

465. Secondary Hydrogen Isotope Effects. Part III.¹ The Mechanism of N-Nitration

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A preliminary kinetic study of the *N*-nitration of *N*-methyl-2,4,6-trinitroaniline in aqueous strong acid showed that deuteration of the methyl group causes a very slight depression of the apparent nucleophilic reactivity of the substrate, although its basicity is increased by some 11%. The suspicion that attack by NO_2^+ might not be rate-determining in these conditions, has now been confirmed as follows:

The rate of nitration of the parent compound, which has a rapidly exchangeable amino hydrogen atom, was measured separately in $\text{H}_2\text{SO}_4\text{-H}_2\text{O}$ and $\text{D}_2\text{SO}_4\text{-D}_2\text{O}$. The solvent isotope effect was eliminated by comparing the rates in the two media under conditions of equal nitrating power, as measured by the rate of *C*-nitration of a reference aromatic compound, toluene- α -sulphonic acid. The primary isotope effect, $k(\text{H})/k(\text{D})$, rises smoothly from 1.0 to 4.8 as the acidity of the medium increases, indicating that proton abstraction, rapid at low acidities, has become rate-controlling in solutions of high nitrating power.

A re-investigation of the effect of methyl deuteration reveals the expected inverse secondary isotope effect, which decreases smoothly from *ca.* 19% in conditions of rate-controlling addition of NO_2^+ , and is eventually reversed to the previously observed slight normal effect (*ca.* 2%) when proton abstraction is rate-limiting.

SHORTLY after it had been observed that α -deuteration decreases the acidity of phenylacetic acid and increases the basicity of benzylamine, and this isotope effect on acid and base strength had been interpreted in terms of effectively greater inductive electron release from deuterium,^{2,3} an attempt was made to obtain a similar "inductive" secondary isotope effect in a kinetic system.⁴ This attempt failed, and (since evidence for "inductive" secondary isotope effects on the rates of several reactions has since been reported from several laboratories *) was never published in full. These negative results will here be outlined briefly, because they constitute what is, to our knowledge, the first instance of a failure to observe an expected secondary isotope effect that has occasioned the re-investigation and modification of a generally accepted mechanism, in the present instance that of nitration at a nitrogen atom. The principal object of this Paper is to describe the subsequent re-investigation, and the eventual confirmation of its conclusions by the appearance of the elusive secondary isotope effect under just those conditions in which the modified mechanism would predict it to occur.

*Summary of Early Results.*⁴—(a) *C-Nitration.* We first attempted to observe a kinetic secondary isotope effect in the "inductive" direction in an aromatic nitration, *i.e.*, that of toluene- α -sulphonic (I) acid added as its sodium salt, under the aqueous acid conditions of Halberstadt, Hughes, and Ingold,⁶ that is, in an aqueous mixture of nitric and perchloric acids). In media of the approximate molar composition $\text{HClO}_4:\text{HNO}_3:\text{H}_2\text{O} =$

* For references, see Part I of this series³ and a recent critical review by one of us.⁵

¹ Part II, E. Halevi and M. Nussim, *J.*, 1963, 876.

² Halevi and Nussim, *Bull. Res. Council Israel*, 1956, 5, A, 263; Halevi, *Tetrahedron*, 1957, 1, 174.

³ Halevi, Nussim, and Ron, *J.*, 1963, 866.

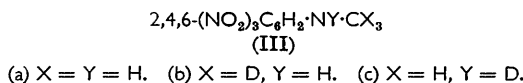
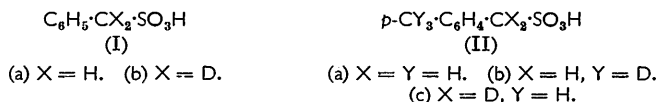
⁴ Ron, M.S. Thesis, Israel Institute of Technology, Haifa, 1958.

⁵ Halevi, in "Progress in Physical Organic Chemistry, vol. I," eds. Cohen, Streitwieser, and Taft, Interscience, New York, 1963, pp. 109—221.

⁶ Halberstadt, Hughes, and Ingold, *J.*, 1950, 2441.

3 : 4 : 18, the rates of nitration at 35° of the acids (Ia and b) were the same within the precision of our dilatometric method ($\pm ca. 2\%$). The nitration was clearly of first order, and (Ib) was shown separately not to exchange its deuterium atoms with the solvent under the conditions of nitration.

