Influence of Steric Hindrance on the Isotope Effect in Aromatic Substitution

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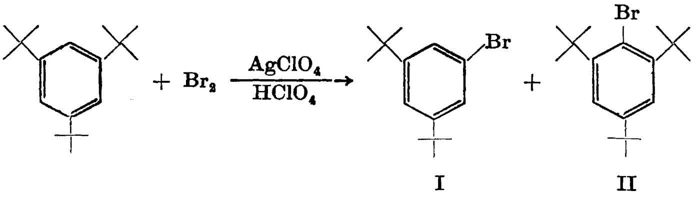
As part of an investigation of the effect of steric hindrance on the mechanism of aromatic substitution, isotope effects in the nitration and bromination reactions of the highly hindered hydrocarbon, 1,3,5-tri-*t*-butylbenzene, have been measured. No isotope effect could be detected when this hydrocarbon was nitrated in acetic acid — acetic anhydride solution in the presence or absence of sulfuric acid catalyst. However, a "full" isotope effect ($k_T/k_H \sim 0.1$) is observed when the same tritium labeled hydrocarbon is brominated in acetic acid — dioxane solution with bromine, silver perchlorate and perchloric acid. The brominating agent in this reaction is believed to be "positive" bromine or a "positive" bromine carrier [1]. Hydrogen exchange was shown to be absent during these reactions.

The nitration of tri-*t*-butylbenzene was effected in essentially quantitative yield using the method of Wepster, Verkade *et al.* [2] Possible fractionation of tritium in the reactant as well as the derivative was investigated in some experiments by using less than the stoichiometric amount of nitric acid and recovering both the nitro derivative and the unreacted hydrocarbon.

Normal bromination of tri-*t*-butylbenzene apparently proceeds only in the presence of a "positive" brominating agent. When the classical catalyst, iron powder, is used, it is reported that only the dealkylated 1-bromo-2,5-di-*t*-butylbenzene (I) is isolated in 70 % yield [3]. Barclay and Betts [4] report a 67 % yield of 1-bromo-2,4,6-tri-*t*-butylbenzene (II) by bromination in aqueous acetic acid with silver nitrate and nitric acid. The brominating conditions used in the present measurements yield a mixture of the desired product (II) and the dealkylated product (I). These compounds were identified by comparison of their infrared spectra with the spectra of known samples.



I

II

A typical reaction was performed by adding bromine (2.4 g, 15 mmole) to a well stirred solution of tri-*t*-butylbenzene [5] (2.4 g, 10 mmole), silver perchlorate (3.0 g, 15 mmole) and perchloric acid (1.0 ml, 11 mmole) in 60 ml of acetic acid-dioxane (5:1 by volume) and allowing the mixture to stand with stirring for about 16 h. The product was isolated by filtration of the silver salts, addition of water to the filtrate and extraction of the organic product with pentane. The following material balance was obtained by infrared analysis of the crude product: I, 21 %; II, 68 %; unreacted hydrocarbon, 8 %. The infrared spectrum of a synthetic mixture of pure components compounded in this ratio agreed well with the spectrum of the crude reaction product. II was isolated by repeated crystallization from ethanol and sublimation *in vacuo*, m. p. 173—174°.

Activity measurements were made in the usual manner [6] by inside counting of hydrogen obtained from the combustion water of the reactants and derivatives.

A general expression [6,7] for aromatic substitution in compounds possessing a symmetry similar to tri-*t*-butylbenzene which relates the molar activity in the derivative and that in the initial reactant to the kinetic isotope effect (k_T/k_H), the extent of reaction and the relative rate of side reactions is

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$$\frac{d}{r_0} = \frac{2 + 2q}{2 + \beta + 3q} \cdot \frac{1}{x}\left[1 - (1 - x)^{(2+\beta+3q)/(3+3q)}\right]$$

where d is the molar activity in the derivative measured after separation from the by-product, r_0 is the molar activity in the initial reactant, β is the ratio k_T/k_H, q is the ratio of the specific rates of dealkylation and substitution and x is the extent of reaction. It is assumed that isotopic hydrogen only influences the reaction rate at its own position.

The function relating the molar activity in the unconsumed reactant and the molar activity in the initial reactant to the kinetic isotope effect is

$$\log \frac{r}{r_0} = \frac{1 - \beta}{3 + 3q}\left[- \log(1 - x)\right]$$

where r is the molar activity in the unconsumed reactant. The other symbols retain their previous meanings. For nitration q vanishes since no evidence of side reactions can be detected. On the basis of product analysis q is assigned a value of 1/3 for the bromination reaction.

All experimentally determined values of the isotope effect for the nitration of tri-*t*-butylbenzene, as shown in Table 1, fall within the interval 1.0 ± 0.1.

