Slow Proton Transfers in Aromatic Nitration

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Abstract: The products resulting from nitration and the kinetic isotope effects in the nitrodeprotonation of a series of 1-X-2,4,6-tri-t-butylbenzenes (X = H, F, NO$_2$, CH$_3$) have been investigated. A variation in the over-all kinetic isotope effect (k_H/k_D) ranging from 1.0 to 3.8 is observed as X is varied from H through CH$_3$. This variation can be correlated with the increasing size of the substituent X. The results are consistent with the two-step mechanism of aromatic nitration and provide the first evidence that aromatic nitrations can proceed with a rate-limiting proton transfer.
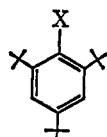
In 1950, Melander demonstrated the absence of a primary kinetic isotope effect on the rate of nitration of several benzene and toluene derivatives.[2] This clearly conceived and interpreted study succeeded in answering a very crucial question concerning the mechanism of aromatic nitration and has served as an important point of departure for many subsequent investigations of aromatic substitution reactions.[3]

The search for isotope effects in aromatic nitration has been active.[3b] However, the failure to observe such an effect in aromatic nitration has become so repetitious that one might be led to the generalization that nitration is an aromatic substitution reaction that always proceeds with a rapid proton transfer.[3a]

Are proton transfers in aromatic nitration always rapid? Since a clear resolution of this problem seemed of considerable mechanistic importance, we initiated studies directed toward this question a number of years ago. We now report data which demonstrate a change from rapid to slow (rate-limiting) proton transfer in nitration of a series of structurally related aromatic compounds. An account of these studies with emphasis on structural factors which are apparently responsible for this changeover in rate-limiting step is the principal concern of this paper.[4,5]

Results

Product distributions in nitration and kinetic isotope effects in nitrodeprotonation of several 1-substituted 2,4,6-tri-t-butylbenzenes (1-X) have been investigated.

X = H, NO$_2$, F, CH$_3$

The isotope effect in the mononitration of 1-H was measured by the use of tritium-labeled 1,3,5-tri-t-butylbenzene (1-^{3}H) which was prepared from inactive

hydrocarbon by acid-catalyzed exchange with tritium-labeled sulfuric acid. The necessary tritium activity measurements of reactant and product were made by use of a Geiger–Müller tube partially filled with tritium-labeled hydrogen gas. The hydrogen was obtained by complete combustion of samples to water and carbon dioxide and subsequent reduction of combustion water over hot (400°) magnesium turnings.[2,6]

In one set of experiments, samples of tritium-labeled hydrocarbon were almost quantitatively (>97%) converted to the mononitration product, and the tritium activity of the nitration product was determined in the manner described. In other experiments larger amounts of labeled hydrocarbon were partially nitrated (ca. 80% conversion), and the tritium activity of the isolated, unconsumed reactant was determined. Pertinent data resulting from these experiments is given in Table I.

For a reaction system of the type

$$sym\text{-}R_3C_6H_2T \begin{cases} \xrightarrow{k_T} sym\text{-}R_3C_6H_2NO_2 \\ \xrightarrow{2k_H} sym\text{-}R_3C_6HTNO_2 \end{cases}$$

$$sym\text{-}R_3C_6H_3 \xrightarrow{3k_H} sym\text{-}R_3C_6H_2NO_2$$

where the labeled compound is present in only tracer concentrations with unlabeled hydrocarbon as carrier, the expressions relating molar tritium activity ratios to the observed kinetic isotope effect and the extent of reaction have been derived (eq 1 and 2).[2,6b] The

$$p/r_0 = f(k_T/k_H, X) =$$
$$\left[\frac{2}{2 + (k_T/k_H)}\right]\frac{1}{X}\{1 - (1 - X)^{[2 + (k_T/k_H)]/3}\} \quad (1)$$

$$r/r_0 = f(k_T/k_H, X) = (1 - X)^{[(k_T/k_H) - 1]/3} \quad (2)$$

ratio p/r_0 is the ratio of molar activities of product with respect to initial reactant; r/r_0 is the ratio of molar activities of unconsumed reactant with respect to initial reactant; X is the fraction of reactant converted to product. Clearly if k_T/k_H is unity, then for any value of X, p/r_0 takes the statistical value 0.667, and r/r_0 is unity. If k_T/k_H differs from unity, the greatest measurement sensitivity will be obtained as X approaches unity.

Comparison of the observed p/r_0 and r/r_0 ratios with plots of these functions shows that all k_T/k_H values,

(1) Petroleum Research Fund Undergraduate Research Scholar, 1966.

(2) L. Melander, Arkiv Kemi, 2, 211 (1950).

(3) Much of this work has been reviewed recently; see (a) E. Berliner, Progr. Phys. Org. Chem., 2, 157 (1964); (b) H. Zollinger, Advan. Phys. Org. Chem., 2, 163 (1964).
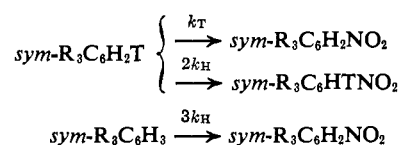
(4) Preliminary reports of portions of this work have been published: (a) P. C. Myhre, Acta Chem. Scand., 54, 219 (1960); (b) P. C. Myhre and M. Beug, J. Am. Chem. Soc., 88, 1569 (1966).

(5) H. Cerfontain and A. Telder, Rec. Trav. Chim., 86, 371 (1967), have reported a kinetic isotope effect upon nitration of anthracene with nitronium tetrafluoroborate.

(6) (a) L. Melander, ibid., 2, 440 (1948); (b) "Peter C. Reilly Lectures in Chemistry," Vol. XI, University of Notre Dame Press, Notre Dame, Ind., 1955.

Table I. Nitration of Tritium-Labeled 1,3,5-Tri-*t*-butylbenzene (1-³H) in Acetic Acid–Acetic Anhydride at 20°

Run no.	Mole ratio $HNO_3/1$	React. time, hr	Crude prodt % yield	Crude prodt Mp, °C	Purif prodt mp, °C	Combustion prodt Water, %	Combustion prodt Spec act., M	React. spec act., M	p/r_0
1	2.9	48	99	203–204	205–206	97.8	29.9 ± 0.4	45.3 ± 0.6	0.661
2	3.0	48	98		205–206	98	30.8	45.3 ± 0.6	0.680
3	3.0	50	98.5		205–207	97.9	29.9	45.3 ± 0.6	0.661
4	3.0ᵃ	50	98.3		205–206	98	0	0	
10	3.0ᵇ	18	97.5	203–205	205–206	98	16.1	24.4	0.659
11	0.85ᵇ	70	83	187–199	204–205.5	96	23.5 ± 0.3	34.0 ± 0.3	0.662
				Analysis of Unconsumed Reactants					
9	0.81	23	79	175–188	72.5–73.3	98	35.9 ± 0.2	36.0 ± 0.2	0.998ᶜ
10	0.85ᵇ	70	83	187–199	71.5–72.8	96	33.2 ± 0.1	34.0 ± 0.3	0.977ᶜ

ᵃ Nitric acid with specific activity of 5×10^3 and unlabeled hydrocarbon were used. ᵇ Trace of sulfuric acid was added to these reaction solutions, 1×10^{-2} equiv with respect to hydrocarbon. ᶜ r/r_0.

except one, lie between 1.05 and 0.95 with the best value 1.03. It is safe to conclude that there is no primary isotope effect in the nitration of 1-H.

Literature reports describing the nitration of 1,3,5-tri-*t*-butylbenzene (1-H) are somewhat varied.[7] Wepster's particularly careful study indicated that this hydrocarbon could be cleanly and almost quantitatively nitrated in solutions of acetic acid and acetic anhydride to yield 2,4,6-tri-*t*-butylnitrobenzene (1-NO₂).[7b] Our results are in complete agreement with this report. Gas–liquid partition chromatography (glpc) of crude products gave no evidence of significant nitrodealkylation or dinitration when these mild reaction conditions were employed.

Some time after the completion of the experiments just described we were prompted to investigate possible changes in product distribution when 1-H is nitrated with nitronium tetrafluoroborate.[7c] We found no evidence for nitrodealkylation of this hydrocarbon when these reaction conditions were used. Rather, partial nitration of 1-H with nitronium tetrafluoroborate in sulfolane gave the normal nitration product, 1-NO₂, together with significant amounts of 1,3-dinitro-2,4,6-tri-*t*-butylbenzene (2). More careful inspection of glpc records indicated the presence of at least three other compounds (3, 4, and 5) with retention times intermediate between those of 1-NO₂ and 2. Nitration of 1-NO₂ with nitronium tetrafluoroborate, mixed nitric and sulfuric acids, or fuming nitric acid gave the same type of product mixtures but with distributions which varied with nitrating agent and temperature. Some of the distribution data are presented in Table II.

Some of the variations in product distribution (Table II) will be more fully discussed later. For the present it is important to note that 4 appears to undergo a subsequent reaction when very vigorous nitrating conditions are used. Thus, the marked diminution in the yield of 4 upon increasing temperature and activity of the nitration conditions can be frequently correlated with the appearance of a new product band with retention time very similar to that of 2. The yields of 2 reported in Table II include, where noted, the yield of product derived from 4.[8]

(7) (a) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, 76, 2349 (1954); (b) B. M. Wepster, *et al.*, *Rec. Trav. Chim.*, 77, 491 (1958); (c) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, 86, 1067 (1964).

(8) The two bands had a difference in retention time of about 15 sec. Thus the product resulting from reaction of 4 was clearly detectable by the increase in band width, but resolution was not sufficient to permit separate integration of both bands.

