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1,3,5-Trineopentylbenzene

IV.* Hydrogen Isotope Effects in the Positive Bromination of 2-Chloro-, 2-Bromo-, and 2-Iodo-1,3,5-Trineopentylbenzene

JÓZSEF MÁRTON**

Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg 5, Sweden

2-Chloro-, 2-bromo- and 2-iodo-1,3,5-trineopentylbenzene were brominated with positive bromine derived from silver perchlorate and molecular bromine in a solvent system containing a large amount of acetic acid and small amounts of dioxane and water. Competitive experiments with partially deuterated compounds gave isotopic rate ratios $k_D/k_H = 0.79 \pm 0.02$, 0.73 ± 0.04, and 0.67 ± 0.04, respectively, for the bromination of the above compounds at room temperature. The results are discussed in terms of a steric repulsion effect increasing gradually with the spatial requirements of the 2-halogen substituents, and in terms of an early-transition-state model for positive bromination.

The results of this investigation are to be compared with previously reported data on the bromination of 1,3,5-tri-*t*-butylbenzene,[1–3] various other polyalkylbenzenes,[2] 1,3,5-trimethoxybenzene,[4] 1,3,5-triethylbenzene, as well as the bromo- and methyl-substituted derivatives of the latter two compounds.[5–8] In these investigations it has been shown that a rate-limiting proton transfer may be involved in aromatic bromination due to a large steric repulsion effect imposed around the reaction site by bulky alkyl substituents, and that this steric repulsion is considerably increased by the buttressing effect of other substituents. This view seems amply supported by studies of other aromatic substitution reactions.[9,10] As the halogenation of 1,3,5-trineopentylbenzene and of its halogenated derivatives was found [11] to be favourable for isotope-effect investigations it was considered to be of interest to see what effect neopentyl groups as well as halogens inserted between such groups would have on the isotope effect in bromination reactions.

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** International Atomic Energy Agency Fellow (1967–68). Permanent address: Department of Organic Chemistry, Institute of Isotopes of the Hungarian Academy of Sciences, Budapest 114, P.O.B. 77, Hungary.

EXPERIMENTAL

Chemicals. 1,3,5-Trineopentylbenzene, 2-chloro-1,3,5-trineopentylbenzene, 2-bromo-1,3,5-trineopentylbenzene, and 2-iodo-1,3,5-trineopentylbenzene were prepared by methods which have been described previously.[11,12] Fischer's certified dioxane had a specified water content of 0.006 % and was used without further purification. May and Baker's bromine (not less than 99.5 % w/w) was also used without further purification. Acetic acid was distilled before use. Reagent-grade anhydrous silver perchlorate was dried over P_2O_5 *in vacuo* for at least 4—5 days before use. Other chemicals were all commercial grade and were used without purification.

Analyses. The determinations of the extent of the bromination reactions and the deuterium content were carried out with a Varian A-60 NMR spectrometer equipped with a V 6040 variable temperature controller. The analyses of the mixture from the competitive bromination of 2-chloro-1,3,5-trineopentylbenzene were carried out at 40°C, and those of the mixtures from the bromination of 2-bromo- and 2-iodo-1,3,5-trineopentylbenzene at 78°C. Isotope effect data have been calculated from the average result of at least three independent scannings of each sample. Only the aromatic and methylene peaks were recorded by expanding the spectra (sweep width 100 Hz, sweep time 250 sec for scanning the appropriate range of the spectrum, and 50 sec for integration). Integrals were recorded 10 times for each of the peaks in all cases. The accuracy of the analyses was checked with mixtures of known composition of light starting material and reaction product, and by analysing reaction mixtures of light materials obtained under conditions identical with those of the competitive experiments. The results have been found to be reliable within ±1 % for the extent of the reaction as well as for the deuterium content.

1,3,5-Trineopentylbenzene-2,4,6-d_3 was prepared by equilibrating freshly prepared deuterotrifluoroacetic acid with 1,3,5-trineopentylbenzene.

50 ml (75.5 g, 0.36 mole) of bis-(trifluoroacetic) anhydride was freshly distilled from P_2O_5 in a nitrogen atmosphere into a round-bottomed flask containing 7.1 g (0.355 mole) of heavy water (99.5 % D) cooled with an ice-sodium chloride mixture and protected from moisture. The product was used directly.