Table 1. Isotope effects in nitration of 2,4,6-tri-*t*-butylbenzene in acetic acid — acetic anhydride solution at about 25°.

	Number of experiments	% Yield derivative	Calculated mean k_T/k_H with maximum experimental deviations
Uncatalyzed nitration (nitro derivative)	3	>97 %	$0.98 \begin{smallmatrix} + 0.05 \\ - 0.06 \end{smallmatrix}$
Catalyzed nitration[a] (nitro derivative)	2	80—83 %	$1.04 \begin{smallmatrix} + 0.06 \\ - 0.06 \end{smallmatrix}$
(recovered reactant)	2	80—83 %	$1.04 \begin{smallmatrix} + 0.01 \\ - 0.02 \end{smallmatrix}$

[a] H_2SO_4 concentration, 0.02 % by weight; mole ratio acid to hydrocarbon, 1:100.

In Fig. 1 the average value of d/r_0 obtained from duplicate counting of two separate bromination runs is compared with the theoretical function $f(x,\beta,q)$ where $q = 1/3$. The experimental data

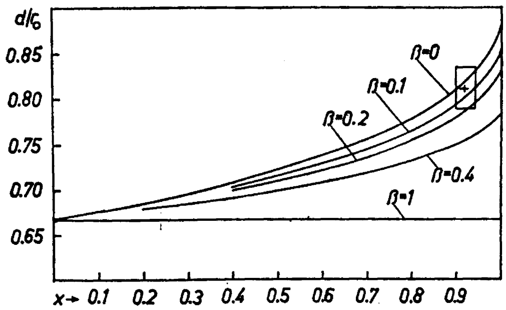
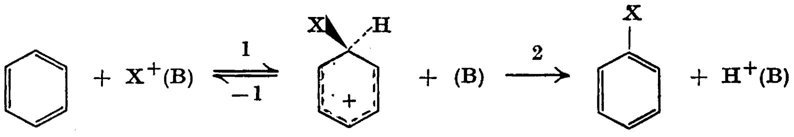


Fig. 1. Tritium content of 1-bromo-2,4,6-tri-*t*-butylbenzene relative to initial hydrocarbon. Curves show the function $f(x,\beta,q)$ for certain values of β.

indicate that β is less than 0.2. The most probable value appears to be 0.1 or less. More experimental work is necessary in order to ascertain the value of β with greater accuracy.

The isotope effect investigations made by Zollinger [8,9] of the azo coupling reaction and Schubert *et al.* [10,11] of the acid-catalyzed decarbonylation of 2,4,6-trialkylbenzaldehydes clearly show that in these reactions steric hindrance around the site of electrophilic substitution increases the kinetic importance of the aromatic C—H bond breaking. Their observations are readily explicable in terms of the generally accepted two-step reaction mechanism of aromatic substitution, and, in fact, constitute very strong evidence in favor of this mechanism. Analysis of the general rate equation of this mechanism reveals that step 2 will be rate-controlling and a hydrogen isotope effect will be observed when the velocity ratio (v_{-1}/v_2) is large. Such a condition should be facilitated when bulky substituents are located *ortho* to the reaction site since the contribution to the total energy of the transition state due to steric repulsion should be larger for step 2 than for step —1. If other factors affecting v_{-1}/v_2 do not counterbalance the steric effects, step 2 should become rate-controlling when a highly hindered compound is subjected to an electrophilic substitution even though an isotope effect is not observed when an unhindered compound is allowed to undergo the same reaction.



The absence of an isotope effect in the nitration of relatively unhindered aromatic compounds is well documented [1,6]. The present work shows this effect is absent even under conditions approaching maximum hindrance. It is concluded that for aromatic nitration other energetic considerations are of far greater importance than steric factors in determining the velocity ratio (v_{-1}/v_2).

There appears to be no isotope effect in the bromination of benzene by hypobromous acid [12] or bromine with iodine catalyst [6]. These results may be contrasted with the strong isotope effect found in the bromination of tri-*t*-butylbenzene and the previously reported isotope effects in the bromination of 2-naphthol-6,8-disulphonic acid ($k_D/k_H = 0.50$)[8] and dimethylaniline ($k_D/k_H = 0.53$)[13]. Although the situation at present is not altogether clear-cut, it would appear that in the aromatic bromination reaction steric hindrance is able to profoundly influence the velocity ratio (v_{-1}/v_2).

Further discussion will be deferred until investigations concerning the isotope effects in the bromination of aromatic hydrocarbons possessing intermediate hindrance and the importance of basic and solvent species on the isotope effect have been completed. The investigations reported here will be published in full detail at a later date.

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