Table II. Product Distributions in Nitration of 2,4,6-Tri-*t*-butylnitrobenzene

Conditions	React. time, hr	% convn	Products, % 2	3	4	5
70% HNO₃, 100°	1.5	<5	90			
90% HNO₃, 0°	1.5	80	55	7	36	2
90% HNO₃, 40°	1.5		48	13	35	4
90% HNO₃, 100°	1.5	95	52ᵃ	26	14	8
HNO₃–H₂SO₄, 0°	1.5	95	61ᵃ	18	17	4
HNO₃–H₂SO₄, 40°	1.5	98	70ᵃ	27	2	1
NO₂BF₄, 25°	1.0	10ᵇ	81	2	16	1

ᵃ Sum of 2 and product formed by nitration of 4. ᵇ Reaction conducted with 0.1 equiv of nitronium salt.

Identification of products 3, 4, and 5 was achieved by a larger scale nitration of 1-NO₂ with 90% nitric acid. The products of intermediate retention time could be separated by trituration of the crude product with ethanol and then individually isolated by column chromatography over alumina and preparative glpc. The definitive nmr spectra coupled with mass spectral data forced the conclusion that the three products were (in order of decreasing glpc retention time): 1,2-dinitro-3,5-di-*t*-butylbenzene (3), 2,4-dinitro-3,5-di-*t*-butyltoluene (4), and 2,6-dinitro-3,5-di-*t*-butyltoluene (5).
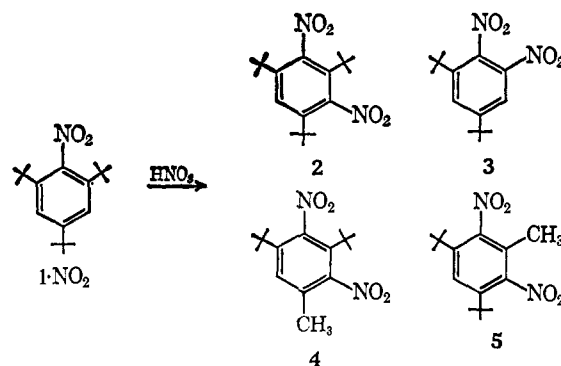
Independent syntheses of 4 and 5 were achieved by sequential nitration of 3,5-di-*t*-butyltoluene (6). Mononitration of 6 gave 2-nitro-3,5-di-*t*-butyltoluene (7) as the major product (98.5%) together with a trace (1.5%) of the other isomer, 4-nitro-3,5-di-*t*-butyltoluene (8). The minor product, 8, was isolated by preparative glpc of concentrated mother liquors from which several crops of crystalline 2-nitro isomer had been collected. Nitration of 8 gave only one product, a

Table III. Product Distribution in Nitration of 1-NO₂ and 1-NO₂-d₂

Run No.	Reactant	Conditions	React. time, hr	Mole % products[a]			
				2	3	4	5
5	1-NO₂	90% HNO₃,	3.5	57.6 ± 1.0	5.2 ± 0.8	35.2 ± 0.5	2.0 ± 0.2
6	1-NO₂-d₂	0–20°		29.7 ± 1.0	7.0 ± 0.3	60.1 ± 1.0	3.2 ± 0.3
7[b]	1-NO₂	HNO₃–H₂SO₄ in		80.6 ± 1.0	3.7 ± 0.3	14.6 ± 0.3	1.1 ± 0.2
8[b]	1-NO₂-d₂	CH₃NO₂, 40°		58.6 ± 1.0	7.3 ± 0.2	31.6 ± 0.5	2.5 ± 0.2
9	1-NO₂	90% HNO₃,		58.7 ± 0.5	11.8 ± 0.5	26.0 ± 0.6	3.5 ± 0.4
10	1-NO₂-d₂	40°	4.5	39.8 ± 0.5	14.4 ± 0.4	40.8 ± 0.5	5.0 ± 0.4
11, 12, 13, 14	1-NO₂	90% HNO₃, 40°		48.9 ± 1.0	12.4 ± 0.3	35.1 ± 0.4	3.6 ± 0.3
15, 16, 17	1-NO₂-d₂		0.5	23.6 ± 1.0	16.4 ± 0.5	53.8 ± 1.0	6.2 ± 0.2

[a] Area per cents were corrected by use of experimentally determined response factors. Error estimates represent the maximum deviations from the average in repetitive chromatograms. [b] Distribution data obtained from aliquots of a direct kinetic study after 15% conversion.
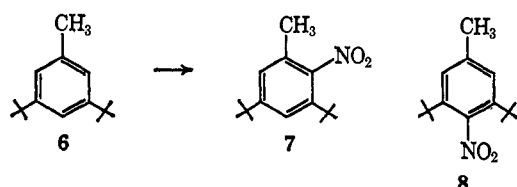
compound identical in properties with previously isolated **4**. Nitration of **7** gave both **5** and **4** in 93.5 and 6.5% yields, respectively.
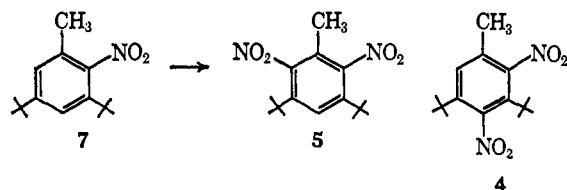
The task of finding a plausible explanation of the unusual and unanticipated transformation of a *t*-butyl group into a methyl group upon nitration of **1-NO₂** led to the design of several sets of experiments. In one series of experiments, the product distributions resulting from nitration of **1-NO₂** and 2,4,6-tri-*t*-butylnitrobenzene-3,5-*d₂* (**1-NO₂-d₂**) were examined. Data resulting from these studies are summarized in Table III.

In all of the paired experiments (Table III) the yield of **2** decreases and the yields of **3**, **4**, and **5** increase upon substitution of deuterium for protium at aromatic carbon. Making the usual assumptions concerning irreversibility and stability of final products, one can treat the product ratios as relative rate constants. Further, assuming that only the rate formation of **2** is sensitive to deuterium substitution, it is possible to determine "partition" isotope effects by combining rate ratios. For example, comparison of the yields of **2** and **4** leads to the isotope effect $(k_H/k_D)_{2/4}$ (eq 3). Partition isotope effects obtained from the data in

$$(k_H/k_D)_{2/4} = \left(\frac{[2]}{[4]}\right)_H \left(\frac{[4]}{[2]}\right)_D \quad (3)$$

Table III are tabulated in Table IV.

In addition, direct kinetic measurement of the rates of nitration of **1-NO₂** and **1-NO₂-d₂** were made in solutions of nitromethane and nitric acid containing added sulfuric acid. The rate of disappearance of reactant was followed by withdrawing aliquots and analyzing the product and reactant composition by glpc. A first-

Table IV. Partition Isotope Effects in Nitration of 2,4,6-Tri-*t*-butylnitrobenzene[a,b]

Run no.	$(k_H/k_D)_{2/3}$	$(k_H/k_D)_{2/4}$	$(k_H/k_D)_{2/5}$
5 and 6	2.6 ± 0.6 (2.8)	3.3 ± 0.3 (3.8)	3.1 ± 1.0 (3.5)
7 and 8	2.7 ± 0.4 (3.0)	3.0 ± 0.3 (3.4)	3.1 ± 1.0 (3.5)
9 and 10[c]	1.8	2.2	2.5
11–17	2.7 ± 0.5 (3.0)	3.2 ± 0.3 (3.6)	3.6 ± 0.6 (4.2)

[a] Error estimates are based on maximum deviations from average values given in Table III. [b] Partition isotope effects in parentheses are those obtained after correction for 5% protium bound to aromatic hydrogen. [c] The prolonged reaction time causes further reaction of product **4** (see text and Tables II and III), and, hence, yields erroneous isotope effect data.

order plot of two direct kinetic runs $(k_H/k_D = 1.8)$ is shown in Figure 1.

In previous work it was found that nitration of 2,4,6-tri-*t*-butylfluorobenzene (**1-F**) resulted in the formation of two products, 3-nitro-2,4,6-tri-*t*-butylfluorobenzene (**9**) and 4-nitro-2,6-di-*t*-butylfluorobenzene (**10**), in approximately 20 and 80% yields, respectively.[9] More detailed study of the product distribu-

tion and change in product distribution upon substitution of deuterium for protium at aromatic carbon has resulted in the data shown in Table V. As above, the partition kinetic isotope effects are calculated assuming that the rate of nitrodealkylation yielding **10** is independent of isotope substitution.
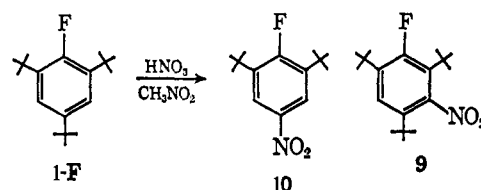
Finally, products resulting from nitration of 2,4,6-tri-*t*-butyltoluene (**1-CH₃**) were examined. Nitration of **1-CH₃** in acetic acid and acetic anhydride solutions afforded three main products and a complex mixture of minor products. The major components of this prod-