In order to ascertain whether side-chain deuteration affected the reactivity of different nuclear positions differently, the rates of nitration of the *p*-methyl acids (IIa, b, and c) were compared. One can assume predominant nitration *ortho* to the methyl group, *i.e.*, respectively *ortho* and *meta* to the deuterated side-chain in (IIb and c); yet all three isotopic variants reacted at identical rates within the precision of our method. At about this time, Swain, Knee, and Kresge⁷ showed, by means of a much more precise competitive method, that side-chain tritiation of toluene does not affect its nitration rate, so our work on aromatic nitration was discontinued.*



(b) *N*-Nitration. *N*-Methyl-2,4,6-trinitroaniline (IIIa) is nitrated to form tetryl at rates similar to those at which toluene- α -sulphonic acid is nitrated. The nitration rates of compounds (IIIa and b) were compared in the expectation that the presumably enhanced basicity of the deuterated methyl aniline (IIIb) would also render it a better nucleophile, so that it would undergo nitration more rapidly. The starting material absorbs strongly ($\log \epsilon = 4.1$) at 425 m μ , so that the rate of its disappearance could be followed spectrophotometrically with ease and accuracy. In solutions of the approximate molar composition $\text{HClO}_4 : \text{HNO}_3 : \text{H}_2\text{O} = 14 : 11 : 75$, the relative nitration rates of compounds (IIa) (k_{H}^{N}) and (IIb) (k_{D}^{N}) were $k_{\text{H}}^{\text{N}}/k_{\text{D}}^{\text{N}} = 1.02 \pm 0.01$, indicating that methyl deuteration has an unexpected slight overall retarding effect on the rate of nitration.

In order to eliminate the suspicion that methyl deuteration in this system does not enhance basicity, the basic dissociation constants of the two compounds were measured, and it was found⁸ that compound (IIIb) is indeed some 11% more basic than compound (IIIa), as expected ($\text{p}K_{\text{a}}$ (IIIa) = -5.83 ; $\text{p}K_{\text{a}}$ (IIIb) = -5.78 at 33°). Moreover, this basicity is low enough for only a very small fraction of the base to be protonated in our nitration media; consequently, the observed retardation could not be ascribed to an isotope-dependent reduction of the concentration of the reactive free base.

Our conclusion could only be that some essential element was lacking in our understanding either of secondary isotope effects or of the mechanism of *N*-nitration; as might be expected, we elected to examine the second alternative.

The Mechanism of N-Nitration.—There can be very little doubt about the basic correctness of the mechanistic scheme outlined by Hughes, Ingold, and Pearson.¹⁰ Under our highly aqueous conditions, in which the equilibrium between nitric acid and nitronium ion

* Suhr and Zollinger⁸ have since demonstrated that the *meta*-position of $\alpha\alpha\alpha$ -trideuterotoluene, where inductive effects should operate unopposed by hyperconjugation, is indeed slightly activated. They, and also Eastham, Bloomer, and Hudson,⁹ have confirmed the lack of an isotope effect in the *ortho*- and *para*-positions. The arguments of the latter authors that there is no effect in the *meta*-position are based on an improper analogy between the effects of nuclear and side chain deuteration.⁵

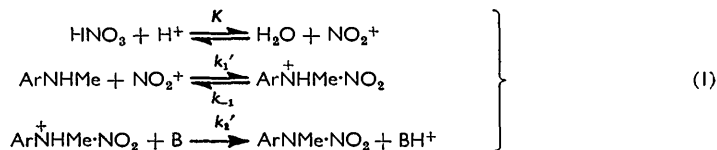
⁷ Swain, Knee, and Kresge, *J. Amer. Chem. Soc.*, 1957, **79**, 505.

⁸ Suhr and Zollinger, *Helv. Chim. Acta*, 1961, **44**, 1011.

⁹ Eastham, Bloomer, and Hudson, *Tetrahedron*, 1962, **18**, 653.

¹⁰ Hughes, Ingold, and Pearson, *J.*, 1958, 4357.

is maintained so that nitration is of first order with respect to the substrate, their mechanism can be rewritten as



This formulation differs from that of Hughes, Ingold, and Pearson in only one essential: it does not discount, *a priori*, the possibility that the rate of proton abstraction may be slow relative to reversion of the intermediate to the substrate and nitronium ion.

The application of the conventional steady-state treatment leads to an expression for the second-order rate coefficient (k^N). [Actually, this is the experimental first-order rate coefficient ($k^N_{(1)}$) divided by the stoichiometric concentration of nitric acid]:

$$k^N = - \frac{1}{[\text{ArNHCH}_3][\text{HNO}_3]} \frac{d[\text{ArNHCH}_3]}{dt} = \frac{k_1'([\text{NO}_2^+]/[\text{HNO}_3])k_2'[\text{B}]}{k_{-1} + k_2'[\text{B}]} \quad (2)$$

Equation 2 can be condensed to

$$k^N = \frac{k_1 k_2}{k_{-1} + k_2} \quad (3)$$

in which k_1 includes the $[\text{NO}_2^+]:[\text{HNO}_3]$ ratio, and thus increases rapidly with acidity, whereas k_2 includes the concentration of base required for proton abstraction. In our conditions, this base would principally be water, with some participation by the anion of the strong acid, so k_2 should decrease as acidity increases.