To a solution of 10.1 g (35 mmoles) of 1,3,5-trineopentylbenzene in 5 ml of carbon tetrachloride 20.0 g (13 ml) of freshly prepared deuterotrifluoroacetic acid was added and the mixture was equilibrated in a closed system at 45°C for 36 h. Then the deuterotrifluoroacetic acid-carbon tetrachloride mixture was distilled off and the partially deuterated 1,3,5-trineopentylbenzene was recrystallized from abs. ethanol and dried *in vacuo* for 48 h. Three additional equilibrations followed by recrystallizations afforded 8.5 g of 1,3,5-trineopentylbenzene-2,4,6-d_3, m.p. 77—78°C. NMR analysis indicated 98.1±0.7 % deuterium bound to aromatic carbon. In parallel experiments the deuterium content varied between 97.2—98.2 % with a similar experimental error to that indicated above.

2-Chloro-1,3,5-trineopentylbenzene-4,6-d_2 was prepared from 1,3,5-trineopentylbenzene-2,4,6-d_3 by direct chlorination as reported [11] for the light compound. NMR analysis of the sample indicated 97.6±0.6 % deuterium in the aromatic positions.

2-Bromo-1,3,5-trineopentylbenzene-4,6-d_2 was prepared from 1,3,5-trineopentylbenzene-2,4,6-d_3 (97.2±0.7 % deuterium content in the aromatic positions by NMR) by direct bromination.[11] The percentage deuterium content was identical with that of the starting material within the experimental error.

2-Iodo-1,3,5-trineopentylbenzene-4,6-d_2 was prepared by the silver perchlorate-induced iodination of 1,3,5-trineopentylbenzene-2,4,6-d_3 elaborated for the light compound.[11] NMR analysis showed 98.2±0.7 % deuterium in the aromatic positions.

Competitive experiments with a mixture of 2-chloro-1,3,5-trineopentylbenzene-4,6-d_2 *and 2-chloro-1,3,5-trineopentylbenzene containing 40.5 % of the deuterated material.* To a vigorously stirred solution of 323 mg (1.0 mmole) of the starting mixture and 207 mg (1.0 mmole) of silver perchlorate (previously dried and stored over P_2O_5 *in vacuo*) in 90 ml of acetic acid-dioxane-water = 63.5:16.5:10.0 v/v), a solution of 160 mg (1.0 mmole) of bromine in 10 ml of acetic acid was rapidly injected with a pipette fitted to a piston. The solution (protected from light) was allowed to react at room temperature for a time which varied from 23 to 30 seconds in different experiments. The reaction was quenched by a large amount of an aqueous solution of sodium sulphite. The mixture was extracted

with 5×20 ml portions of carbon tetrachloride, the organic layer was filtered, washed with dilute sodium hydroxide solution, then with water until neutral. The carbon tetrachloride solution was filtered again and dried over anhydrous calcium sulphate. The solvent was evaporated and the total quantity of the residue transferred to an NMR tube, dissolved in carbon tetrachloride and analyzed. GLC analysis showed only unreacted 2-chloro-1,3,5-trineopentylbenzene and the 2-bromo-4-chloro-1,3,5-trineopentylbenzene product. No higher and/or side-chain-brominated products could be detected. The extent of the reaction was determined by NMR spectroscopy, by comparing the integral of the protons of one methylene group (situated in between the two halogen substituents) in the product with the sum of the integral of the protons of one methylene group (*para* to the substituent) in the unreacted starting material and that of the protons of the methylene groups in the product. The fraction of deuterated material in the unconsumed starting material was determined by comparing the intensity of the aromatic protons with the intensity of the methylene protons in the position *para* to the 2-chloro substituent within the same compound.

Competitive experiments with a mixture of 2-bromo-1,3,5-trineopentylbenzene-4,6-d_2 *and 2-bromo-1,3,5-trineopentylbenzene containing 36.3 % of the deuterated material.* The experiments were carried out with the same molar amounts and with exactly the same technique as those with the corresponding chlorine compounds. The reaction time was also the same.

Competitive experiments with a mixture of 2-iodo-1,3,5-trineopentylbenzene-4,6-d_2 *and 2-iodo-1,3,5-trineopentylbenzene containing 36.6 % of the deuterated material.* Reagents: 415 mg (1.0 mmole) of the starting mixture, 207 mg (1.0 mmole) of anhydrous silver perchlorate dissolved in 35.6 ml of a mixture of acetic acid-dioxane-water (27.0:6.6:2.0 v/v) and 160 mg (1.0 mmole) of bromine dissolved in 4.4 ml of acetic acid. The other experimental details were exactly the same as with the corresponding chlorine compounds except that the reaction times varied from 60 to 80 seconds.