(9) P. C. Myhre, J. W. Edmonds, and J. D. Kruger, *J. Am. Chem. Soc.*, **88**, 2459 (1966).
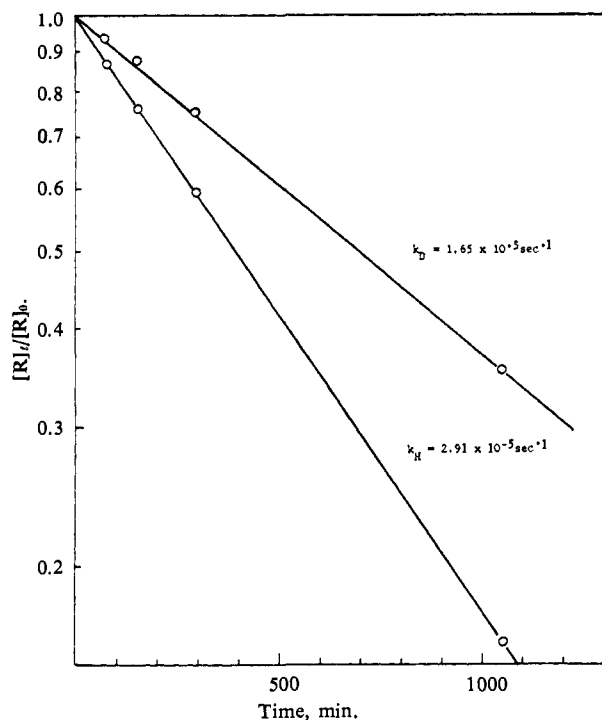
Figure 1. First-order plots of nitration of 1-NO₂ and 1-NO₂-d₂ in nitromethane–nitric acid at 40°. $[R]_t/[R]_0$ represents the mole fraction of reactant.

uct mixture were isolated and identified as 3-nitro-2,4,6-tri-*t*-butyltoluene (**13**), 4-nitro-2,6-di-*t*-butyltoluene (**12**), and 2-nitro-4,6-di-*t*-butyltoluene (**11**). The normal nitrodeprotonation product, **13**, was found in only

Table V. Product Distribution and Kinetic Isotope Effects in Nitration of 2,4,6-Tri-*t*-butylfluorobenzene (1-F) and 2,4,6-Tri-*t*-butylfluorobenzene-3,5-d₂ (1-F-d₂) in Nitromethane

| Reac-tant	Temp, °C	Product, % 9	10	k_H/k_D
1-F[a]	−10	84.3 ± 0.6	15.7 ± 0.6	2.2 ± 0.4
1-F-d₂[a]		92.2 ± 0.3	7.8 ± 0.3	(2.3)[c]
1-F[b]	21	89.7 ± 0.6	10.3 ± 0.6	2.1 ± 0.4
1-F-d₂[b]		95.2 ± 0.6	4.8 ± 0.6	(2.2)[c]

[a] Average of three pairs of runs. [b] Average of two pairs of runs. [c] Values in parentheses are isotope effects corrected for 5% protium bound to aromatic carbon.

about 10% yield. Fortunately, nitration of **1-CH₃** in nitromethane gave a much cleaner product mixture containing only the products identified above in significant concentration. Again product distributions
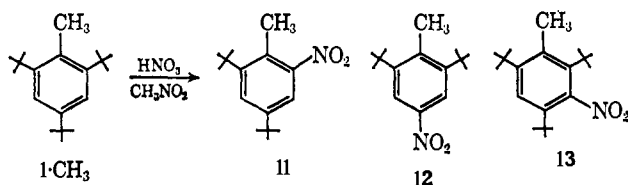
and isotope effects were determined by parallel nitration of **1-CH₃** and **1-CH₃-d₂** in nitromethane solvent. The data are summarized in Table VI.

Discussion

It will be convenient to: (1) present a summary of the isotope effect data obtained in this work; (2) discuss in greater detail particular experimental results, kinetic analyses, assumptions, and sources of error; (3) finally, interpret the experimental results in terms of the probable effects of structure on the energetics of aromatic nitration.

The kinetic isotope effect data accumulated from study of nitration of various 1-X-2,4,6-tri-*t*-butylbenzenes is summarized in Table VII together with estimates of the van der Waals volumes of the X substituent and approximate values for the over-all rate of nitration.

The data clearly show that one can find aromatic systems in which the nitrodeprotonation reaction occurs with a slow or rate-limiting proton transfer. Further, the occurrence of slow proton transfers in nitration, within a series of closely related compounds, appears to be mainly a function of steric effects and substantially independent of electron-donating or -releasing properties of substituent groups.

Nitrodealkylation. Studies of nitrodeprotonation are the major concern of this work. However, nitration of many highly alkylated aromatic compounds results in significant nitrodealkylation. Indeed, the degree of dominance of the nitrodealkylation reaction has proved to be a major experimental consideration, since many compounds of interest do not yield a sufficiently large amount of nitrodeprotonation product to make isotope effect studies feasible. If a reasonable balance between nitrodealkylation and nitrodeprotonation exists, however, the former serves as a very convenient reference in the study of kinetic isotope effects.

A number of nitrodealkylation reactions are known.[7c,10] Examination of the available data indicates that effective competition of nitrodealkylation with normal nitrodeprotonation depends on the following factors: (1) a tertiary or secondary alkyl group which can form a reasonably stable cationic leaving group; (2) attachment of an alkyl group at a site which is activated or of comparable reactivity in comparison with a competitive nitrodeprotonation site; (3) the existence of steric effects which tend to retard the rate of competitive nitrodeprotonation and, possibly, accelerate the rate of nitrodealkylation.

Our failure to find nitrodealkylation products in nitration of 1,3,5-tri-*t*-butylbenzene under any type of nitration conditions is quite explicable in terms of the generalizations cited above, particularly number 2. That is, the activation at a site of nitrodealkylation relative to a site of nitrodeprotonation is very poor. Since *both* reactions should be subject to considerable steric retardation, the activation effects would be expected to dominate.[11]

The nitrode-*t*-butylation reactions which have been observed in these studies appear to be subject to the same substituent effects as nitrodeprotonation reactions in simple benzene derivatives. The relatively small amount of nitrodealkylation product found in the nitration of **1-NO₂**, compared with nitration of **1-F** or **1-CH₃**, correlates with the positional reactivities observed in the

(10) D. V. Nightingale, *Chem. Rev.*, 40, 117 (1947).

(11) Nitrode-*t*-butylation presents a steric problem somewhat analogous to nucleophilic displacement in the neopentyl series.

Table VI. Product Distributions and Kinetic Isotope Effects in Nitration of 2,4,6-Tri-t-butyltoluene (1-CH₃) and 2,4,6-Tri-t-butyltoluene-3,5-d_2 (1-CH₃-d_2) in Nitromethane

Reactant	Conditions	11	Product, % 12	13	$(k_H/k_D)_{13/11}$	$(k_H/k_D)_{13/12}$
1-CH₃	HNO₃-CH₃NO₂, 0°	40.3 ± 0.6	51.0 ± 0.5	8.7 ± 0.2	3.4 ± 0.4 (3.8)[a]	3.5 ± 0.4 (3.7)[a]
1-CH₃-d_2		42.4 ± 0.5	54.6 ± 0.5	2.7 ± 0.2		

[a] Values in parentheses are isotope effects corrected for 3% protium bound to aromatic carbon.

Table VII. Over-all Kinetic Isotope Effects in Nitration of 1-X-2,4,6-Tri-t-butylbenzenes[a]

X	k_H/k_D	van der Waals vol of X, cm³ mol⁻¹ [b]	Approx rel rate
H	1.0		1
F	2.3	5.8	0.1
NO₂	3.0[c]	11.8	0.001
CH₃	3.7	13.7	10

[a] All nitrations except that of parent hydrocarbon were conducted in nitromethane solution. [b] Data taken from a compilation of A. Bondi, J. Phys. Chem., 68, 451 (1964). [c] The calculation of over-all isotope effect in nitration of 1-NO₂ is discussed; see below.

nitration of analogous monosubstituted benzenes. In addition the ortho:para ratios found in nitrodealkylation of these compounds parallel reasonably the ortho: para ratios found in nitration of monosubstituted benzenes. A comparison of these data is presented in Table VIII. Qualitative discussion of the reactivity

Table VIII. Comparison of ortho:para Ratios in Nitration of Monosubstituted Benzene Derivatives and Nitrodealkylation of 1-X-2,4,6-Tri-t-butylbenzenes

X	Conditions	o:p for C₆H₅X	Ref	o:p for 2,4,6- (t-Bu)₃C₆H₂X
CH₃	HNO₃-CH₃NO₂, 25°	1.7	a	0.76[c]
F	HNO₃, 0°	0.14	b	<0.1[d]
NO₂	HNO₃, 0°	20	b	>15[e]

[a] A. Holleman, J. Vermeulen, and W. J. DeMooy, Rec. Trav. Chim., 33, 1 (1914). [b] A. F. Holleman, Chem. Rev., 1, 187 (1925). [c] A much larger ortho:para ratio is observed when acetic acid–acetic anhydride solvent is used. [d] No ortho product was detected. [e] A trace of the para isomer was found in large-scale column chromatographic separations. The glpc retention time is very close to that of 5.

and orientation in nitrodealkylation appears to follow the arguments developed for nitrodeprotonation, although some of the mechanistic aspects of nitrodealkylation present rather intriguing and as yet unanswered questions.[12]

Molecular Rearrangement Attending Nitration—Kinetic Analysis. The discovery that the dinitrodi-t-butyltoluenes, 4 and 5, were formed as products in the nitration of 1-NO₂ elicited, perhaps understandably, considerable interest and concern. One of the more reasonable paths of formation of these products appeared to be by intramolecular rearrangement and

(12) To our knowledge the question of rate-limiting step in aromatic nitrodealkylation has not been investigated. In view of the apparently more facile nitrodeisopropylation vs. nitrode-t-butylation (compare nitrations of p-cymene and p-diisopropylbenzene with p-t-butyltoluene and p-di-t-butylbenzene[7c]), a rather delicate and easily shifted balance between the rate of addition and rate of expulsion of a cation may obtain which is subject to alkyl, steric, and cationic stability effects.

subsequent fragmentation of the cyclohexadienyl cation, which is also the precursor of 2 (eq 4).[13]

$$ (4) $$
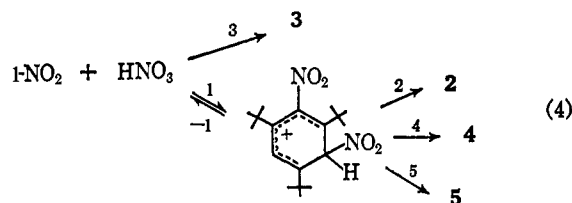
If the cyclohexadienyl cation shown in eq 4 is the precursor of 4 and 5 as well as 2 (the formation of 4 and 5 from the cyclohexadienyl cation involves a migration of methyl from benzylic carbon to aromatic carbon[13]), then replacement of aromatic protium in 1-NO₂ by deuterium should result in marked increase in the yields of 4 and 5. That is, regardless of the rate-determining step in formation of 2 (addition of the electrophile or loss of the proton), the relative rates of formation of 2 and 4 from a common intermediate will reflect a primary isotope effect. Such an effect would be discernible as a change in product distribution.