Our failure to observe an increased k^N with the methyl-deuterated substrate (IIIb) could not be rationalised so long as we maintained the analogy with *C*-nitration, according to which $k_2 \gg k_{-1}$, equation (3) reduces to:

$$k^N = k_1, \quad (4)$$

and k^N is thus a genuine measure of nucleophilicity. On the other hand, if in our conditions, $k_{-1} \gg k_2$, the limiting expression becomes

$$k^N = \frac{k_1}{k_{-1}} k_2 = K_1 k_2. \quad (5)$$

K_1 , the equilibrium constant for reversible formation of the intermediate, should increase with the nucleophilic power of the substrate, but any substituent effect tending to increase the basicity (and nucleophilicity) of the amino nitrogen atom would tend to depress k_2 , the rate coefficient for proton abstraction. If the latter effect slightly overbalanced the former, our 2% secondary isotope effect in the "wrong" direction could be rationalised.

There are several indications in the literature that k_{-1} and k_2 may indeed be of comparable magnitude. For example, Williams and Simkins¹¹ have raised doubts about the analogy between the timing of the steps in *N*- and *C*-nitration on the basis of their kinetic study of nitration of guanidine and denitration of nitroguanidine. In their recent study of the closely related *N*-nitrosation reaction, Challis and Ridd¹² have shown that the dependence on acidity of the rate of diazotisation of aniline, and also the relative rates in sulphuric and deuteriosulphuric acids, strongly suggest that proton abstraction has become rate-determining at high acidities.

Neither of the two classical criteria for determining the timing of the steps in nucleophilic substitution, general base catalysis¹³ and primary hydrogen-isotope effects,^{13,14} is

¹¹ Williams and Simkins, *J.*, 1953, 1386.

¹² Challis and Ridd, *Proc. Chem. Soc.*, 1960, 245.

¹³ Ernst, Stamm, and Zollinger, *Helv. Chim. Acta*, 1958, **41**, 2274; Zollinger, "Diazo and Azo Chemistry," Interscience, New York, 1961, pp. 233-238.

¹⁴ Melander, *Arkiv. Kemi*, 1950, **2**, 211; "Isotope Effects on Reaction Rates," Ronald, New York, 1960, pp. 107 ff.

simply applicable to our system. The demonstration of general base catalysis in concentrated aqueous acid would be difficult. A study of a primary isotope effect requires a comparison of the rates of nitration of compounds (IIIa and c), but the amino deuterium atom of the latter, like those of *N*-deuterated aniline in the nitrosation study by Challis and Ridd,¹² exchanges instantaneously with the solvent. Consequently, compound (IIIc) must be nitrated in a fully deuterated solvent, and any observed isotope effect would then include not only that on proton abstraction, but an indeterminate solvent isotope effect as well.

de la Mare¹⁵ has kindly pointed out how the solvent isotope effect could be circumvented. Our procedure, based on his suggestion, calls for a comparison of the rates of *N*-nitration of compounds (IIIa and c) respectively in protio- and deutero-media of equal nitrating power, as calibrated by the rate of *C*-nitration of a suitable aromatic reference compound.

The Reference Compound and the Choice of Experimental Conditions.—Toluene- α -sulphonic acid (Ia) was chosen as the reference compound, because it is soluble in the nitration medium and is nitrated at a convenient rate. Under strongly acid conditions, it might undergo nuclear or perhaps even methylene-hydrogen exchange with the medium, but in the absence of appreciable primary¹⁴ or secondary isotope effects on *C*-nitration, such exchange would hardly constitute a drawback.

An experimental difficulty was that neither compound (Ia) nor its mononitration products absorb appreciably in the visible range. The nitration rate could best be determined spectrophotometrically by following the increase of the absorption of the product at 260 μ , where nitric acid has a moderately weak absorption. Consequently, the concentration of nitric acid had to be kept as low as possible, but still high enough ($\cong 0.03M$) relative to that of the substrate ($\cong 0.002M$) to be regarded as being in effectively constant excess. In order to render the nitration rate measurable, the acidity had to be raised considerably; for convenience in the preparation of the deuterated media, we used sulphuric rather than perchloric acid.