Control experiments on the absence of hydrogen exchange during the competitive experiments. The control experiments were carried out on the isotopic mixtures of 2-bromo-1,3,5-trineopentylbenzene and 2-iodo-1,3,5-trineopentylbenzene described above. The initial mixtures were treated with anhydrous silver perchlorate and 1.0 mmole of 70 % perchloric acid in the solvent system used for the competitive experiments at room temperature for 15 min. No change in the isotopic composition was observed in either case.

Control of the reaction rate. A necessary condition for fair competition between the different isotopic species in the competitive experiments is that the reactions should not be too rapid as compared to the time of mixing the reagents. Therefore the initial rates of the reactions have been checked in two independent ways.

1. An approximate kinetic analysis of these reactions has been reported previously.[11] Approximate second-order rate constants of 4.75, 4.68, and 0.25 (l $mole^{-1}$ sec^{-1}) for the bromination of 2-chloro-, 2-bromo-, and 2-iodo-1,3,5-trineopentylbenzene, respectively, have been obtained under the same conditions. From these data 4.75 %, 4.68 %, and 0.63 % conversion per second in the initial stage of the brominations of the corresponding compounds may be estimated.

2. An additional control experiment for the most rapid reactions, *i.e.* for the bromination of 2-chloro- and 2-bromo-1,3,5-trineopentylbenzene has been carried out under conditions identical to those in the competitive runs but using ordinary light material. The reactions were immediately quenched after the bromine addition, the estimated reaction time being approximately one second. The resulting mixtures were worked up, and gas-chromatographic analysis indicated 3.8 % conversion for the bromination of 2-chloro-1,3,5-trineopentylbenzene, and 3.7 % conversion for the bromination of 2-bromo-1,3,5-trineopentylbenzene. These results were not changed appreciably if a dioxane solution of the aromatic compound was added to a preformed bromine perchlorate reagent solution.

Considering the experimental difficulties involved, the results of the two independent methods are in good agreement. The initial rates observed are considered to be just at the upper limit for obtaining reliable 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 amounts of 2-X-1,3,5-trineopentylbenzene (X=Cl, Br, I) molecules 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 initial starting material. In such cases the isotopic rate ratios (k_D/k_H) may be calculated from the following equation:[5,13]

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

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

In an independent investigation [14] it has been found that rotation about the $Ar-CH_2$ bonds (in positions 1 and 5) in the 2,4-X_2-1,3,5-trineopentylbenzenes * is sterically hindered and that the activation parameters for these rotational barriers may be calculated by the use of complete lineshape analysis. It is believed that the values for the free energies of activation ($\Delta F^{\ddagger}$) thus derived represent a "measure" of the steric effect of the X substituents in the 2,4-X_2-1,3,5-trineopentylbenzenes. These $\Delta F^{\ddagger}$ data, along with estimates of the van der Waals volumes of the X substituents [15] and approximate values for the relative rates of brominations of 2-X-1,3,5-trineopentylbenzenes are summarized in Table 2 with the isotope effects found in the present work.

Table 1. Summary of the isotope effects found in the positive bromination of 2-X-1,3,5-trineopentylbenzenes at room temperature. The errors given are maximum deviations from the mean values. For symbols, see the text.

Substituent X	x	y_H'	y_H	k_D/k_H	k_D/k_H mean value
Cl	0.359	0.595	0.568	0.77	
	0.366		0.571	0.81	
	0.433		0.562	0.78	0.79 ± 0.02
Br	0.396	0.637	0.602	0.73	
	0.399		0.606	0.76	
	0.405		0.595	0.69	0.73 ± 0.04
I	0.329	0.632	0.595	0.66	
	0.379		0.595	0.71	
	0.408		0.580	0.64	0.67 ± 0.04

* An attempt to prepare 2,4-diiodo-1,3,5-trineopentylbenzene was unsuccesful so far, and thus the $\Delta F^{\ddagger}$ value for this compound is not yet available. It might be possible to determine $\Delta F^{\ddagger}$ values of mixed compounds, and this work is now under way.

Table 2. Comparison of kinetic isotope effects with the steric effects of X substituents and relative rates of bromination.

