until neutral, filtered again if necessary and finally dried over anhydrous calcium sulphate. The solvent was evaporated and the residue (300–330 mg in different experiments) transferred quantitatively to an NMR tube and analyzed as described above.

GLC analysis showed only unreacted 1,3,5-trineopentylbenzene and 2-iodo-1,3,5-trineopentylbenzene.

Control experiments on the absence of hydrogen exchange during the competitive halogenation experiments. a.) *Chlorination and bromination.* The control experiments were carried out by treating the starting mixtures of isotopic organic molecules with 1 mmole of anhydrous hydrogen chloride and anhydrous hydrogen bromide, respectively, 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.

b.) *Iodination.* In this case the control experiment was carried out by treating the starting mixture of isotopic organic molecules and anhydrous silver perchlorate in the same solvent system at the same concentration and at room temperature with 1.0 mmole of 70 % perchloric acid for 15 min. No change in isotopic composition was observed.

Control of the reaction rates. A necessary condition for fair competition between different isotopic species of organic molecules in the competitive experiments is that the reactions should not be too rapid as compared to the time for mixing the reagents. Therefore the initial rates of the reactions were checked with ordinary light materials as follows:

a.) *Chlorination and bromination.* The reactions were followed under conditions identical to those used for the competitive experiments. At suitable time intervals the reactions were quenched with an aqueous solution of sodium sulphite and sodium carbonate and the mixtures extracted with carbon tetrachloride. The extent of the reactions was determined by GLC analysis. For chlorination the concentration of the chlorine solution in dimethylformamide might have slightly changed during pipetting, but this was the case in the competitive experiments as well. Therefore, the analytical results are rather approximate, but reliable. The following results were obtained: Time/ % chlorination: 2–3 sec/4 %, 15 sec/14.6 %, 30 sec/19.6 %, 60 sec/25.2 %. Time/ % bromination: 2–3 sec/3.6 %, 15 sec/16.2 %, 30 sec/31.4 %, 45 sec/39.0 %, 60 sec/47.8 %, 2 min/53.4 %, 5 min/63.8 %, 10 min/71.4 %. The initial rates were considered to be around the upper limit for obtaining measurements of the isotope effect with the present technique.

b.) *Positive iodination.* An approximate kinetic analysis was carried out under conditions identical to those used for the competitive experiments, but equimolar initial

concentrations of all of the reagents were used. The reaction mixtures were quenched at different time intervals and after work-up analyzed by CGL. A plot of $1/c$ versus t gave a straight line and an approximate second-order rate constant of $5 \times 10^{-2} \text{ l mole}^{-1} \text{ sec}^{-1}$ could be calculated. This value and the true initial concentrations of the reagents predict 0.25 % reaction per second in the initial stage. This was considered to be a fairly low initial rate allowing isotope effect investigations with the present technique.

CALCULATIONS AND RESULTS

In all competitive experiments there was purely intermolecular competition. No corrections have been made for the small amounts of 1,3,5-trieopentylbenzene containing both deuterium and protium in nuclear positions.* The fraction of deuterium in the recovered unreacted starting material is compared to the same fraction in the starting material. In such cases the isotopic rate ratios (k_D/k_H) could be calculated from the following equation:^{6,7}

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

where y_D and y_D' denote the fraction of deuterium in the recovered unreacted starting material and in the initial starting material, respectively, y_H and

Table 1. Summary of the isotope effect data found in the chlorination,^a bromination,^b and positive iodination^c of 1,3,5-trieopentylbenzene. The errors given are maximum deviations from the mean values. For symbols, see the text.

Reaction	x	y_H'	y_H	k_D/k_H	k_D/k_H mean value
Chlorination	0.270	0.617	0.616	0.98	0.99 ± 0.03
	0.293		0.615	0.96	
	0.391		0.618	1.01	
	0.472		0.619	1.01	
Bromination	0.518	0.589	0.569	0.89	0.91 ± 0.02
	0.584		0.565	0.89	
	0.638		0.571	0.93	
	0.666		0.566	0.91	
	0.692		0.556	0.89	
	0.771		0.561	0.92	
Positive iodination	0.362	0.609	0.518	0.39	0.38 ± 0.02
	0.397		0.498	0.36	
	0.433		0.492	0.39	
	0.563		0.438	0.40	

^a In dimethylformamide at room temperature. ^b In dimethylformamide at $+45 \pm 0.2^\circ\text{C}$.
^c In acetic acid-dioxane (10:1 v/v) at room temperature.