Another more fundamental question, raised many years ago by Ingold, Ingold, and Shaw,¹⁶ is whether toluenesulphonic acid or its anion is the species undergoing nitration. Reasoning on the basis of the distribution of isomers in the product, these authors favoured the anion as the reactive species, particularly as sulphonic acids are so strong as to be completely dissociated in aqueous solution. Although their acid strengths are generally not great enough ($pK_a = 0$ to $+3$)¹⁷ for more than a small fraction of the anion to survive protonation in our highly acidic solutions, the reactivity of the anion might well be sufficiently greater than that of the free acid to outweigh its lower relative concentration. The identification of the reactive species is a matter of some importance, since the acid (Ia) is a good reference compound only if the free sulphonic acid is the reactant. Otherwise, we should have to correct the rate for the decreasing concentration of the reactive anion as the acidity of the medium is increased. The point was settled in favour of the free sulphonic acid, as follows:

Conventionally, the logarithm of the true nitration rate should be linear with respect to $(-H_R)$ with near unit slope.* The experimental rate coefficient (k^C) should show a similar dependence if the free sulphonic acid is the reactive species. If it reacts as the anion, the decrease in relative concentration (on a logarithmic scale) should follow $(-H_-)$

* We are using Deno's¹⁸ symbol for this function, which has also been denoted by J_0 and C_0 . For a discussion of acidity functions and their use as mechanistic criteria, see the two reviews by Paul and Long.¹⁹

¹⁵ de la Mare, cited by Ingold, personal communication, October 1958.

¹⁶ Ingold, Ingold, and Shaw, *J.*, 1927, 813.

¹⁷ Kortüm, Vogel, and Andrussov, "Dissociation Constants of Organic Acids in Aqueous Solutions," Butterworths, London, 1961, pp. 465–466.

¹⁸ Deno, Berkheimer, Evans, and Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 6534.

¹⁹ (a) Paul and Long, *Chem. Rev.*, 1957, **57**, 1; (b) Long and Paul, *ibid.*, p. 935.

or—to reasonably good approximation—($-H_0$), so that $\log k^0$ should be linear, with near unit slope, with respect to $(H_0 - H_R)$.

The relevant plots, made from the data in the fourth column of Table 1a are shown in Figure 1. The plot against $(H_0 - H_R)$ is nearly linear, but its slope is much too great. That against $(-H_R)$ is also adequately linear, and although closer to unity, its slope is still about 40% too great. This, however, is just the general behaviour that Deno and Stein²⁰ observed in 65–85% sulphuric acid, where the acid-dependence of the logarithms of the rates of nitration of a variety of substrates was invariably 35–50% higher than predicted by simple dependence on H_R .

There can remain no reasonable doubt that the sulphonate has not only been largely converted to the free acid, but that the latter is the reactive species. Consequently,

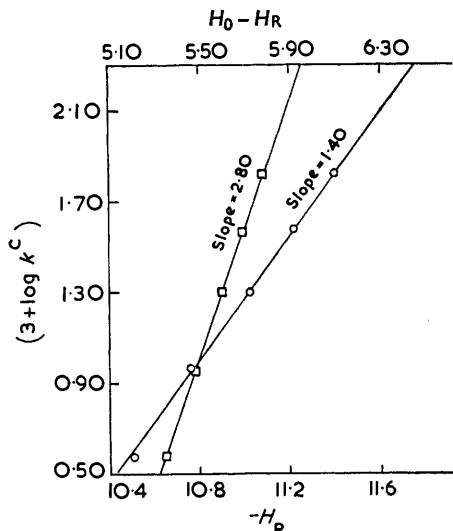


FIGURE 1. Acidity function dependence of $\log k^0$
 □, plot against $H_0 - H_R$; ○, plot against $-H_R$

the acid (Ia) was regarded as an acceptable reference compound for calibrating our nitration media.

Isotope Effects on N-Nitration.—(a) *The protonation correction.* An additional complication was that in the strongly acid solutions with which we were obliged to work, *N*-methyl-2,4,6-trinitroaniline is partly protonated. The experimental rate constant k^N_{exp} , which refers to the stoichiometric amine concentration, [B], must be corrected for protonation in the usual manner:^{19b}

$$k^N = k^N_{\text{exp}} \frac{[B]}{[B]} \quad (6)$$

$$k^N = k^N_{\text{exp}} (1 + h_0/K_a),$$

in which $h_0 = \text{antilog}(-H_0)$ and K_a is the dissociation constant of the conjugate acid of the aniline. The pK_a values of compounds (IIIa and b) were available, that of compound (IIIc) in D_2SO_4 - D_2O was determined as described³ in Part I by using Högfeldt and Bigeleisen's²¹ values of D_0 , and found to be -5.67 at 33° . It might be noted that whereas all the pK_a values are anchored to Paul and Long's H_0 scale, the protonation correction in equation (6) is not; this is because the experimentally determined quantity is $(H_0 - pK_a)$, and a shift of the H_0 scale would cause a corresponding shift in pK_a , leaving the ratio h_0/K_a unaltered.