X	k_D/k_H	$\Delta F^{\ddagger}$ kcal/mole [14] (see text)	van der Waals volume of X cm³/mole [15]	Approx. rel. rates [11]
H	0.91[17]		3.4	1
Cl	0.79	14.6	12	7.1×10^{-3}
Br	0.73	16.2	15.12	7.0×10^{-3}
I	0.67		19.6	3.8×10^{-4}

DISCUSSION

It may be seen from Tables 1 and 2 that the isotope effects found in this investigation are rather weak. The observed slight increase in the strength of the isotope effects, is, however, characteristic and appears to be related to the size of the substituents rather than to the approximate relative rates of bromination. A similar correlation has been found recently by Myhre *et al.*[16] in a study of the nitration of 2-X-1,3,5-tri-*t*-butylbenzenes (X=H, F, NO_2, CH_3), where the contrast between the strength of the isotope effects and the relative rates of nitration was even more characteristic than in the present case. The observed correlation between the strength of the isotope effects and the spatial requirements of X substituents, and the analogy with Myhre's results, suggests that the occurrence of a slow proton transfer in the positive bromination of 2-X-1,3,5-trineopentylbenzenes is mainly a function of steric effects and probably independent of the inductive and mesomeric properties of the substituents.

It is assumed that the well-established two-step mechanism

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

is effective for the positive bromination of 2-X-1,3,5-trineopentylbenzenes and that this mechanism remains unchanged although the rates of the individual steps will be a function of the structure of the aromatic reactant.

In aromatic substitution reactions primary isotope effects result [9,10] only if the rate of step 2 is less than, or at most, comparable to the rate of step -1 ($v_{-1}\gtrsim v_2$). The rather weak isotope effects found in the bromination of most members of a series of highly crowded polyalkylbenzenes [1-10] have always been interpreted as primary ones, the second step being partially rate determining. As it is rather difficult to interpret the possible secondary effects,* they are generally ignored in this kind of discussion and they will also be omitted in the present case.

* Secondary isotope effects arise mainly from changes in hybridization of the ring carbon atom when it is attacked by the electrophile, and from hyperconjugative effects. They could therefore be expected to be rather insensitive to changes in the steric requirements of the ring substituents if the transition states do not differ too widely. This is fulfilled in the present case (see discussion), and therefore a correlation of isotope effects with the spatial requirements of 2-X substituents is considered to support the view that these effects are mainly primary ones, but they could be somewhat masked by secondary effects.

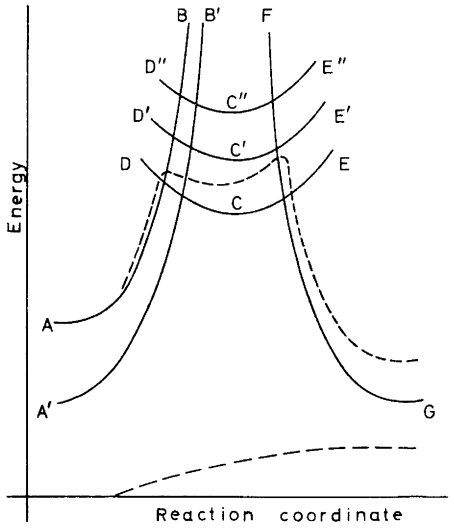

Fig. 1. Potential energy diagram for the bromination of aromatic molecules. Rounding off by resonance at the intersections and π-complex formation is omitted for the sake of simplicity.

The present weak isotope effects are most likely best interpreted in terms of the potential energy curves for these reactions (Fig. 1). For the sake of simplicity, however, π-complex formation between the reagent and the aromatic compound will be omitted.

At point A the system consists of the unperturbed aromatic starting material, the positive bromine reagent (presumably bromine perchlorate *) and the solvent. The curve AB represents the increasing potential energy of the dissociation and/or desolvation of the attacking electrophile. Point C represents the intermediate of the reaction, which is probably best thought of as a σ-complex, and the solvent plus any residue of the brominating agent. The position of the transition state of step 1 (or step -1) may be best approximated by the point of intersection of curves AB and CD, the latter representing the potential energy increase for step -1, *i.e.* for the detaching of Br^+ from the intermediate.

The potential energy curve for the second reaction step may be constructed accordingly. The point of intersection of curves CE and FG represents the potential energy of the transition state of step 2, and point G the unperturbed aromatic product and the conjugate acid of the base (solvent) assisting in the proton removal step plus any residue of the brominating agent.