* The competitive brominations were carried out with a starting mixture in which the 1,3,5-trieopentylbenzene-2,4,6- d_3 contained 97.0 % deuterium in the aromatic position. This was the lowest degree of deuteration used in these experiments. A correction of the isotope effect data for the approximately 9 % 1,3,5-trieopentylbenzene-2,4- d_2 molecules gave a change in the value of the isotope effects much smaller than the experimental uncertainty of the measurements.

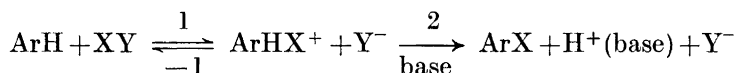
y_{H}' the corresponding fraction of protium, and x denotes the over-all extent of the reaction.

The results from the various calculations of the isotope effect are summarized in Table 1.

DISCUSSION

It may be seen from Table 1 that there is no isotope effect in the chlorination, a rather weak isotope effect appears in the bromination and a strong effect was found in the iodination of 1,3,5-trineopentylbenzene. The spread of the present data between the different types of reaction is, however, much larger than that found for the positive bromination of 2-X-1,3,5-trineopentylbenzenes¹ (X=Cl, Br, I; $k_{\text{D}}/k_{\text{H}}=0.79, 0.73, 0.67$, respectively). If the weak isotope effect found for the bromination of 1,3,5-trineopentylbenzene is compared to previous data,¹ the small change in the isotope effect with the degree of substitution suggests that this weak effect is probable a primary, rather than a secondary one,* similar to the strong effect found for iodination.

It is assumed that the well established two-step mechanism is effective in the halogenation of 1,3,5-trineopentylbenzenes



(where X=Y for chlorination and bromination with the molecular halogens) and that this mechanism remains in principle unchanged for chlorination, bromination and iodination, although the rates of the individual steps will be functions of the attacking electrophile.

In aromatic substitution reactions primary isotope effects result^{2,3} only if the rate of step 2 is less, or at most, comparable to the rate of step -1 ($v_{-1} \gtrsim v_2$). There is no direct method for the estimation of the magnitudes of the rates v_{-1} and v_2 , but the isotope effect might give some information according to this principle.

The absence of an isotope effect has been found in the chlorination of benzene^{8,9} and of 3-bromodurene,¹⁰ but recently Myhre *et al.*¹¹ mentioned a weak isotope effect ($k_{\text{H}}/k_{\text{D}}=1.15$) as a preliminary result for the chlorination of 1,3,5-tri-*t*-butylbenzene.

Brominations are, however, much more predisposed to isotope effects, and if the structural features of the aromatic compound are favourable for a changeover in mechanism, they may render step 2 partly or fully rate determining. Thus, there is no isotope effect in the bromination of benzene,¹² bromobenzene,¹³ and toluene,¹⁴ but weak isotope effects were found in the bromination of mesitylene,¹⁵ pentamethylbenzene and some other substituted mesitylene derivatives,¹⁵ derivatives of 1,3,5-triethylbenzene,^{16,17} and 2-X-1,3,5-trineopentylbenzenes¹ (X=Cl, Br, I). The bromination of the exceptionally crowded 1,3,5-tri-*t*-butylbenzene, however, gives rise to a strong isotope effect ($k_{\text{H}}/k_{\text{T}} \approx 10$,¹⁸ $k_{\text{H}}/k_{\text{D}}$ about 3.6^{11,15}). These isotope effects have been

* A similar conclusion has been recently reached in the interpretation of the origin of isotope effects found in the bromination of 1,3,5-triethylbenzene and its derivatives.^{16,17}

interpreted in terms of steric hindrance at the reaction site, which differentially increases the energy of step 2 relative to that of step -1 , *i.e.* it retards the entrance of the bromine into the plane of the aromatic ring in the proton removal step.