²⁰ Deno and Stein, *J. Amer. Chem. Soc.*, 1956, **78**, 578.

²¹ Högfeldt and Bigeleisen, *J. Amer. Chem. Soc.*, 1960, **82**, 15.

(b) *The primary isotope effect.* The results for the *N*- and *C*-nitrations in the two media are given in Table I, along with the relevant auxiliary values. Two ways of presenting the results are plots of $1/k^N$ against $1/k^C$ or simply of k^N against k^C . The two pre-

TABLE I

Rates of *N*- and *C*-nitration in deuterated and normal media at 33.0°(a) H₂SO₄-H₂O solutions

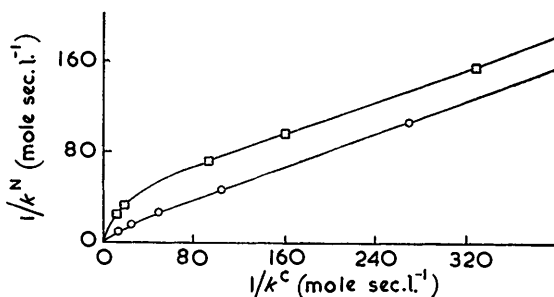
[H ₂ SO ₄] (mole/l.)	-H ₀ §	[HNO ₃] (mole/l.)	10 ² × k ^C ₍₁₎ * (min. ⁻¹)	10 ² × k ^N ₍₁₎ * † (min. ⁻¹)
10.55	5.173	0.0348	0.764 ± 0.014	1.533 ± 0.038
10.78	5.308	0.0337	1.935 ± 0.001	3.283 ± 0.049
11.05	5.453	0.0333	4.008 ± 0.200	4.918 ± 0.019
11.20	5.520	0.0321	7.255 ± 0.027	7.395 ± 0.031
11.35	5.599	0.0333	13.16 ± 0.01	11.86 ± 0.20

(b) D₂SO₄-D₂O solutions

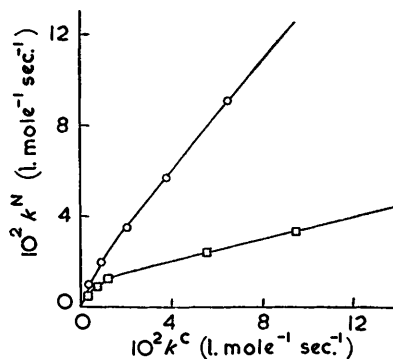
[D ₂ SO ₄] (mole/l.)	-D ₀	[DNO ₃] (mole/l.)	10 ² × k ^C ₍₁₎ * (min. ⁻¹)	10 ² × k ^N ₍₁₎ * † (min. ⁻¹)
10.50	5.150	0.0329	0.596 ± 0.006	0.958 ± 0.022
10.58	5.185	0.0332	1.182 †	1.442 †
10.80	5.310	0.0316	2.010 ± 0.012	1.717 ± 0.000
11.09	5.450	0.0357	12.25 ± 0.35	4.018 ± 0.040
11.18	5.500	0.0316	18.44 ± 0.28	4.535 ± 0.076

* Values of experimental first-order rate coefficients and average deviation from mean of duplicate determinations. † A single determination. ‡ Uncorrected for partial protonation. § Interpolated from values in ref. 19a. || Interpolated from values in ref. 21.

sentations, shown in Figures 2 and 3, are complementary rather than redundant, since each expands a different region of the acidity range. The fact that both plots are curved is in

FIGURE 2. Plot of $1/k^N$ against $1/k^C$ in light and heavy media

□, deuterated media. ○, undeuterated media

FIGURE 3. Plot of k^N against k^C in light and heavy media

□, deuterated media. ○, undeuterated media

itself sufficient evidence that *N*-nitration differs from *C*-nitration in that its intermediate is formed in a step that is reversible to a varying extent in media of varying composition.

Let us consider Figure 2 more closely. Equations (3) and (5) require that

$$\frac{1}{k^N} = \frac{1}{k_1} + \frac{1}{K_1 k_2} \quad (7)$$

At large values of $1/k^C$, *i.e.*, in media of low nitrating power and relatively rapid proton abstraction, $1/k^N$ becomes a linear function of $1/k_1$. The fact that Figure 2 shows it to be a linear function of $1/k^C$, requires $1/k_1$ and $1/k^C$ to be linear with respect to one another. Moreover, since in the limit of very weak acid (*cf.* Figure 3) k_1 and k^C necessarily tend to

zero together, they, and their reciprocals, must simply be proportional to one another. If we now note that the slopes of the linear portions of the plots in Figure 2 for the deuterated and normal acid solutions are identical, we must conclude that the constant of proportionality between k_1 and k^0 is the same. In other words, the comparison of N -nitration rates in isotopic solutions of equal k^0 is equivalent to comparing them under conditions of equal k_1 .