The observed product distributions shown in Table III reveal the anticipated decrease in yield of 2 and increases in yields of 4 and 5 upon use of deuterium-labeled reactant.

In addition it can be seen from the data in Table III that the yield of nitrodealkylation product, 3, also increases upon deuterium substitution in the reactant. However, the partition isotope effect obtained when 3 is used as a reference is not as large (see Table IV).

This result might be anticipated by examination of the kinetic scheme, eq 4. Assuming the stationary-state character of the cyclohexadienyl cation intermediate and that deuterium substitution at aromatic carbon affects only the rate of step 2, the previously defined distribution isotope effects can be related to the rate constants of the scheme shown in eq 4. Thus

$$ (k_H/k_D)_{2/4} = \left(\frac{[2]}{[4]}\right)_H \left(\frac{[4]}{[2]}\right)_D = k_2{}^H/k_2{}^D \qquad (5) $$

$$ (k_H/k_D)_{2/5} = \left(\frac{[2]}{[5]}\right)_H \left(\frac{[5]}{[2]}\right)_D = k_2{}^H/k_2{}^D \qquad (6) $$

but

$$ (k_H/k_D)_{2/3} = \left(\frac{[2]}{[3]}\right)_H \left(\frac{[3]}{[2]}\right)_D = $$

$$ (k_2{}^H/k_2{}^D) \times $$

$$ \frac{(k_{-1}/k_2{}^D + 1 + k_4/k_2{}^D + k_5/k_2{}^D)}{(k_{-1}/k_2{}^D + k_2{}^H/k_2{}^D + k_4/k_2{}^D + k_5/k_2{}^D)} \qquad (7) $$

(13) More detailed studies of the rearrangement yielding 4 and 5 will be considered in a subsequent paper.

Table IX. Evaluation of the Over-all Isotope Effects and Other Rate Ratios in the Nitration of 1-NO$_2$

React. no. and conditions	$k_{-1}/k_2{}^D$	$k_{-1}/k_2{}^H$	$\dfrac{k_{-1}}{k_2{}^D + k_4 + k_5}$	$\dfrac{k_{-1}}{k_2{}^H + k_4 + k_5}$	$(k_H/k_D)_2$
5 and 6, HNO$_3$, 0°	4.7	1.2	1.5	0.8	2.6
7 and 8, HNO$_3$–H$_2$SO$_4$, 40° in CH$_3$NO$_2$	15	4.4	9.3	3.7	3.0
11–17, HNO$_3$, 40°	4.5	1.2	1.2	0.7	2.7

where the k_n's represent rate constants of the individual steps shown in eq 4.[14] Thus, $(k_H/k_D)_{2/3}$ is a composite of many rate constants and must be less than $k_2{}^H/k_2{}^D$ except in the limiting case when $k_{-1} \gg k_2$.

Continued use of the kinetic scheme shown in eq 4 necessitates recognition that the observed partition isotope effects, $(k_H/k_D)_{2/4}$, $(k_H/k_D)_{2/5}$, or $(k_H/k_D)_{2/3}$, do not measure what could be called the "over-all" kinetic isotope effect in the formation of 2. This over-all isotope effect, $(k_H/k_D)_2$, takes into consideration only those steps which are directly involved in the formation of 2, and can be defined in the familiar way (eq 8).

$$(k_H/k_D)_2 = \frac{k_2{}^H(k_{-1} + k_2{}^D)}{k_2{}^D(k_{-1} + k_2{}^H)} \qquad (8)$$

It will be useful to evaluate this isotope effect for the nitration of 1-NO$_2$, since it can be more meaningfully compared with the other nitration data obtained in this study. Such an evaluation requires knowledge of the ratios $k_{-1}/k_2{}^H$ and $k_{-1}/k_2{}^D$. The ratios can be obtained from eq 7, since experimental data permit evaluation of all the rate constant ratios of eq 7 except the term $k_{-1}/k_2{}^D$. Solution of eq 7 for $k_{-1}/k_2{}^D$ yields the values tabulated together with values of $k_{-1}/(k_2{}^D + k_4 + k_5)$ and $(k_H/k_D)_2$ in Table IX.

In terms of the mechanistic scheme proposed, nitration of 1-NO$_2$ appears to be a fairly delicately balanced reaction in the sense that the rate ratio $k_{-1}/(k_2{}^H + k_4 + k_5)$ is fairly close to unity. The variations in the ratios obtained from runs made under different reaction conditions can be reasonably associated with the basicities of the different reaction media, the least basic reaction medium, HNO$_3$ and H$_2$SO$_4$ in nitromethane, yielding the largest $k_{-1}/k_2{}^H$ ratio.

A comparison of the isotope effect observed by direct measurement of the rates of disappearance of 1-NO$_2$ and 1-NO-d_2 with the value estimated on the basis of product ratios provides one check of the self-consistency of the kinetic scheme. Assuming the scheme shown in eq 4, the rate of disappearance of 1-NO$_2$ can be written as shown in eq 9. The corresponding

$$-\mathrm{d}[1\text{-NO}_2]/\mathrm{d}t = k_{\mathrm{obsd}}[1\text{-NO}_2] =$$
$$\left[k_3 + \frac{(k_2 + k_4 + k_5)k_1}{(k_{-1} + k_2 + k_4 + k_5)} \right][1\text{-NO}_2] \qquad (9)$$

(14) In the derivation of the kinetic scheme, the role of basic species is not explicitly taken into account; hence, the k's must be considered composites of rate constants and base concentration terms. In comparative parallel runs the medium remains essentially constant, and it seems appropriate to assume cancellation of base concentration terms. The effect of base catalysis on the kinetic isotope effect remains substantially unexplored; however, see the discussion to follow.

ratio of observed rate constants is shown in eq 10.

$$\frac{k^D{}_{\mathrm{obsd}}}{k^H{}_{\mathrm{obsd}}} =$$

$$\left[\frac{k_3}{k_1} + \cfrac{1}{1 + \cfrac{k_{-1}}{k_2 + k_4 + k_5}} \right]_H \times$$
$$\left[\frac{k_3}{k_1} + \cfrac{1}{1 + \cfrac{k_{-1}}{k_2 + k_4 + k_5}} \right]_D^{-1} \qquad (10)$$

The second term in each of the square brackets (eq 10) may be evaluated with the aid of values tabulated in Table IX. The first term, k_3/k_1, may be estimated to be approximately 10^{-2} on the basis of yield data and the previously evaluated ratio, $k_{-1}/(k_2{}^H + k_4 + k_5)$.

With the use of product distribution data obtained in a paired kinetic run (runs 7 and 8) the ratio of observed kinetic rate constants, $k_{\mathrm{obsd}}{}^H/k_{\mathrm{obsd}}{}^D$, is *predicted* to be 2.0 or less. The *observed* value of this ratio is 1.8, which increases to 1.9 upon correction for protium in the deuterium-labeled reactant.

The nitration of 1-NO$_2$ yields a complex array of products, but the complexity can be used to advantage. In terms of the kinetic scheme proposed, one can extract several pieces of useful data including estimates of the isotope effect in the proton loss step, $(k_H/k_D)_{2/4}$, and estimates of the over-all kinetic isotope effect, $(k_H/k_D)_2$.

It should be emphasized that the construction of crucial, quantitative arguments based upon these extensively manipulated rate constant ratios presupposes experimental data of a high order of accuracy, higher, perhaps, than can presently be claimed. The wealth of information that can be derived from this reaction system makes more detailed study appear quite attractive.

In this regard, the experimental limitations in the treatment of this system should be noted. The kinetic analysis includes the assumption that products are formed irreversibly and that products are stable with respect to further reaction. We have been unable to detect protodenitration of 2, although steric hindrance around the nitro group would favor such a reaction.[15,16] Experimental data do show, however, that product 4

(15) (a) P. C. Myhre, *Acta Chem. Scand.*, 14, 947 (1960); (b) P. C. Myhre, S. Murov, R. Clark, and L. Armi, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963, Abstracts, p 19M.