Unlike chlorination and bromination, the iodination of a series of phenol and aniline derivatives almost invariably shows appreciable isotope effects ($k_H/k_D \approx 3-4$).^{2,3} In these reactions, however, the resonance stabilization of the intermediate may more significantly influence the strength of the isotope effects than in the case of alkylbenzenes, and therefore a more safe comparison would be possible if isotope effect data were available for the iodination of alkylbenzenes. However, no such data have so far been reported in the literature.

Although only the bromination is thoroughly investigated, and the nature of the solvent should be of importance, particularly for step 2 where it may act as the base, the data cited support the general view that significant differences should exist between the energy profiles of the different aromatic halogenation reactions. For a given aromatic substrate, such as 1,3,5-trineopentylbenzene, this could be pictorially represented as shown in Fig. 1. Although the "normal"

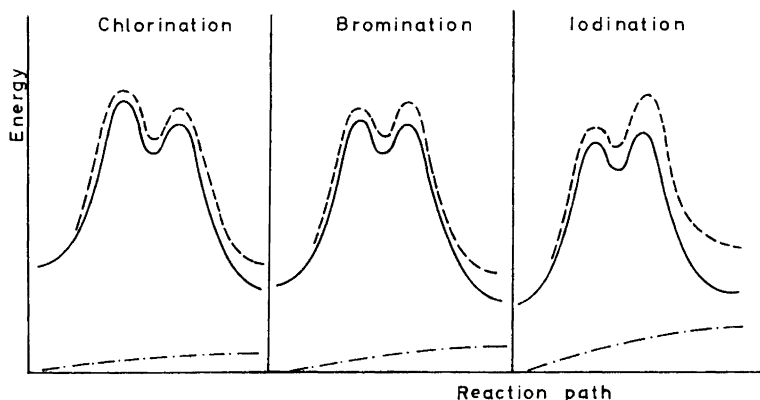


Fig. 1. Probable "normal" energy profiles for electrophilic aromatic chlorination, bromination and iodination (solid curves), and the effect of imposed steric hindrance (lowest curves). In each case the resultant energy profiles (upper dashed curves) are taken as the sum of the former.

energy profiles for chlorination, bromination, and iodination are arbitrarily drawn, they probably show the main differences in energy profile among these reactions. The addition of a given repulsion energy term of these "normal" energy profiles is also shown in the figure.

For chlorination, the first energy barrier should probably be much higher than the second ($v_{-1} \ll v_2$) as shown by the absence of isotope effects in the chlorination of alkylbenzenes, and especially by the very weak effect found for the chlorination of 1,3,5-tri-*t*-butylbenzene. In addition, chlorine is the least bulky electrophile among the halogens, and therefore the increase in non-

bonded repulsion energy when the relatively large electrophile replaces the proton at a sterically crowded site of the 1,3,5-trineopentylbenzene will also be comparatively small in this case. The difference in increase of the energy of step 2 with respect to step -1 is, therefore, not sufficient in this case to give rise to an isotope effect.

For bromination, however, the relative heights of the energy maxima for step -1 and step 2 appear to be nearly comparable ($v_{-1} \lesssim v_2$) and in this case the steric repulsion energy term is sufficiently large to bring about a change-over in the energy profile ($v_{-1} \gtrsim v_2$) resulting in a weak isotope effect.

The energy maximum for step 2 appears to be the highest relative to that of step -1 in the case of iodination.* This should mainly be due to the fact that the iodination is the least exothermic reaction among halogenations, and that the carbon-iodine bond is the weakest among the carbon-halogen bonds. This argument is actually equivalent to those already offered to account for the relatively strong isotope effects in iodination namely the weaker acidifying effect¹⁹ of iodine compared to that of bromine (or chlorine), and the low bond strength of the carbon-iodine bond.²⁰ The relatively high steric repulsion energy (iodine is the most bulky among the halogens) superimposed onto such an energy profile may well account for the relatively strong isotope effect found for the iodination of 1,3,5-trineopentylbenzene.

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* It would be of interest to see whether there is any measurable isotope effect in the iodination of benzene and/or sterically uncrowded alkylbenzenes. The present iodination technique can be a suitable method for such an investigation.

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