At high values of k^0 , equation (3) reduces to equation (5). There is no *a priori* reason to expect the product ($K_1 k_2$) to be as linear in k^0 as it turns out to be in Figure 3.* However, the approximate linearity over our narrow acidity range allows us to identify the ratio of the slopes of the "linear" parts, with the isotopic ratio, $(K_1 k_2)_H / (K_1 k_2)_D$. The solvent isotope effect on K_1 should be very similar to that on k_1 , and so should nearly cancel. This is because the former depends on the equilibrium between the substrate and the intermediate, whereas the latter depends on the quasi-equilibrium between the same substrate and the transition state immediately preceding the intermediate and very similar to it in structure and charge distribution. The limiting slope ratio ("Slope" H/

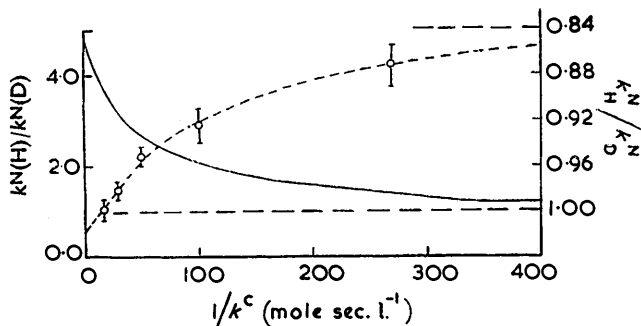


FIGURE 4. Primary and secondary isotope effects on N -nitration. —, Primary effect $k^N(H)/k^N(D)$ (constructed from Figures 2 and 3). ---, secondary effect k_H^N/k_D^N

"Slope" D = 4.8) would thus seem to be a good estimate of the isotope effect on the proton abstraction step.

Alternatively, we can plot the $k^N(H)/k^N(D)$ ratio, constructed from Figures 2 and 3, directly as a function of k^0 or $1/k^0$. From the latter plot, shown in Figure 4 it is seen that $k^N(H)/k^N(D)$ can be extrapolated to a value of 4.8 in conditions of rapid nitration, and falls smoothly to an asymptotic value of unity as the nitrating power of the solution decreases and proton abstraction ceases to be rate-determining. One further comment might be added: although a primary isotope effect of 4.8 is more than ample to demonstrate rate-limiting proton transfer, its absolute magnitude cannot tell us much about the extent of bond rupture in the transition state. This is because, although we have eliminated the solvent isotope effect on k_1 , and presumably on K_1 , we have not eliminated that on k_2 ; this may be considerable, since proton abstraction is effected primarily by water in one case and by deuterium oxide in the other.

The Secondary Isotope Effect.—The predictions that can be made from our modification of the Hughes, Ingold, and Pearson¹⁰ mechanism are self-evident: in conditions of rapid nitration (low $1/k^0$ and large primary isotope effect) the secondary isotope effect reflects the effect of methyl deuteration on the product $K_1 k_2$. Since K_1 should increase with electron

* This linearity is in fact somewhat disturbing, since it requires the k_2/k_{-1} ratio, having decreased enough at lower acidities to ensure rate-determining proton abstraction, to remain effectively constant in more concentrated acid. A possible rationalisation is that removal of either H^+ or NO_2^+ requires solvation by at least one water molecule. If, because of the more effective hydration of H_3O^+ , proton removal benefits more than that of NO_2^+ from the availability of additional water molecules, it can be understood why the k_2/k_{-1} ratio decreases at first as the availability of the additional water molecules decreases, but remains constant at acid concentrations in which no more than a single free molecule of water is available.

accession to the nitrogen atom and k_2 should decrease, there could remain a net residual effect in either direction. This, of course, was the rationalisation of the small effect in the "wrong" direction ($k_{\text{H}}^{\text{N}}/k_{\text{D}}^{\text{N}} = 1.02 \pm 0.01$) observed in the preliminary study that led to the present investigation. The modified mechanism now requires the missing inverse secondary isotope effect on k_1 to appear under conditions of slow nitration, where the primary isotope effect vanishes. The nitration rates of compounds (IIIa and b) under identical conditions are given in Table 2, and their ratio is plotted in Figure 4 against