(16) Protodenitration of 9-nitroanthracene has been reported by P. H. Gore, *J. Chem. Soc.*, 1437 (1957).

is not completely inert to further nitration (see Tables II and III). Prolonged reaction times or vigorous nitration conditions result in further nitration yielding a compound, mp 171–173°, with glpc retention time very close to that of **2** and an nmr spectrum consistent with that expected for 2,4,6-trinitro-3,5-di-*t*-butyltoluene **(14)**. In contrast, product **5** is inert with respect to further nitration.[17]
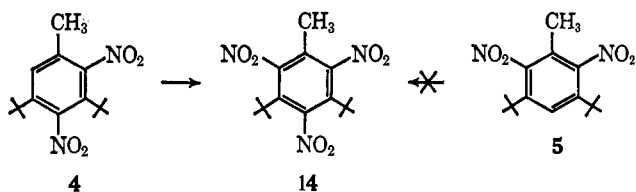
Experimental conditions were chosen so as to minimize as much as possible the subsequent reaction of **4** and maximize the yield of **3**.[18] However, it is difficult to rigorously exclude some conversion of **4** to **14**. The net result on the distribution isotope effects is *a priori* difficult to predict, since possible isotope effects in the nitration of **14** have not been studied. However, the experiments which did give clear evidence of the conversion of **4** to **14** (runs 9 and 10, Table IV) yield partition isotope effects which are considerably lower than those obtained when no subsequent nitration of **4** could be detected.

Nitration of Tri-*t*-butylfluorobenzene and Tri-*t*-butyltoluene. Nitration of both **1-F** and **1-CH₃** yield mainly nitrodealkylation product together with small amounts of protodenitration product. No significant molecular rearrangement attending nitration has been detected. The absence of rearrangement results in a system where partition data yield the over-all isotope effects directly (eq 11). The experimental data show that both of these

$$(k_H/k_D)_{9/10} = \left(\frac{[9]}{[10]}\right)_H \left(\frac{[10]}{[9]}\right)_D = \frac{k_2^H(k_{-1} - k_2^D)}{k_2^D(k_{-1} + k_2^H)} \quad (11)$$

nitration reactions proceed with a rate-limiting proton transfer. It is not possible, however, to compare the observed isotope effects with the maximum kinetic isotope effect, since rearrangement products are absent. Clearly, direct kinetic studies are of little value in determining kinetic isotope effects in nitration of **1-F** and **1-CH₃**, since the major products are those of nitrodealkylation.

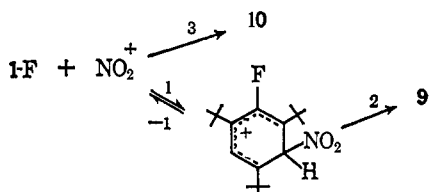**Structural Effects.** In the treatment of the data we have tacitly assumed that the operative mechanism of nitrodeprotonation is the well-established, two-step sequence involving addition of a nitronium ion to an aromatic ring to form a cyclohexadienyl cation which can then decompose by loss of a proton to yield re-

(17) J. Geuze, C. Ruinard, J. Soeterbroek, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, 75, 305 (1956).

(18) Nitrodealkylation reactions show a marked temperature dependence relative to nitrodeprotonation reactions (see Tables III, V, and VI). Attempts were made to optimize the distribution in order to increase the accuracy of the isotope effect measurements.
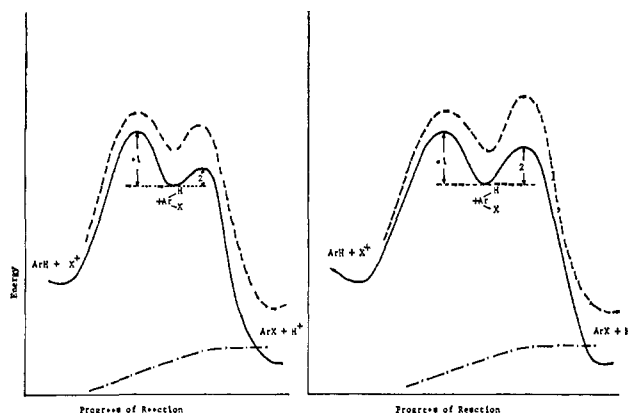
Figure 2. Energy profiles for two aromatic electrophilic substitution reactions showing the effect of imposed steric hindrance (lowest curves) on the "normal" energy profiles (solid curves). In each case the resultant energy profiles (upper dashed curves) are taken as the sums of the lower curves.

aromatized product (eq 12). Furthermore, it is assumed that this mechanism remains unchanged, al-

$$ArH + NO_2^+ \underset{-1}{\overset{1}{\rightleftharpoons}} {}^+Ar \begin{matrix} NO_2 \\ / \\ \backslash \\ H \end{matrix} \overset{2}{\longrightarrow} ArNO_2 + H^+ \quad (12)$$
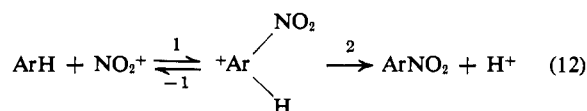
though the rates of individual steps will be a function of the structure of the aromatic reactant. The observation of a change in rate-limiting step upon variation of the X substituent in a series of 1-X-2,4,6-tri-*t*-butylbenzene is conveniently accommodated by this mechanism. In this context, the data appear to yield a much more detailed picture of the energetics of aromatic nitration.

The absence of a primary kinetic isotope effect in a large number of aromatic nitrations clearly demonstrated that the transition state normally occurs before the carbon–hydrogen bond has lost significant zero-point energy. The correlation of these results with a rate-limiting step, 1 (eq 12, where $v_{-1} \ll v_2$), is well known. Energy diagrams of the type shown in Figure 2 have frequently been drawn to pictorially represent the energetics of this reaction. It is clear that there is no direct way to gain the information about the relative heights of the second maxima in the energy diagrams. The second barrier in normal aromatic nitration must be lower than the first ($v_{-1} \ll v_2$), but how much lower has remained an unanswered question. The extreme view, that it may not exist, could not be rigorously dispatched.

The effect of steric hindrance on the rates of various steps in the two aromatic substitution reactions, diazo coupling and protodeformylation, has been clearly elucidated by Zollinger and Schubert, respectively.[19,20] Since that time the same considerations have been successfully applied to studies of aromatic bromination.[4a,21] Basic to the interpretation of these studies

(19) G. Zollinger, *Helv. Chim. Acta*, 38, 1597, 1617, 1623 (1955).

(20) (a) W. M. Schubert and H. Burkett, *J. Am. Chem. Soc.*, 78, 64 (1956); (b) W. M. Schubert and P. C. Myhre, *ibid.*, 80, 1775 (1958).

(21) (a) M. Christen and H. Zollinger, *Helv. Chem. Acta*, 45, 2066 (1962); (b) E. Helgstrand, *Acta Chem. Scand.*, 18, 1616 (1964); 19, 1583 (1965); (c) E. Baciocchi, G. Illuminati, G. Sleiter, and F. Stegel, *J. Am. Chem. Soc.*, 89, 125 (1967); (d) E. Helgstrand and Å. Nilsson, *Acta Chem. Scand.*, 20, 1463 (1966); Å. Nilsson, *ibid.*, 21, 2423 (1967).

is the idea that nonbonded repulsion energy increases as a large electrophile replaces hydrogen at a crowded or sterically confined site, and that this increase in repulsion energy will be of greater importance in step 2, when the electrophile starts assuming product configuration. Hence in the most simple view, the energy profile for substitution at a crowded reaction site can be taken as the sum of a "normal" energy profile (representative of substitution at unhindered aromatic carbon) and a repulsion energy term which increases through the region of the two energy maxima. The results of addition of a given repulsion energy term to two arbitrarily drawn "normal" energy profiles are shown in Figure 2.

It is clear that steric repulsion retards the over-all rate of reaction in both cases. Of greater interest, however, is the implication that the imposed steric effects may or may not be able to cause a changeover in the rate-determining step. One could conclude that a measurement of the degree of repulsion required to change the rate-determining step in aromatic substitution provides an indirect measure of the velocity ratio, v_{-1}/v_2.[22]

The examples of positive bromination and nitration of 1-H have been mentioned earlier.[4b] Silver-induced bromination proceeds with a large kinetic isotope effect while nitration of the same hydrocarbon proceeds with no kinetic isotope effect. Nevertheless the structure of the aromatic reactant is constant, the two electrophiles have about the same "size,"[23] and the ρ values for the two reactions are about the same.[3a] We have rationalized this in terms of a difference in "normal" rate ratios, $(v_{-1}/v_2)_{\text{bromination}} > (v_{-1}/v_2)_{\text{nitration}}$. Hence, nitration requires more imposed steric hindrance around the reaction center (more than is present in 1-H) in order to observe a change in rate-limiting step.

An inequality has been established, but in order to bound the inequality it was necessary to find a nitration reaction which proceeded with a rate-limiting proton transfer. Such reactions have been found in systems which differ structurally from the hydrocarbon 1-H only by the replacement of one aromatic hydrogen with a larger atom or functional group. Thus, 1-F, 1-NO$_2$, and 1-CH$_3$ all undergo nitrodeprotonation with a rate-limiting proton transfer.

To what type of substituent effect can this change in rate-limiting step be attributed? The lack of correlation of these isotope effects with the relative rates of nitration (Table VII) indicate that electronic effects are not of primary importance. While the potential energy profile will be altered as a function of the electronic properties of the substituent, it seems reasonable to assume that this effect will affect the energy of both barriers about equally, so that the change in v_{-1}/v_2 with changing electronic properties of the 1 substituent is small.

The magnitude of the over-all kinetic isotope effect does appear to be related to the size of the substituent group. This observation reinforces the initial hypoth-

esis that increased repulsion energy is the main cause of change in the rate-limiting step.