For structurally similar aromatic compounds such as 2-X-1,3,5-trineopentylbenzenes the positions of the intermediates and the potential energy

* The positive bromine reagent obtained under identical conditions in a solvent system similar to those used in the present investigation was believed [3] to be acetyl hypobromite. Although the problem about the nature of positive halogenating species is not yet solved, the present author prefers bromine perchlorate as reagent, to account for the reactivity differences observed [11] for the bromination of 1,3,5-trineopentylbenzene and its derivatives by $BrClO_4$ and CF_3COOBr, respectively, in acetic acid-dioxane solvent systems containing various amounts of water.

changes involved in their disappearance may be represented by curves D'C'E' and D''C''E'', the potential energy level being the lowest for the intermediate formed from the most reactive aromatic compound. The electronic effects arising from the difference in properties of the 2-X substituents chlorine, bromine and iodine will influence the two transition states in approximately the same way, as the departures of Br^+ and H^+ are analogous in the decomposition of the intermediate. Therefore these curves may probably be best represented by nearly parallel lines. This means that all of the electronic influences are cancelled in the isotope effect method, which is sensitive exclusively to differences in the *relative* rates of the reaction steps -1 and 2.

For sterically crowded molecules such as 2-X-1,3,5-trineopentylbenzenes with X equal to halogen a non-bonded steric repulsion energy will also influence the potential energy barrier of the substitution reaction. This view is now amply supported for different kinds of aromatic substitutions.[9,10] This non-bonded repulsion energy term increases along the reaction coordinate (lower dashed curve in the figure), resulting in a greater increase in potential energy at transition state 2 than at transition state 1. The resulting energy profile for the substitution of a sterically hindered aromatic compound is most simply approximated by the addition of this non-bonded repulsion energy term to the potential energy of the non-hindered system (upper dashed curve in the figure). If the increase in potential energy due to the addition of this repulsion energy term will result in a higher energy level for the second transition state than for the first one, step 2 becomes partially rate determining if the rates v_{-1} and v_2 are still comparable, or fully rate determining if the reverse reaction proceeds much faster than the forward one ($v_{-1} \gg v_2$).

Steric hindrance of this kind is the most probable source of the kinetic isotope effect found in the positive bromination of 2-X-1,3,5-trineopentylbenzenes. The observed steric hindrance of free rotation about the 1 and 5 $Ar-CH_2$-bonds in 2,4-X_2- and 2-X-4-Y-1,3,5-trineopentylbenzenes [11,14] may serve as additional strong evidence that the products are sterically rather overcrowded and that this steric repulsion could be expected to increase the height of the energy barrier, particularly in step 2.

For the bromination of 1,3,5-triethylbenzene and 2-bromo-1,3,5-triethylbenzene by molecular bromine in dimethylformamide isotope effect values of $k_D/k_H = 0.99 \pm 0.02$ and 0.80 ± 0.04, respectively, have been reported.[7] These compounds are rather closely related to 1,3,5-trineopentylbenzene and its 2-halogenated derivatives. The trineopentyl compounds are probably somewhat more crowded. This conclusion is supported by the finding that in the bromination of 1,3,5-trineopentylbenzene with molecular bromine in dimethylformamide at $+45$°C a weak isotope effect ($k_D/k_H = 0.91 \pm 0.02$) has been observed.[17] If there is a weak isotope effect already in the introduction of the first bromine into 1,3,5-trineopentylbenzene, this would suggest somewhat stronger effects than those which have been observed for the bromination of 2-X-1,3,5-trineopentylbenzenes. As a matter of fact, stronger effects would be more probable for brominations with molecular bromine. Molecular bromine has a lower potential energy in the initial state (A') than the positive bromine reagent. Therefore the first transition state for brominations with molecular species should come somewhat later on the reaction coordinate (intersection

of curves A′B′ and DC) than the one for reactions with a more energetic positive reagent (intersection of curves AB and DC). Thus an early transition state will have a higher potential-energy level than a late one, if the other conditions (aromatic substrate, base) are identical. In such a case a more energetic reagent will result in a decrease in the rate of the reverse reaction step (v_{-1}) and hence also in the strength of the observed isotope effect. The somewhat early transition state characteristic for brominations with energetic positive bromine species might well account for the rather weak isotope effects found in the present investigation. Such a shift in the strength of the isotope effect has previously been observed by Vainshtein and Shilov [18] who found $k_H/k_D=2.6$ for the bromination of *m*-anisolesulfonate ion by molecular bromine, but no isotope effect when the reagent was positive bromine (presumably H_2OBr^+).

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