TABLE 2
Relative rates of nitration of methyl deuterated (IIIb) and normal (IIIa)
N-methyl-2,4,6-trinitroaniline at 33.0°

[H ₂ SO ₄] * (mole/l.)	10 ² × k^{C} † (l./mole sec.)	10 ² × k_{H}^{N} † (l./mole sec.)	10 ² × k_{D}^{N} †‡ (l./mole. sec.)	$k_{\text{H}}^{\text{N}}/k_{\text{D}}^{\text{N}}$
10.55	0.366 ± 0.007	0.900 ± 0.030	1.04 ± 0.00	0.868 ± 0.033
10.78	0.957 ± 0.000	2.11 ± 0.05	2.28 ± 0.02	0.922 ± 0.025
11.05	2.00 ± 0.10	3.49 ± 0.02	3.68 ± 0.06	0.949 ± 0.007
11.20	3.75 ± 0.01	5.73 ± 0.03	5.85 ± 0.03	0.980 ± 0.010
11.35	6.51 ± 0.01	10.37 ± 0.15	10.49 ± 0.00	0.989 ± 0.016

* These are the same solutions as in Table 1a. † The first-order coefficients were converted to the corresponding second-order coefficients and, for the nitroanilines, also corrected for partial protonation, as described in the text. ‡ Determined on a portion of the same solution as the undeuterated substrate, and similarly corrected for protonation by using the pK_{a} of compound (IIIb) (−5.78) as determined³ in Part I.

the same abscissa as the primary isotope effect. It is seen to change smoothly over our measured range from near zero when the primary isotope effect is large to an inverse effect of about 15% in the slowest nitrating solution employed. The limiting value for the secondary isotope effect on (K_1k_2), obtained from an extrapolation to $1/k^{\text{C}} = 0$ in Figure 4, is about $k_{\text{H}}^{\text{N}}/k_{\text{D}}^{\text{N}} = 1.02$. An extrapolation to $k^{\text{C}} = 0$ of a similar plot (not shown) of $k_{\text{H}}^{\text{N}}/k_{\text{D}}^{\text{N}}$ against k^{C} , yields $k_{\text{H}}/k_{\text{D}} = 0.84$ as the isotope effect on k_1 . In Figure 4, this value is approached asymptotically as $1/k^{\text{C}}$ tends to infinity.

Conclusions.—The modified mechanism of N-nitration in aqueous acid media outlined in equation (1) is thus established. It is of interest that proton abstraction should begin to become rate-determining in the same acidity region (>60% sulphuric acid) as in nitrosation,¹² in which the electrophilic power and relative concentration of the reagent, as well as the basicity and extent of protonation of the substrate, are quite different. Since k_2 depends on the availability of water in the solvent, it must fall when the activity of water decreases strongly, as occurs in just these concentrations.²² If the stable form of the hydrated proton²³ is $\text{H}(\text{H}_2\text{O})_4^+$, one would indeed expect the availability of free water to decrease sharply at concentrations above 58% sulphuric acid, corresponding to a ratio of four water molecules to one of sulphuric acid.

For the purpose of the present series of Papers, the most significant result of this investigation is the fact that the predictive power of secondary isotope effects, which must be established before they can become genuine criteria of mechanism, has been demonstrated for the first time.

EXPERIMENTAL

Preparation of Deuterated Compounds.—The general procedures outlined³ in Part I for ensuring chemical and isotopic purity were followed.

Sodium toluene- α -sulphonate. The methylene-deuterated and normal compounds, (Ia) and (Ib), were prepared by the method of Bunton and Halevi²⁴ from the respective benzyl chlorides, which had been prepared as described in Part I. Because of the relatively high solubility of

²² E.g., Table III of Gold and Hawes, *J.*, 1951, 2102.

²³ Wicke, Eigen, and Ackermann, *Z. phys. Chem.*, 1954, 1, 340.

²⁴ Bunton and Halevi, *J.*, 1952, 4541.

the product in water, the aqueous mother-liquor was not discarded, but evaporated to dryness; the sodium iodide was then washed off with acetone and the residue collected. The product was obtained in 70% yield after recrystallisation from ethanol.

ααα-Trideutero-p-toluic acid. This was prepared by carbonation of the Grignard reagent from *p*-bromo-*ααα*-trideuterotoluene, which had been prepared from *p*-bromobenzoic acid as described under *ααα*-trideuterotoluene in Part II.

Mass spectrometric analysis (see Part I for method) of the toluic acid, kindly performed by Dr. D. R. Christman, confirmed the presence of 3.0 atoms of deuterium per molecule.