The most favorable way of relieving nonbonded repulsion energy is through bending deformations of interacting atoms. The rates of racemization of *ortho*-substituted biphenyls are strongly dependent upon the size of groups at 3 and 3' positions, because the major avenue for relief of repulsion energy, bending of the interacting 2 and 2' substituents, is blocked by the insertion of a buttressing group at an adjacent site. Similarly, substitution of a group larger than hydrogen in tri-*t*-butylbenzene will result in much larger repulsion energies attending substitution at one of the remaining carbon atoms bearing hydrogen.[24]

It is attractive to associate the relation between the magnitude of the over-all kinetic isotope effect and the substituent group size with corresponding changes in the rate ratio, v_{-1}/v_2. The interpretation of the data from nitration of 1-NO$_2$ permits a comparison of the maximum isotope effect with the observed over-all isotope effect. In this case, v_{-1} is not too much larger than $v_2{}^H$. Studies of nitration of 1-F and 1-CH$_3$ yield no information concerning the maximum isotope effect. However, it is not unreasonable to assume that the maximum isotope effects in these nitrations are close to that indicated in the nitration of 1-NO$_2$. That is, in the same solvent the position of the maximum for step 2 along the reaction coordinate is about the same for the three nitrations.[25] This assumption permits ordering of the nitration rate ratios for runs conducted in nitromethane as follows: $(v_{-1}/v_2)_{1-H} < 1 < (v_{-1}/v_2)_{1-F} < (v_{-1}/v_2)_{1-NO_2} \cong 5 < (v_{-1}/v_2)_{1-CH_3}$.

In summary, the observed isotope effects in aromatic nitration can be qualitatively interpreted in terms of the operation of steric repulsion effects which differentially increase the energy of step 2 with respect to step -1 (eq 12). The steric requirements necessary for the observation of a kinetic isotope effect have been qualitatively determined. The more formidable problems of quantitative definition of the repulsion energy at various stages of reaction, accurate location of the position of the energy maxima along the reaction coordinate, and more precise definition of "normal" v_{-1}/v_2 ratios for different aromatic substitution reactions remain. Subsequent reports will describe some approaches to the solution of these problems.

Experimental Section

Tritium determinations and quantitative combustions of tritium-labeled compounds were conducted with the use of apparatus and techniques previously described.[2,6] The unit of specific activity reported is a function of the effective volume of the Geiger-Müller tube, the standard hydrogen pressure, and the scaler. In these studies the unit corresponds to about 250 disintegrations min^{-1} mmol^{-1}. Different Geiger–Müller tubes were used in different runs, but in any one run, activity determinations of product and reactant were made with the same tube. Data were rejected unless the plateaus were of about equal duration and at least 400 V.

An Aerograph A-90P3 chromatograph equipped normally with an SE 30 column and a recorder equipped with a Disc Instruments integrator were used for glpc analyses. Preparative separations were performed on an Aerograph A-700 Autoprep similarly

(22) The method of determining relative strengths of strong acids by the use of differentiating solvents serves as an analogy. Introduction of steric repulsion can remove the leveling effects of aromatic structure and permit differentiation of rate processes which are indistinguishable under normal conditions.

(23) Certain data might imply that the size of the electrophile in positive bromination is, if anything, somewhat "smaller" than that in nitration; see P. B. D. de la Mare, "Theoretical Organic Chemistry," Butterworth & Co. (Publishers) Ltd., London, 1959, p 223.

(24) Nmr spectral data of a number of derivatives of 1-H and the interpretation of some of these data in terms of buttressing effects have been presented; see ref 9.

(25) (a) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960; (b) F. H. Westheimer, *Chem. Rev.*, 61, 267 (1961).

equipped. Nmr spectra were recorded on a Varian A-60 spectrometer. Chemical shift data are reported in δ values. Spectral solution were about 10% by weight in carbon tetrachloride unless otherwise noted. A Hitachi mass spectrometer was used to obtain mass spectral data. Elementary analyses were performed by Mr. C. F. Geiger, Ontario, Calif.

1,3,5-Tri-*t*-butylbenzene-2-³H. A solution of 1.35 g (5.46 mmol) of 1,3,5-tri-*t*-butylbenzene in 10 ml of carbon tetrachloride was added to a solution containing 10 ml of 87.1% sulfuric acid and 1.00 ml of tritium-labeled water (specific activity 1 × 10⁵). The resulting two-phase mixture was vigorously mixed at room temperature (20°) with the aid of a rocker arm shaker[26] operating at about 1200 oscillations/min for a 24-hr period. The separated, washed, and dried carbon tetrachloride layer yielded 1.32 g of hydrocarbon with an estimated specific activity of 1.9 × 10³. A portion of this material (0.207 g) was combined with 8.90 g of inactive hydrocarbon and twice recrystallized from absolute ethanol yielding 7.2 g, mp 72.5–73.2°. Specific activity determinations gave values of 44.6, 45.4, and 45.9.

Nitrations of 1,3,5-Tri-*t*-butylbenzene-2-³H. A. The procedure described is that used in nitrations where almost complete conversion to products was effected. Nitric acid (0.25 ml, specific gravity 1.5, 6 mmol) was added from a delivery pipet to a cooled (5°) solution of tri-*t*-butylbenzene-2-³H (0.492 g, 2 mmol) in acetic acid (3 ml) and acetic anhydride (8 ml). After a 48-hr reaction period, during which the temperature was raised to ambient, the product was isolated by hydrolysis of the acetic anhydride with water and subsequent filtration of the pale yellow solid. The crude nitration product was crystallized at least twice from absolute ethanol and carefully dried before combustion.

Glpc analyses (at a later date) of the products used in tritium determinations indicated greater than 99.5% purity.

B. An alternative method of nitration consisted of partially nitrating the hydrocarbon and then separating the resulting product and unchanged reactant for combustion and tritium assay. The following description is typical. Nitric acid (1.40 ml, specific gravity 1.5, 33.4 mmol) was added dropwise *via* a pipet to a stirred solution of 10.0 g of the tritium-labeled hydrocarbon dissolved in 60 ml of acetic acid and 200 ml of acetic anhydride. After a 70-hr reaction period at about 20°, the acetic anhydride was hydrolyzed by addition of water and the resulting crystalline product collected, 11.95 g, mp 187–199°. The yield of product was found to be 83% by infrared analysis.[27] The tailing mother liquors resulting from three fractional crystallizations (ethanol–acetone) were evaporated to yield 0.921 g of material, mp 70–85°. Four fractional sublimations gave 0.302 g of unconsumed reactant, mp 72.0–73.0°, lit. 72.5–73°.[7a] The nitration product was purified by fractional crystallization to yield a sample, mp 204–205.5° (lit.[7b] 205–206). Tabulation of pertinent data for the several runs is given in Table I.

Test for Hydrogen Exchange. A sample of unlabeled tri-*t*-butylbenzene was nitrated following the procedure described in part A above, except that 5 μl of tritium-labeled water (specific activity 1 × 10⁵) was added to the reaction solution before addition of the nitric acid. The specific activity of the resulting product was indistinguishable from the normal background, 1.22 and 1.25, respectively. Complete exchange would have afforded a sample with specific activity of about 100.

Nitronium Tetrafluoroborate. The method follows that described by Kuhn.[28] An 8-oz, polyethylene, screw-cap bottle equipped with a Teflon-coated magnetic stirring bar was converted to a vapor condensation trap by boring two 0.25-in. holes in the cap and threading 0.25-in. polyethylene tubing through the holes. Anhydrous hydrogen fluoride (4.3 g, 0.22 mol) was collected in the trap. Nitric acid (90%, 10.1 ml, 0.22 mol) dissolved in 25 ml of nitromethane was then added. Finally, anhydrous boron trifluoride was slowly passed into the trap with strong cooling (ice–salt bath) and magnetic stirring. After the uptake of 31.8 g of boron trifluoride, the reaction vessel was capped and transferred to a polyethylene drybag filled with dry nitrogen. Colorless, crystalline nitronium tetrafluoroborate was collected by suction filtration (aspirator bulb), and the resulting product was washed five times with anhydrous nitromethane (*ca.* 25-ml portions) and twice with methylene chloride and dried at 60° (1 mm) for 6 hr; 23.3 g, 85%.

Nitration of 1-H with Nitronium Tetrafluoroborate. Nitration of a vigorously stirred suspension of 1,3,5-tri-*t*-butylbenzene (1.96 g, 8.0 mmol) in 10 ml of sulfolane by dropwise addition (30 min) at room temperature of a sulfolane solution containing 8.0 mmol of nitronium tetrafluoroborate afforded 2.23 g of crude, dry nitration product. Glpc of the crude product showed three major bands. The first two bands had retention times identical with those of starting material and mononitration product (1-NO₂). The third component was isolated by heating the crude product at reflux temperature with ethanol–benzene and collecting the undissolved portion, 0.87 g. Recrystallization from benzene afforded 0.51 g of 1,3-dinitro-2,4,6-tri-*t*-butylbenzene (2), mp 293–295° (lit.[29] 290–292°). The nmr spectrum contained two *t*-butyl absorption lines at 1.38 (18 H) and 1.45 (9 H), and an aromatic proton at 7.72 (1 H).

Anal. Calcd for C₁₈H₂₈N₂O₄: C, 64.26; H, 8.39; N, 8.33; mol wt, 336.4. Found: C, 64.46; H, 8.34; N, 8.20; mol wt (mass spectrum), 336.

Traces of at least three other products with retention times intermediate between 1-NO₂ and 2 were observed in the glpc record. The same products were observed when suspensions of either 1-H or 1-NO₂ were nitrated with 0.1 equiv of nitronium tetrafluoroborate.