Sodium p-methyltoluene-α-sulphonate. Each of the appropriately labelled sulphonates (IIa, b, and c) was prepared from the corresponding *p*-methylbenzyl chloride as described above under sodium toluene-*α*-sulphonate. The isotopic methylbenzyl chlorides were obtained, as described under phenylacetic acid in Part I, by reduction with lithium aluminium hydride (or lithium aluminium deuteride, as required) of either commercial ethyl *p*-toluate or *ααα*-trideutero-*p*-toluate.

N-Methyl-2,4,6-trinitroaniline. Compounds (IIIa and b) were prepared from picryl chloride and respectively methylamine and trideuteromethylamine, as described in Part I. The *N*-deuterated compound (IIIc) was formed *in situ* whenever compound (IIIa) was dissolved in the deuterated medium.

Deuterium oxide (99.5—99.7%). Material from several commercial sources was used without further purification.

Nitric deuterioacid. The material (50% in D₂O), from Merck (Canada) was used without further purification.

Deuterium sulphate. Samples of commercial material [Merck (Canada) and Fluka] were found to absorb strongly in the 200—300 mμ region. We therefore prepared our own strong aqueous deuterium sulphate by the method of Freeman and Richards,²⁵ as follows: sulphuryl chloride (Eastman, Pract. Grade) that had been twice distilled through a Vigreux column, was refluxed with the stoichiometric amount of heavy water. After completion of the reaction, as could be judged by coalescence of the two layers, a short period of further heating removed traces of deuterium chloride. The product, *ca.* 75% of deuterium sulphate in deuterium oxide, was adequately transparent over the spectral range employed.

Check of Isotopic Exchange.—(a) Sodium *αα*-dideuterotoluene-*α*-sulphonate (120 mg.) were dissolved in 12M-hydrochloric acid (10 ml.), and kept at 40° for 1 hr. (This solution is of approximately the same acidity, $H_0 = -4.4$, as our nitric acid-perchloric acid mixtures.) After the solvent had been evaporated off, the product was crystallised from ethanol. Its infrared spectrum (KBr pellet) was identical with that of the starting material, indicating no loss of deuterium.

(b) *N*-Trideuteromethyl-2,4,6-trinitroaniline (500 mg.) was dissolved in 90% sulphuric acid (10 ml.), a solution much more strongly acid than our nitrating mixtures, and kept at 35° for 2 hr. The solution was then poured into ice-water (20 ml.) to precipitate the aniline. After crystallisation from water, the infrared spectrum of its solution in chloroform was identical with that of the starting material.

Kinetic Procedure.—The preliminary *C*-nitrations were followed dilatometrically at 30.0° ± 0.03° and at 35.0° ± 0.02°, by the procedure of Halberstadt, Hughes, and Ingold.⁶ The results, calculated by Guggenheim's method,²⁶ were reproducible to within ± 2—3%.

The preliminary *N*-nitration studies were carried out with a Unicam model 500 spectrophotometer fitted with a constant-temperature cell holder. Alternate readings of the optical density at 425 mμ of two solutions containing compounds (IIIa and b) in portions of the same nitrating solution, both in the same cell holder, were taken against the same blank. The HClO₄:HNO₃:H₂O concentration ratios were adjusted to yield convenient nitration rates, 2.5—6.5 × 10⁻⁴ sec.⁻¹. The standard deviation of the mean for four pairs of runs was 0.005, from an average value of $k_H/k_D = 1.020$.

The bulk of the kinetic runs listed in Table 1 and 2 were carried out with a Bausch and Lomb Spectronic 550 recording spectrophotometer. Each run was carried out individually, and the trace of optical density against time was analysed by Guggenheim's method.²⁶ No deviations from first-order kinetics were observed. All the runs were carried out in a constant-temperature cell holder at 33°. *C*-Nitration of the reference compound was followed by the increased

²⁵ Freeman and Richards, AERE GP/R2479 (1958) (*Chem. Abstracts*, 1958, **52**, 11640d).

²⁶ Guggenheim, *Phil. Mag.*, 1926, **2**, 538; Frost and Pearson, "Kinetics and Mechanism," (2nd edn.) Wiley, New York, 1961, p. 49.

absorption at 264 $m\mu$ due to the mononitration products of toluene- α -sulphonic acid, and *N*-nitration by the decreased absorption of *N*-methyl-2,4,6-trinitroaniline at 425 $m\mu$

In the deuterated media, duplicate runs each of *N*- and *C*-nitration, four runs in all, were carried out as a rule on portions of the same acid solution at each concentration. In the normal nitration media, six runs were generally carried out in aliquots of the same acid; two each for compounds (IIIa), (IIIb), and (Ia).

The precision is as indicated in the Tables. The poorer reproducibility of the slower runs is a result of the rather poor long-range stability of our spectrophotometer.

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