Nitration of 1-NO₂ with 90% Nitric Acid. Characterization of Products. Fuming nitric acid (90%, 44 ml) was added dropwise over a 2-hr period to a cold (0°), magnetically stirred flask containing 5.43 g of finely ground 1-NO₂. Oxides of nitrogen evolved during the initial stages of reaction. After 3 hr at 0°, the temperature of the reaction mixture was allowed to come to room temperature and remain so for about 20 hr. At this time the reaction mixture, a pale yellow solid and a yellow-orange liquid, was poured into 300 ml of cold water; the solid product was collected by suction filtration and washed free of acid with water yielding 5.65 g of crude product. Glpc (SE 30, 0.25 in. × 6 ft, 207°, 100 ml min⁻¹) showed about 95% conversion and four product bands identified (see below) as: 1,3-dinitro-2,4,6-tri-*t*-butylbenzene (2), 8.6 min; 1,2-dinitro-3,5-di-*t*-butylbenzene (3), 6.2 min; 2,4-dinitro-3,5-di-*t*-butyltoluene (4), 5.7 min; and 2,6-dinitro-3,5-di-*t*-butyltoluene (5), 3.3 min.[30]

1,3-Dinitro-2,4,6-tri-*t*-butylbenzene (2) was isolated in crude form by trituration of the nitration product with three 75-ml portions of absolute ethanol. Three recrystallizations of the undissolved solid from toluene gave pale yellow crystals, mp 293–295°.

Concentration of the ethanol mother liquor from the trituration afforded a yellow crystalline mixture which could be most efficiently separated by column chromatography over alumina. Product 3 was fairly tightly adsorbed, while 5 and 4 were eluted with pentane, in that order.

1,2-Dinitro-3,5-di-*t*-butylbenzene (3), eluted from an alumina column with benzene and recrystallized, mp 132.5–133.5°, had an nmr spectrum with two singlet *t*-butyl absorption lines at 1.40 (9 H) and 1.43 (9 H) together with an aromatic AB quartet centered at 7.87 (2 H), *J* = 2 Hz (calcd mol wt, 280; found (mass spectrum), 280).

2,4-Dinitro-3,5-di-*t*-butyltoluene (4), isolated by column chromatography and recrystallization from ethanol (colorless prisms which yellow rapidly in light), mp 129–130°, gave an nmr spectrum showing two *t*-butyl absorption lines at 1.37 (9 H) and 1.43 (9 H), a weakly coupled (*J* = 0.6 Hz) aromatic methyl absorption at 2.23 (3 H), and an aromatic proton absorption which could be resolved as a quartet (*J* = 0.6 Hz) at 7.57.

Anal. Calcd for C₁₅H₂₂N₂O₄: C, 61.20; H, 7.50; N, 9.53; mol wt, 294.3. Found: C, 61.46; H, 7.54; N, 9.72; mol wt, 294 (mass spectrum).

2,6-Dinitro-3,5-di-*t*-butyltoluene (5), isolated in pure form by preparative glpc, mp 176–177° (lit.[17] 176–177°), showed an nmr spectrum with only one *t*-butyl absorption line at 1.39 (18 H), a weakly coupled (*J* = 0.5 Hz) aromatic methyl absorption at 2.05 (3 H), and a resolvable aromatic quartet (*J* = 0.5 Hz) at 7.57 (1 H) (calcd mol wt, 294.3; found (mass spectrum), 294).

Nitration of 3,5-Di-*t*-butyltoluene. Isolation of 2-Nitro- and 4-Nitro-3,5-di-*t*-butyltoluenes. 3,5-Di-*t*-butyltoluene (25 g) was nitrated in a mixture of glacial acetic acid and acetic anhydride as previously described.[17] Glpc analysis of the crude product, 22.5 g, indicated about 90% conversion. The major product (98.5%) was the 2-nitro isomer, mp 63–64° after recrystallization from

(26) S. Olsson, *Arkiv Kemi*, **14**, 85 (1959).

(27) The intensity of the strong absorption band of the hydrocarbon at 712 cm⁻¹ was measured with the aid of a Perkin-Elmer 112 spectrometer and the absorption was compared to that of a series of standard mixtures.

(28) S. J. Kuhn, *Can. J. Chem.*, **40**, 1660 (1962).

(29) S. Watari, *Bull. Chem. Soc. Japan*, **37**, 204 (1964).

(30) The product distribution was found to be: 2, 76.1%; 3, 5.7%; 4, 16.8%; 5, 1.4%. The band assigned to product 2 was very broad and the yield of 4 was low, indicating some conversion of 4 to 14; see text.

methanol. The minor component (with glpc retention time slightly longer) was concentrated in the recrystallization mother liquors. Preparative glpc (SE 30, 20 ft × $^3/_8$ in., 230°) yielded 60 mg of material identified as the 4-nitro isomer on the basis of its nmr spectrum which showed only one t-butyl absorption line at 1.36 (18 H), a broadened aromatic methyl line at 2.34 (3 H), and a barely resolvable aromatic quartet ($J = 0.3$ Hz) at 7.14 (2 H).[31]

Nitration of 2-Nitro-3,5-di-t-butyltoluene. Isolation of 4 and 5. A 250-ml flask containing 10.3 g of finely ground 7 was placed in an ice bath, and nitric acid (90%, 60 ml) was added dropwise to the magnetically stirred reactant. After 3 hr the reaction was allowed to come to room temperature, and after 18 hr reaction was terminated by pouring the mixture into 500 ml of cold water. The organic products were extracted with three portions (175 ml, total) of toluene, and the toluene extract was washed free of acid with water. Glpc analysis of the dried toluene solution indicated 99% conversion of the reactant to two products, 5 (93.5%) and 4 (6.5%). Recrystallization of the residue from ethanol–benzene afforded 5, mp 176–177° (lit.[17] mp 176–177°), identical with that isolated from the nitration of 1-NO₂. The mother liquor resulting from the recrystallization was concentrated, and the minor product was isolated by preparative glpc and shown to be identical in all respects with the product 4 isolated from the nitration of 1-NO₂.

3,5-Di-t-butyl-2,4,6-trinitrotoluene (14). A sample of 4 (0.80 g) was treated with 30 ml of mixed nitric and sulfuric acids (2:1) at room temperature for 4 days. At the end of this period the crystalline product which had formed was collected by suction filtration, washed free of acid, and recrystallized from ethanol–benzene to yield glistening platelets, 0.60 g, mp 171–173°. The nmr spectrum showed only one t-butyl absorption line at 1.48 (18 H) and an aromatic methyl at 2.10 (3 H). No aromatic proton absorption could be detected.

Anal. Calcd for $C_{15}H_{21}N_3O_6$: C, 53.09; H, 6.24; N, 12.38; mol wt, 339.4. Found: C, 53.26; H, 6.30; N, 12.40; mol wt (mass spectrum), 339.

1,3,5-Tri-t-butylbenzene-2,4,6-d_3 (1-H-d_3). The following procedure proved to be convenient. To a dry, two-necked 500-ml flask equipped with a condenser, drying tube, dropping funnel, and stirring bar, was added 24.6 (0.10 mol) of recrystallized, dried 1-H, 50 ml of dry carbon tetrachloride, and 157 g (0.75 mol) of trifluoroacetic anhydride (freshly distilled from phosphorus pentoxide). The flask was thoroughly cooled in an ice bath, and 15 g (0.75 mol) of deuterium oxide was added dropwise to the magnetically stirred mixture. After addition the flask was brought to room temperature, the condenser and dropping funnel were removed, and the stoppered flask was stirred for a period of 24–36 hr. The extent of exchange was monitored by withdrawing a small portion of the carbon tetrachloride layer and recording the nmr spectrum. Finally, the trifluoroacetic acid and carbon tetrachloride were removed by vacuum evaporation. Four additional equilibrations using 0.5-mol amounts of trifluoroacetic acid, prepared *in situ* as above, afforded 23.9 g of slightly colored crystalline product which was purified by four recrystallizations from absolute ethanol, mp 73–74°. Repetitive integration of the residual aromatic proton absorption *vs.* the t-butyl absorption indicated 97.1 ± 0.5% deuterium bound to aromatic carbon.[32]

2,4,6-Tri-t-butylnitrobenzene-3,5-d_2 (1-NO₂-d_2). This compound was prepared from 1-H-d_3 by nitration in acetic acid and acetic anhydride solutions.[7b] Nmr analysis of the purified product showed no change in deuterium content.

Product Distribution Studies in Nitration of 1-NO₂ and 1-NO₂-d_2. Product distribution studies reported in Table III were conducted in the following way. Samples of 1-NO₂ or 1-NO₂-d_2[33] (20–50 mg) were placed in small, round-bottomed flasks and thermostated. Nitric acid (90%, 1–2 ml) was added and the mixture stirred magnetically for the stated period. Reactions were quenched by addition of water and isolated by careful extraction with toluene.[34] After the toluene solution had been washed free of acid with water,

dried over sodium sulfate, and concentrated, product distribution data were obtained by glpc analysis.

Direct Kinetic Study of the Nitration of 1-NO₂ and 1-NO₂-d_2. Parallel kinetic runs in nitromethane solvent were conducted with the normal and deuterated tri-t-butylnitrobenzenes. To two thermostated (40°) flasks containing, respectively, 10.0 ml of a nitromethane solution of 1-NO₂ and 1-NO₂-d_2 (4 × 10⁻³ M) was added 10.0 ml of a temperature-equilibrated solution made by mixing 20 ml of nitromethane, 20 ml of 90% nitric acid, and 1 ml of 96% sulfuric acid. The resulting solutions were thoroughly mixed and carefully inspected for homogeneity. Aliquots were withdrawn periodically and quenched by addition to ice water. The organic products were carefully extracted with toluene, and the toluene layer, after counter-extraction with water and drying, was analyzed by glpc. Area per cents of unconsumed reactant and products were measured, and, after conversion to mole per cents, the log of the mole fraction of remaining reactant was plotted *vs.* time (Figure 1).

Product distribution studies were also made with aliquots from the direct kinetic run. These data permitted an intercomparison of the observed kinetic isotope effect with the observed distribution isotope effect.

2,4,6-Tri-t-butylfluorobenzene-3,5-d_2 (1-F-d_2). Exactly 2.00 g of rigorously purified 2,4,6-tri-t-butylnitrobenzene-3,5-d_2 was reduced with 1% sodium amalgam (120 g) and 40 ml of absolute methanol to yield the corresponding amine (1.67 g, 99% pure) in a 2-hr period.[7b] The amine was then converted to the corresponding fluoride in 36% yield (no detectable hydrocarbon impurity) by low-temperature (−10°) diazotization in 48% hydrofluoric acid.[9] Nmr analysis indicated at least 95% deuteration at aromatic carbon.[35]

Product Distribution Studies in the Nitration of 1-F and 1-F-d_2. Parallel nitrations were conducted by dissolving 20-mg samples of the appropriate aryl fluoride in 1.00 ml of a nitromethane and 90% nitric acid solution (70:30 by volume). The paired reactions were maintained at the specified temperature for the same period of time and then quenched by addition of about 8 ml of water. Organic products were extracted with cyclohexane, and after being counter-extracted with water and dried, the cyclohexane solutions were analyzed by glpc.

2,4,6-Tri-t-butyltoluene (1-CH₃) and 2,4,6-Tri-t-butyltoluene-3,5-d_2 (1-CH-d_2). These compounds were prepared by conversion of the appropriate tri-t-butylbromobenzene[4a] to the corresponding aryllithium derivative by treatment with n-butyllithium and then to the desired toluene by reaction of the aryllithium with methyl iodide.[36] The product from this reaction sequence was invariably contaminated with 1,3,5-tri-t-butylbenzene and 2,4,6-tri-t-butylbromobenzene, plus a component believed to be 1-n-butyl-2,4,6-tri-t-butylbenzene, Some of these impurities, particularly the parent hydrocarbon, were not efficiently removed by crystallization. Consequently purification of material for product distribution studies was effected by preparative glpc. Nmr analysis of the deuterated derivative indicated at least 97% deuterium bound to aromatic carbon.[37]

Nitration of 2,4,6-Tri-t-butyltoluene (1-CH₃) in Nitromethane. Characterization of Products. A sample of 1-CH₃ (3.10 g, 11 mmol) was dissolved in 150 ml of nitromethane at about 60° and then partially precipitated as a fine suspension by cooling to 0°. To the suspension was added 25 ml of a solution of 90% nitric acid and nitromethane (3:7 by volume), and the mixture was stirred magnetically for 4 hr at ice bath temperature. Glpc analysis of an aliquot at this time revealed only partial reaction. The nitration was continued for an additional 48-hr period at room temperature. At this time the nitromethane solution (some suspended material) was poured into about 1 l. of water; the layers were made homogeneous by careful addition of ammonia, and the organic products were extracted with cyclohexane (200 ml, total). After being extracted with water and dried over sodium sulfate, the cyclohexane was evaporated yielding 2.97 g of crude product. Glpc analysis (SE 30, 6 ft × 0.25 in., 210°) showed >98% reaction of the 1-CH₃ and three major products which were identified (see below) as: 2-nitro-4,6-di-t-butyltoluene (11), 5.2 min; 4-nitro-2,6-di-t-butyl-

(31) The nmr spectrum of the 2-nitro isomer is consistent with the previous structural assignment:[17] two t-butyl absorption lines at 1.32 (9 H) and 1.36 (9 H), a broadened aromatic methyl at 2.20 (3 H), and *meta* aromatic protons, broadened doublets centered at 7.06 (1 H) and 7.32 (1 H), $J = 3$ Hz.

(32) Another preparation used in these studies had 95.0 ± 0.4% deuterium bound to aromatic carbon.

(33) Samples used in these studies had 95.0 ± 0.5% deuterium at aromatic carbon.

(34) Control experiments were conducted to ensure complete extraction of nitration products.

(35) Acid-induced hydrogen exchange of 1-F or its precursor, 2,4,6-tri-t-butylaniline, could not be effected without extensive protodealkylation.

(36) W. A. Gibbons and G. Fischer, *Tetrahedron Letters*, 43 (1964).

(37) Protodealkylation of tri-t-butyltoluene occurs much more rapidly than hydrogen exchange. This consideration dictated the method of synthesis of 1-CH₃-d_2.

toluene (12), 9.0 min; and 3-nitro-2,4,6-tri-*t*-butyltoluene (13), 11.1 min.

3-Nitro-2,4,6-tri-*t*-butyltoluene (13) was isolated by trituration of the crude reaction product with hot methanol followed by filtration. The residue collected (0.85 g) was recrystallized from toluene–ethanol with poor recovery yielding 0.19 g, mp 253–255°. The nmr spectrum showed three *t*-butyl absorption lines at 1.33 (9 H), 1.49 (9 H), and 1.55 (9 H), an aromatic methyl at 2.67 (3 H), and an aromatic proton at 7.66 (1 H).

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 75.66; H, 9.84; N, 4.41. Found: C, 75.29; H, 10.06; N, 4.49.

4-Nitro-2,6-di-*t*-butyltoluene (12) was isolated in pure form by preparative glpc of the concentrated mother liquor. Crystallization of the 500 mg isolated, from 3 ml of absolute ethanol, yielded 320 mg of faintly yellow silken spars, mp 119–120°. The nmr spectrum showed only one *t*-butyl absorption line at 1.54 (18 H), an aromatic methyl absorption at 2.76 (3 H), and one aromatic absorption at 8.31 (2 H).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.61. Found: C, 72.49; H, 9.57; N, 5.89.

2-Nitro-4,6-di-*t*-butyltoluene (11) was also isolated by preparative glpc.[38] The nmr spectrum showed two *t*-butyl absorption lines at 1.32 (9 H) and 1.50 (9 H), an aromatic methyl at 2.51 (3 H), and an AB ($J = 2$ Hz) aromatic quartet with doublet lines centered at

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(38) Column chromatography over alumina with pentane elution gave fair separation of the isomers, 11 being eluted shortly before 12.

7.50 (1 H) and 8.70 (1 H) indicating nonequivalent *meta*-oriented aromatic protons.

Product Distributions in Nitration of 1-CH_3 and 1-CH_3-d_2. Three milliliters of a precooled solution of nitric acid in nitromethane (3:7) was added to flasks containing 3.00 ml of stock solutions of 1-CH_3 or 1-CH_3-d_2 (1.5×10^{-2} M in nitromethane) which were held at 0° in a large dewar. A noticeable brown color developed in all of the reaction solutions upon addition of the colorless nitrating solution, and this color disappeared as the reaction proceeded. After a 1-hr reaction period, the contents of each flask were poured into about 50 ml of water, and nitration products were extracted with 5.00 ml of purified toluene. Residual nitromethane was removed by extraction of the toluene solutions with dilute aqueous ammonia and the dried toluene solutions, after concentration, were subjected to glpc analysis.

Reactions of Cyclohexadienyl Cations. Aromatic Acetoxylation Accompanying Halogenation[1]

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Abstract: Halogenation of 1,3,5-tri-*t*-butylbenzene and other alkylbenzenes with positive halogenating agents in acetic acid solvent results in the formation of aryl acetate products. Yields of aryl acetates increase upon addition of sodium acetate to the solvent. Data derived from studies of product distributions, kinetic isotope effects, and structural effects indicate that acetoxylation accompanying halogenation occurs by addition–elimination.

Some time ago we reported that the silver ion induced bromination of 1,3,5-tri-*t*-butylbenzene proceeds with a slow proton transfer from aromatic carbon.[3] This result represented one of the first observations of a rate-limiting proton transfer in aromatic bromination of a benzene system, and it was suggested at that time that the change-over in rate-limiting step was due to the large steric repulsion effects imposed around the reaction site by the *t*-butyl substituents. This view seems amply supported by subsequent studies of aromatic bromination of this and related systems and also by studies of other aromatic substitution reactions.[4,5]

During this interval we have attempted to examine the effects of changing the concentration of solvent acid–base species on the isotope effect in bromination of 1,3,5-tri-*t*-butylbenzene. These and supporting studies have shown that bromination of this hydrocarbon is considerably more complex than originally proposed. Of perhaps greatest interest is the observation that significant quantities of acetoxylation product accompany aromatic halogenation in acetic acid solutions containing added acetate ion. In this report we describe product distribution and kinetic isotope effect studies in the bromination and chlorination of 1,3,5-tri-*t*-butylbenzene and some related compounds, and discuss the attending acetoxylation reaction in terms of the long-discarded but recently revitalized addition–elimination mechanism of aromatic substitution.

(1) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) (a) Petroleum Research Fund Undergraduate Research Participant; (b) National Science Foundation Undergraduate Research Participant.

(3) P. C. Myhre, *Acta Chem. Scand.*, 14, 219 (1960).

(4) (a) E. Baciocchi, G. Illuminati, G. Sleiter, and F. Stegel, *J. Am. Chem. Soc.*, 89, 125 (1967); (b) M. Christen and H. Zollinger, *Helv. Chim. Acta*, 45, 2066 (1962); (c) E. Helgstrand, *Acta Chem. Scand.*, 18, 1616 (1964); 19, 1583 (1965); (d) E. Helgstrand and Å. Nilsson, *ibid.*, 20, 1463 (1966); (e) Å. Nilsson, *ibid.*, 21, 2423 (1967).

(5) The occurrence of rate-limiting proton transfers in aromatic nitration of benzene derivatives has also been attributed to increasing steric effects; see P. C. Myhre, M. Beug, and L. James, *J. Am. Chem. Soc.*, 90, 2105 (1968).